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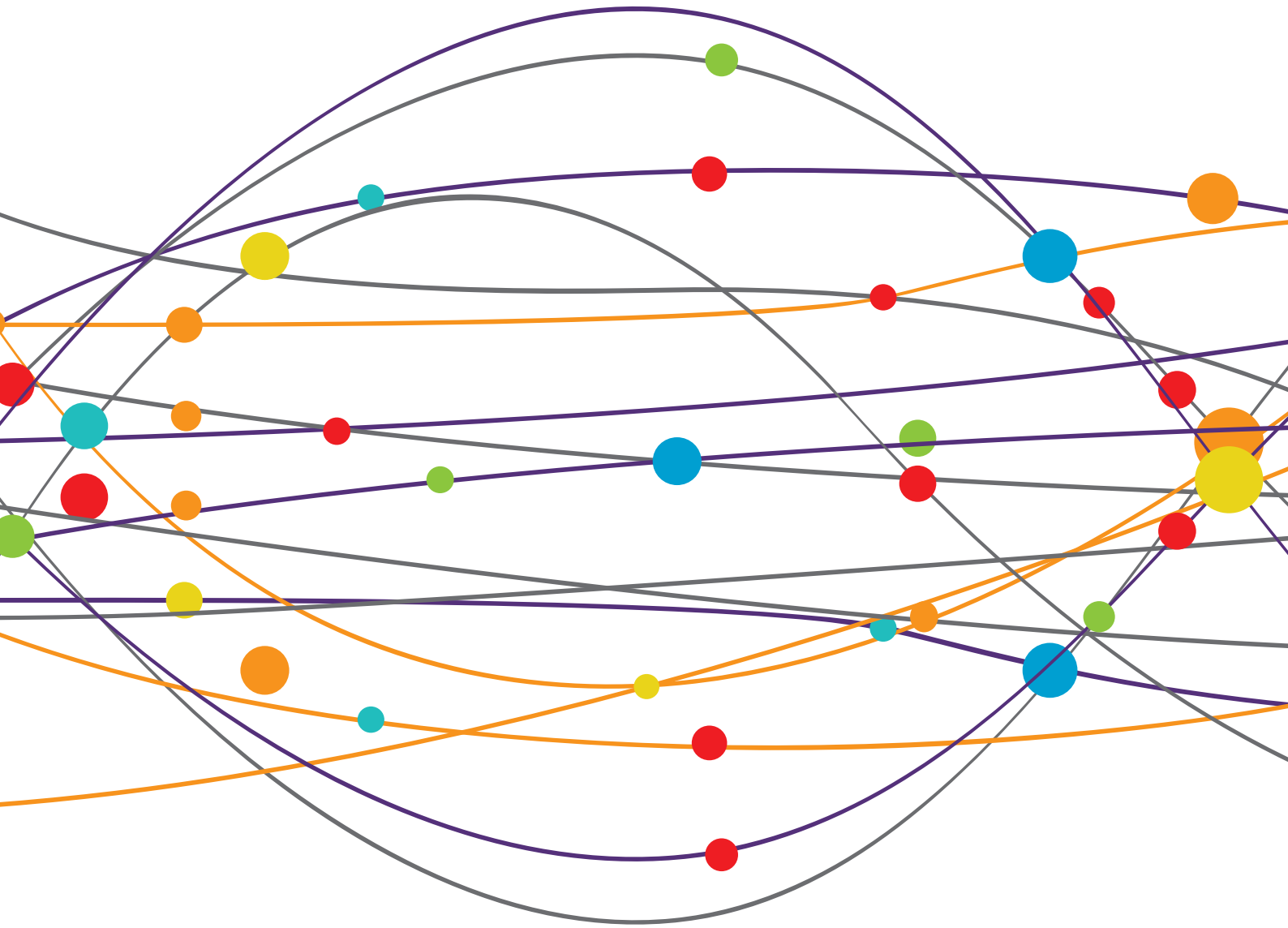

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MULTIPLE SCLEROSIS AND NEUROIMMUNOLOGY – CASE REPORT COLLECTION , VOLUME I

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Editorial: Multiple Sclerosis and Neuroimmunology—Case Report Collection, Volume I

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KEYWORDS

autoimmunity, central nervous system, multiple sclerosis, autoimmune encephalitis, COVID-19, SARS-CoV-2, HSV2, peripheral nervous system

Editorial on the Research Topic
Multiple Sclerosis and Neuroimmunology—Case Report Collection, Volume I

Introduction

Why does Frontiers in Multiple Sclerosis and Neuroimmunology publish Case Reports? There are several reasons. First, we can learn from case reports regarding novel disease entities and rare diseases. Second, case reports can give insight into better pathophysiological understanding of rare diseases. Third, case reports can be of interest regarding translational aspects and modeling in animal models. Fourth, case reports can be important regarding exploration of novel treatment regimen. Possibly, more reasons in favor of case reports can be found, the above indicated are most relevant for the Speciality Chief Editors of Frontiers in Multiple Sclerosis and Neuroimmunology. Of course, it is important that the presented cases bring additional value to the field. The ideal type of case report would contain data regarding the clinical manifestation, immunological, genetic, and pathological aspects of the disease and a novel treatment approach would be presented. Also, the findings should be discussed in the context of the relevant literature. Ideally, there should be two or more similar patients per case report. This is not trivial, especially if the case reports are coming from an individual center. Sometimes, case reports are the entrance into research for the involved physicians especially early in career, since the case has initiated a scientific argument. Therefore, the value of case reports also in gaining scientific thinking should not be underestimated. Frontiers of Multiple Sclerosis and Neuroimmunology is proud to present the "Multiple Sclerosis and Neuroimmunology—Case Report Collection I". This collection contains 27 case studies that were published between 2021 and 2022. We would like to thank the Associate and Review Editors who have evaluated the manuscripts and significantly contributed with their constructive criticism.

Topics of the 27 published case reports of "multiple sclerosis and neuroimmunology – case report collection I"

The 27 case reports of "Multiple Sclerosis and Neuroimmunology—Case Report Collection I" can be ordered as follows: (1) Reports regarding neurological manifestations of coronavirus disease 2019 (COVID-19). (2) Case reports regarding vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) and nervous-system related side effects. (3) Case reports with novel aspects of the emerging field of autoimmune encephalitis (AE). (4) Case reports of viral encephalitis. (5) Case reports regarding autoimmune peripheral nervous system disease. (6) Reports of cases of neuroimmunological side effects by pharmacological treatment. (7) Case reports regarding rare disease variants leading to demyelination within the central nervous system (CNS). (8) Case reports of rare disease variants successfully treated by immune therapy.

Reports regarding neurological manifestations of COVID-19 and long-COVID

There are several neurological manifestations that can be associated with COVID-19 and post- and long COVID. Ishaq et al. present a case of a patient with opsoclonus myoclonus syndrome a rare neurological disease entity that was successfully treated with intravenous immunoglobulins (i.v. Ig). Gilio et al. present findings regarding the overlap of functional neurological disorders with long COVID. They indicate that stress and inflammation might drive disease precipitation of functional neurological disorders. Kimura et al. reports a patient with Bickerstaff brainstem encephalitis possibly triggered by COVID-19 and emerging Takotsubo cardiomyopathy (TC). They indicate that TC should be considered early when hemodynamic status remains unstable in patients with Bickerstaff brainstem encephalitis.

Case reports regarding vaccination against SARS-COV-2 and nervous-system related side effects

Maniscalco et al. present a patient with multiple sclerosis (MS) with a relapse shortly after vaccination with BNT162b2 from Pfizer-BioNTech. Nistri et al. present 16 cases regarding relapse manifestation of MS triggered by vaccination against SARS-COV-2 with 10 patients vaccinated with BNT162b2 from Pfizer-BioNTech, two patients vaccinated with mRNA-1273 from Moderna and four patients vaccinated with ChAdOx1 from AstraZeneca. In a case series by Ancau et al. three patients are reported with acute hemorrhagic encephalomyelitis (AHE) after SARS-COV-2 vaccination with ChAdOx1 from AstraZeneca. The authors indicated that these vaccination-related neurological diseases are rare events. They argue for the need of a robust post-vaccination surveillance.

Case reports with novel aspects of the emerging field of autoimmune encephalitis

Different types of autoimmune encephalitis (AE) are rare diseases with varying clinical presentations. Much can be learned regarding neurobiology from these diseases. Song et al. report a patient with coexistence of anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor encephalitis and biomarkers of Alzheimer's disease. There are AE that are antibody-negative. Possibly, the relevant antigen has not been defined for these disease entities so far. Park and Kim present a patient of antibody negative AE that was successfully treated with B cell depletion by rituximab arguing for an underlying immunological disease-driving pathophysiology. Beside autoimmunity as driver for AE, there is paraneoplasia as disease initiator of AE, mediated by the anti-neoplasia-directed immune response. Gogia et al. report a case with amphiphysin antibody-associated stiff limp syndrome and myelopathy in a patient with breast cancer. Fang, Pan, et al. report a patient with relapses of anti-AMPA encephalitis with progressive brain atrophy and speculate regarding the underlying mechanisms. They observe partial functional recovery even in presence of severe brain atrophy after treatment with immunotherapy. Vaux et al. present a patient that was diagnosed with schizophrenia and was subsequently identified as a patient with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis. Treatment with immune therapy led to improvement of symptoms in this patient. This case argues that patients with psychiatric diagnosis should be routinely explored for AE as a potential cause of their disease. This is important since immunotherapy can lead to improvement of symptoms and can in some patients even result in cure. Hashimoto's encephalopathy is a highly debated and questioned disease entity. Amano et al. present a patient with Hashimoto's encephalopathy associated with lymphomatosis cerebri and periodic synchronous discharges resembling prion, namely Creutzfeld-Jacob disease.

Case report of virus-induced encephalitis

Kolesnik et al. report a patient with herpes simplex virus 2 (HSV-2) encephalitis presenting

with the clinical manifestation of chorea. This is a very rare clinical manifestation in HSV-2 encephalitis.

Case reports regarding autoimmune peripheral nervous system disease

Huang et al. report a patient with Guillain-Barré syndrome (GBS) and unilateral facial palsy. They summarize the current literature regarding such clinical presentations and report 28 cases. They speculate regarding the underlying immune response. Belgrado et al. had two patients with GBS and posterior reversible encephalopathy (PRES). They speculate that autoimmune dysregulation associated with GBS may be a trigger factor for co-emergence of PRES. A patient with reported combined central and peripheral demyelination (CCPD) was presented by Alshamrani et al. This patient had the coexistence of radiologically isolated syndrome (RIS) and Miller-Fisher-syndrome (MFS). Most so far reported cases of CCPD were diagnosed as having co-existence of MS and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Reports of neuroimmunological side effects by pharmacological treatment

Koska et al. (a) report a patient with MS with severe lymphopenia due to treatment with fingolimod. The discontinuation of fingolimod treatment led to clinical deterioration with presence of neuropsychological symptoms that was difficult to overcome. Progressive multifocal leukoencephalopathy (PML) should be also taken early into consideration regarding differential diagnosis in such patients. Tang et al. present a patient with recurrent encephalopathy after treatment with ornidazole. Ornidazole is an antibiotic used for the treatment of protozoan infections. The patient recovered after discontinuation of the treatment with ornidazole. Longitudinal extensive transverse myelitis (LEMS) evolved and novel autoantibodies emerged in a patient treated with pemprolizumab reported by Charabi et al. The humanized antibody pemprolizumab targets programmed cell death protein 1 (PD1) on lymphocytes. Pemprolizumab is used in the treatment of various types of cancers. The emergence of LEMS was B cell mediated. A putative novel autoantigen was hypothesized in this disease condition that has not been defined so far.

Case reports regarding rare disease variants leading to demyelination within the CNS

The expression of a proliferation inducing ligand (APRIL), belonging to the TNF superfamily, in the CNS was investigated in a patient with neuromyelitis optica (NMO) reported by Baert et al. APRIL provides a favorable environment for plasmocytes in the NMO lesion. In addition, APRIL induces an anti-inflammatory response in the NMO lesion. This indicates that targeting of APRIL by novel immunological therapies should only be executed with extreme caution since there is a dichotomy of APRIL-related functions in the NMO lesion. Differential diagnosis can be challenging in patients with atypical clinical presentations. Fang, Tong, et al. report a patient with primary CNS lymphoma that was initially misdiagnosed with glial fibrillary acidic protein (GFAP) astrocytopathy. Early diagnosis to differentiate these diseases is important, due to grossly different treatment approaches. Gao et al. report a patient with GFAP astrocytopathy associated with an area postrema syndrome. Ma et al. report a patient with bilateral meningo-cortical involvement of anti-myelin-oligodendrocyte-glycoprotein (MOG) IgG associated disease. Štourač et al. present the difficulties in the diagnosis and treatment of progressive tumefactive demyelination. The presented patient had an unfavorable outcome. Neurosarcoidosis can be difficult to diagnose. Braun et al. present a patient with myelopathy that was finally diagnosed with neurosarcoidosis.

Case reports of rare disease variants successfully treated by immune therapy

Koska et al. (b) report a patient with Marburg variant of MS who was successfully treated with cyclophosphamide and ocrelizumab. Eculizumab was successfully used to treat a patient with seronegative NMO by Digala et al. This argues for a role of complement in seronegative NMO.

Conclusion

The case series "Multiple Sclerosis and Neuroimmunology—Case Report Collection I" demonstrates the power of case studies as well as their limitations. Possibly, the cases will help to gain progress regarding clinical, pathophysiological, immunological, and treatment-related understanding in clinical and research environments dealing with related patient groups and evolving scientific topics in neuroimmunology. Interested physicians, physician-scientist and researchers will possibly have a benefit

that will help to transform scientific thinking in medicine to a patient-focused research approach regarding disease biology and rationally well-founded medical and rehabilitative treatments.

Author contributions

RW outlined and wrote the editorial.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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CASE REPORT
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Case Report and Literature Analysis: Guillain-Barré Syndrome With Delayed Unilateral Facial Palsy

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Guillain-Barré syndrome (GBS) is an acute inflammatory polyradiculoneuropathy in which most patients have cranial nerve involvement, with facial nerve involvement being the most common. However, delayed facial palsy (DFP) with asymmetric facial palsy is a rare manifestation of GBS, and the mechanism is unclear. We report a case of GBS combined with delayed unilateral facial palsy and review previously reported cases of GBS combined with DFP. A total of 28 cases of GBS with DFP, including the case in this report, were included in this study. The occurrence of DFP may be related to early subclinical demyelination of the facial nerve, the blood-nerve barrier of the facial nerve, facial movement, and descending reversible paralysis. The occurrence of unilateral facial palsy may be related to *Campylobacter jejuni,* specific anti-ganglioside antibodies, and the site of central nervous system anatomical involvement. There is no evidence that immunotherapy is related to the shortening of DFP course and improving patients' prognosis.

Keywords: Guillain-Barré syndrome, delayed unilateral facial palsy, threshold, anti-ganglioside antibodies, asymmetric, retreatment

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INTRODUCTION

Guillain-Barré syndrome (GBS) is an autoimmune-mediated acute inflammatory polyradiculo-neuropathy with symptoms peaking at about 2 weeks and a monophasic self-limiting course involving the spinal nerve roots, peripheral nerves, and cranial nerves. Cranial nerve involvement is most common with bilateral facial nerve palsy, rarely with unilateral involvement, and facial palsy mostly occurs in the early stage of the disease (1, 2). Delayed facial palsy (DFP) is facial palsy that occurs after other neurological signs have peaked or after symptoms have begun to improve, with an incidence of only 6% (3). Here we report on a case of a 54-years-old man who presented with both lower limb pain and weakness as the first clinical manifestation. The patient developed facial palsy after other neurological symptoms have reached nadir. Based on clinical manifestations, the same damage type of facial nerve and limb nerve as suggested by electrophysiological examination, and good treatment response to intravenous immunoglobulin (IVIG), the patient was diagnosed with GBS with delayed unilateral facial palsy. Further, we review all previous GBS cases combined with DFP, summarizing the clinical features, examination results, and treatment prognosis of such patients. Our study included a total of seven articles (3–9), with a total of 28 cases, including 14 GBS, 13 MFS, and one MFS/GBS overlapping case. Cases that met the criteria are listed in **Table 1**. Our purpose was to explore the mechanism of DFP and asymmetric facial palsy in GBS and clarify the main points of diagnosis and treatment options.

TABLE 1 | Review all reported GBS/MFS with DFP cases.

	Diagnosis	Age/sex	Symmetry of FP	Course time (days)					Retreatment	Antibodies	MRI	Pathogen testing
				Nadir	Appearance of FP	Resolution of FP	Course time of FP	Course time of GBS/MFS				
Case 1	GBS	54/M	-	7	23	49	26	Incomplete resolution	IVIG	-	-	NA
Fisher (4)												
Case 2	MFS	45/M	-	5	13	42	29	-	NA	-	NA	NA
Chida et al. (5)												
Case 3	MFS	65/M	+	8	17	45	28	85	IAP	GQ1b	-	NA
Case 4	MFS	60/M	+	4	12	36	24	126	MP	GQ1b	NA	NA
Tatsumoto et al. (3)												
Case 5	GBS	55/M	-	5	14	29	15	38	-	GQ1b	NA	NA
Case 6	MFS	32/M	NA	6	10	NA	NA	NA	-	NA	NA	NA
Case 7	MFS	18/M	NA	6	7	NA	NA	NA	-	NA	NA	NA
Case 8	MFS	29/F	NA	10	11	NA	NA	NA	-	NA	NA	NA
Case 9	MFS	35/M	NA	5	15	NA	NA	NA	-	NA	NA	NA
Case 10	GBS	79/F	NA	6	7	NA	NA	NA	-	NA	NA	NA
Case 11	GBS	29/M	NA	6	14	NA	NA	NA	-	NA	NA	NA
Case 12	GBS	81/F	NA	7	9	NA	NA	NA	-	NA	NA	NA
Case 13	GBS	55/F	NA	9	30	NA	NA	NA	-	NA	NA	NA
Case 14	GBS	15/M	NA	9	10	NA	NA	NA	-	NA	NA	NA
Case 15	GBS	25/F	NA	10	14	NA	NA	NA	-	NA	NA	NA
Case 16	GBS	55/M	NA	11	16	NA	NA	NA	-	NA	NA	NA
Case 17	GBS	68/M	NA	6	7	NA	NA	NA	-	NA	NA	NA
Case 18	GBS	31/M	NA	4	12	NA	NA	NA	-	NA	NA	NA
Course time (days)												
Case 19	GBS	35/M	NA	6	15	NA	NA	NA	-	NA	NA	NA
Case 20	GBS	67/M	NA	3	10	NA	NA	NA	-	NA	NA	NA
Case 21	GBS	32/F	NA	6	7	NA	NA	NA	-	NA	NA	NA
Liu et al. (6)												
Case 22	MFS	40/M	+	9	10	18	8	18	MP	GM1	-	NA
Yamamoto et al. (9)												
Case 23	MFS	55/M	-	11	16	42	26	Incomplete resolution	VCV	GQ1b	-	-
Tan et al. (7)												
Case 24	MFS	52/M	-	9	14	66	52	66	-	-	NA	NA
Case 25	MFS	45/M	+	6	12	35	23	78	PE	GQ1b, GT1a, GD1b	NA	NA
Case 26	MFS	21/F	+	4	8	64	56	100	-	GQ1b, GT1a	NA	NA
Case 27	MFS/GBS	57/F	-	6	14	43	29	44	-	GQ1b, GT1a	NA	NA
Umekawa et al. (8)												
Case 28	MFS	47/M	+	7	14	43	29	NA	-	GQ1b, GT1a, Ga1NAc, GD1a	+	-

M, male; F, female; GBS, guillain-barre syndrome; MFS, miller fisher syndrome; DFP, delayed facial palsy; MRI, magnetic resonance imaging; NA, not available; FP, facial palsy; C.jejuni, campylobacter jejuni; IVIG, intravenous immunoglobulin; IAP, immunoadsorbent plasma exchange; MP, methylprednisolone; PE, plasma exchange; VCV, valacyclovir.

CASE DESCRIPTION

A 54-year-old male with previous physical fitness was admitted to the hospital with "both lower limb pain and weakness for 1 month, and right facial palsy for 1 week." The patient started with weakness in both lower limbs and pain in the buttocks, the back of both thighs, calves, and feet. On the 7th day of onset, his loss of muscle strength in both lower limbs peaked, and his muscle strength began to gradually recover. Nervous system physical examination revealed incomplete closure of the right eye, shallowing of the right frontal lines and nasolabial folds, deviation of the mouth angle to the left, and normal function of the remaining cranial nerves. The power was grade 4/5 in the lower limbs and grade 5/5 in the upper limbs. Deep tendon reflexes were absent in all limbs. Sensory system examination showed that the pain of all toes was decreased and the rest were normal. Pathological reflex examination was negative. Laboratory test results indicated that routine blood, liver, and kidney function, electrolytes, and blood sugar tests all returned normal. Brain magnetic resonance imaging (MRI) revealed no abnormalities. Cerebrospinal fluid results suggested protein cell separation (cerebrospinal fluid protein 868.46 mg/L, total cell count 68 $\times$ 10^6/L, white blood cell count 18 $\times$ 10^6/L). Western blot analysis of serum and erebrospinal fluid anti-ganglioside antibodies (including anti-sulfatide, anti-GM1, anti-GM2, anti-GM3, anti-GM4, anti-GD1a, anti-GD1b, anti-GD2, anti-GD3, anti-GT1a, anti-GT1b, and anti-GQ1b antibodies), cell-based assay method to detect serum and cerebrospinal fluid central nervous system (CNS) demyelinating disease antibodies (including AQP4 antibody, anti-MOG antibody, anti-MBP antibody), and serum and cerebrospinal fluid IgG oligoclonal zone analysis results were negative. Complete serum and cerebrospinal fluid virus tests showed herpes simplex virus type 1 IgG (+). The latency and conduction velocity of the deep tibial and fibula motor nerve conduction velocity (NCV) were normal bilaterally, and the amplitude of the compound muscle action potential (CMAP) was reduced. A sensory nerve conduction study showed that the CMAP amplitude of the sural sensory nerve was reduced. F wave waveform was discrete on the right tibial nerve. The NCV of facial movement showed that the amplitude of the right cheek branch, cheekbone branch, and temporal lobe branch was reduced, and the conduction was normal. Blink reflex results showed that R1 and R2 on the right side were later than on the left side and had a lower amplitude than on the left side. The conclusion showed that the right facial nerve and lower limb nerves were demyelinated, accompanied by polyneuropathy and secondary axonal degeneration. The patient was diagnosed with GBS with unilateral DFP. On the 38th day of onset, the patient was administered IVIG 0.4 g/kg/day for five consecutive days. On the 49th day of onset, the patient's facial palsy completely disappeared, and the pain and weakness of the lower extremities and numbness of the feet partially resolved. After 12 months of follow-up after discharge, the patient still had mild pain in both lower extremities.

DISCUSSION

We report a rare case of GBS with delayed unilateral facial palsy. Unlike the symmetrical facial palsy and the typical monophasic course of GBS patients (10), this patient developed delayed unilateral facial palsy after recovery of limb muscle strength, and the results of the electrophysiological examination suggested the same type of facial nerve and limb nerve damage, and a diagnosis of GBS combined with DFP was considered. After treatment with IVIG, the patient's facial palsy rapidly improved, further confirming that delayed onset facial palsy is still part of the GBS course. As a variant of GBS, MFS usually involves ophthalmoparesis, ataxia, and areflexia as the main symptoms, without limb weakness. A positive anti-GQ1b antibody is helpful for the diagnosis (11). Although both can be combined with facial palsy, MFS rarely recurs after the condition improves. Even if relapse occurs, the interval is very long (12). Based on our literature review, the ratio of GBS combined with DFS is consistent with that of MFS (3); therefore, we presume that DFS is a delayed type that may be secondary to multiple GBS variants. If facial palsy occurs in the above situation, GBS disorder and the relative disease are priorities for diagnosis.

So far, few cases of GBS combined with DFP have been reported. Only 28 cases in seven studies have been described (including our case, listed in **Table 1**) (3–9). Patients' age range was 15–81 years (mean $\pm$ SD: 45.44 $\pm$ 17.71), 20 (71.4%) were male, and 8 (28.6%) were female, with a male to female ratio of 5:2. Twenty-one out of 28 patients (77.8%) had a history of antecedent illness; the upper respiratory was the main cause, followed by diarrhea. Pathogen testing was completed in only two cases, and both were negative. The neurological level of all patients peaked within 3–10 days (mean $\pm$ SD: 6.82 $\pm$ 2.20). DFP occurred 7–30 days after onset (median: 12 days). Fifteen of 15/28 patients (53.6%) had bilateral facial palsy, and 13/28 patients (46.4%) had unilateral facial palsy. Among the 16 patients reported by Tatsumoto (3), seven had unilateral facial palsy and nine had bilateral facial palsy. We can only obtain detailed symptom data of 16 patients from all articles, of which 14/16 patients (87.5%) had symptoms of cranial nerve involvement other than the facial nerve, such as ophthalmoplegia and bulbar palsy. This included 13 MFS and one MFS/GBS patient, and 2/16 patients (12.5%) had facial nerve involvement alone. Detailed cerebrospinal fluid data were available from all articles for 12 patients, and 9/12 patients (75.0%) showed protein cell separation. Fifteen out of 28 patients (53.6%) were positive for anti-ganglioside antibodies, and multiple antibodies could be positive in the same patient at the same time. Of the 15 patients, 11 tested positive for anti-GQ1b antibody, 4/15 patients tested positive for anti-GT1a antibody, of which 4/16 patients reported by Tatsumoto (3) tested positive for anti-GQ1b antibody, and two patients tested positive for anti-GM1, GM1b, GD1a, or GalNAc-GD1a antibody. Twenty-two out of 28 patients (78.6%) received immunotherapy after admission, of which 11/22 patients (50.0%) received IVIG treatment, and 5/22 patients (22.7%) received IVIG combined with methylprednisone treatment, 3/22 patients (13.6%) received

plasma exchange (PE) treatment, 2/22 patients (9.1%) received immunoadsorbent plasma exchange (IAP) treatment, and 1/22 patients (4.5%) received immunoadsorption therapy. Six out of 28 patients (21.4%) received specific treatment after the onset of DFP, of which 2/6 patients (33.3%) were treated with methylprednisone, one patient (14.3%) developed DFP during treatment with PE and IAP and continued treatment, and one patient (14.3%) received IVIG and valacyclovir. The course of facial palsy was roughly 3 weeks in all 16 patients reported by Tatsumoto (3), regardless of whether they received retreatment after the onset of DFP. In addition, 6/28 patients (21.4%) did not receive any treatment during the entire course of the disease. We were able to obtain complete prognostic data from 10 patients, with all symptoms resolved in a total of eight patients, including four who did not receive retreatment after the onset of DFP, except for one patient who remained with mild bilateral abduction limitation and diplopia after treatment with IVIG and valacyclovir, and one patient who remained with mild pain in both lower extremities after treatment with IVIG. Whether the patient received retreatment after the onset of DFP did not appear to affect the course of facial palsy or the prognosis. However, we still wondered, "how does delayed unilateral facial palsy occur and what is its possible pathogenesis?" For this purpose, we launched a careful literature analysis.

In 2004, Vucic conducted a retrospective analysis of the clinical data of 38 early Acute inflammatory demyelinating polyneuropathy (AIDP) patients. Among them, the blink reflex results of 16 patients suggested that the ipsilateral R1 and R2 and the contralateral R2 were prolonged or disappeared, indicating that the facial nerve's early demyelination changes, but only 11 patients developed facial palsy (13). Similar results were obtained in a study by Wali (14). There were 17 patients with abnormal blink reflex results without facial palsy. These findings confirm that early facial neuropathy in GBS patients may be subclinical. At the same time, some researchers suggested that the progression pattern of "descending reversible paralysis" in the course of MFS leads to the emergence of DFP (15). Among 11 patients with MFS combined with DFP, nine of the patients' facial palsy symptoms appeared after the upper cranial nerves (III, IV, and VI) involved. The authors speculate that the pathophysiology of MFS may include this pattern, but it cannot explain the group of GBS patients with lower cranial nerve involvement as the first symptom and single cranial nerve involvement. In addition, in a study on proximal conduction abnormalities of the facial nerve in MFS patients, subclinical demyelinating lesions of the proximal facial nerve were detected in all three MFS patients (16). Therefore, we speculate that in some patients with GBS and DFP, the lesions of the proximal facial nerve segment may be subclinical demyelination and conduction block in the early stage. As the disease progresses, the lesion reaches a "threshold," and the time taken to reach the threshold determines the timing of facial palsy, and this process of development leads to the emergence of "delayed onset." Therefore, we suggest that the atypical monophasic course of GBS combined with DFP patients may be related to early subclinical demyelination of the facial nerve, the blood-nerve barrier of the facial nerve, facial movements, and the pattern of "descending reversible paralysis."

The positive rate of anti-ganglioside antibodies in typical GBS patients is <33.3%(17), the positive rate of anti-GQ1b antibodies in patients with MFS is 80–90% (11), and the positive rate of antibodies in GBS combined with DFP is between the two (53.6%), mainly with anti-GQ1b and anti-GT1a antibodies. Therefore, we speculate that anti-ganglioside antibodies may be involved in the occurrence of DFP. In a review of previous literature, Fan et al. found that GBS patients presenting with facial palsy had a high rate of anti-ganglioside antibody IgM positivity, including 40% for anti-GM1 and GM2 antibodies and 33.3% for anti-GM3 antibodies, while the rate of positivity for other antibodies was extremely low. Therefore, they proposed that anti-ganglioside antibodies GM1, GM2, and GM3 are associated with the appearance of facial palsy (17). Greco reported a case of recurrent facial palsy in a child with elevated serum anti-GQ1b IgG and IgM titers, which decreased as clinical symptoms improved, thus suggesting that anti-GQ1b antibodies are associated with recurrent facial palsy (18). In another study, more than half of the patients with positive anti-GT1a IgG antibodies developed facial palsy. The authors speculated that patients with positive anti-GT1a IgG usually have multiple cranial nerve involvement, including the facial nerve (19). However, the mechanism of action of these antibodies in DFP still needs further research. In fact, the high positive rate of anti-GQ1b, anti-GT1a, and other antibodies in GBS patients with DFP is not directly related to the expression of gangliosides on the facial nerve. For example, GQ1b is abundantly distributed on nerves II, III, IV, and VI but less on the facial nerve and other nerves (20). Combining statistical data analysis, we propose the following hypothesis: there is more GQ1b on the facial nerve in GBS patients with combined DFP than in those with classic GBS. This remains to be confirmed in future clinical studies. It is worth noting that of the 28 cases of GBS combined with DFP summarized in this article, 13 cases still had negative anti-ganglioside antibody tests. We speculate that there may also be antibodies involved in the occurrence of DFP that have not yet been discovered. Combined with the clinical characteristics of DFP, we found that the sequence of the antibody's effects on different receptors may be affected by the abundance of blood supply and the blood-nerve barrier. For example, the blood supply of the extraocular muscle capillaries is abundant, and toxins and antibodies in the circulation preferentially enter this site, so that conduction abnormalities appear in the early stage of the disease. However, the blood-nerve barrier of the facial nerve is relatively intact, and antibodies to the facial nerve reach the target later, resulting in delayed facial nerve involvement. Previous literature suggests that physical factors, such as limb movement and body posture, may affect the initial distribution of weakness symptoms. For example, the arms and legs are in a state of exercise for a long time, and blood flow increases at certain critical moments when inflammatory cells or humoral factors enter the nerves, which leads to the first appearance of fatigue symptoms (21). For some patients with relatively less facial muscle activity than limbs, this may be one of the reasons for DFP.

GBS usually presents with widespread and symmetrical muscle weakness, often involving the bilateral extremities

and accompanied by hyporeflexia/absence of reflexes (22). In contrast, the case reported here presented with asymmetric bilateral facial nerve involvement, a manifestation that occurred in only 4.9% of GBS (1). The common clinical unilateral facial palsy is easily misdiagnosed as Bell's palsy. The main treatment to promote the recovery of facial palsy in Bell's palsy patients is corticosteroids, but it has no effect on improving the prognosis of GBS and may even have adverse effects (23). Therefore, the distinction between the two is important. Studies have shown that more than 57% of patients with Bell's palsy have pathological enhancement of the facial nerve (24). Kinoshita compared head-enhanced MRI of 125 patients with Bell's palsy to 300 controls without facial nerve disease and showed that 67 and 43% of Bell's palsy patients had distal intrameatal and facial nerve labyrinthine segment enhancement, respectively, compared to 0% of the controls (25). Head-enhanced MRI of patients with GBS with facial palsy rarely shows facial nerve enhancement, and the enhancement segments are irregular (26–29). Therefore, when DFP appears in GBS patients, enhanced head MRI can be performed to help identify Bell's palsy. A study reported a patient with GBS with marked asymmetry in clinical symptoms and electrophysiological manifestations, whose serologic testing suggested a recent *Campylobacter jejuni* infection and anti-ganglioside antibody testing suggested a significantly elevated titer of anti-GM1 IgG. Therefore, the researchers concluded that this asymmetry was associated with *C. jejuni* infection and high titers of anti-GM1 IgG (30). Campylobacter jejuni is the most common pathogenic microorganism that mediates GBS/MFS autoimmunity (10). Autoreactive immunoglobulin G1 (IgG1) is a common antibody subtype after human Campylobacter jejuni infection, and the IgG1 titer is related to the severity of GBS and prognosis (31). Malik et al. showed that IgG1 can cross-react with peripheral gangliosides GM1 and GD1a to induce the production of anti-ganglioside antibodies (32). Campylobacter jejuni in MFS can also induce autoimmunity to produce anti-GQ1b antibodies (10). In this study, only two patients underwent the pathogenic test and were negative. Compared with patients with classic GBS/MFS, patients with DFP have a lower positive rate of Campylobacter jejuni, which may be related to the lack of attention to pathogenic examination by previous researchers. Therefore, we suggest that in the future, more attention should be paid to the pathogenic examination of patients with GBS/MFS with DFP to better study the role of Campylobacter jejuni in the occurrence of DFP and asymmetric facial palsy. Osaki reported a case of a significantly asymmetric pharyngeal-cervical-brachial variant GBS. The anti-GT1a antibody titer increased in parallel with the clinical symptoms. The authors proposed that the evaluation of anti-ganglioside antibodies (including anti-GT1a IgG antibodies) should help in diagnosing GBS with asymmetric involvement (33). In addition, an autopsy study of GBS patients confirmed that GBS can affect the CNS, which involves axons with secondary myelin damage, microglial activation, and inflammatory infiltration (34). Some researchers have suggested that CNS involvement can lead to asymmetric symptoms and signs in patients with GBS (35). Thus, *C. jejuni* infection, anti-ganglioside antibodies, and asymmetric CNS involvement may all contribute to the asymmetric distribution of GBS symptoms.

To date, there have been no systematic studies on the treatment of patients with GBS combined with DFP. In the cases reviewed in this article, 78.6% of the patients received specific treatment and achieved complete remission of symptoms. Therefore, the recommended treatment options for such patients, IVIG and PE, are still preferred (22). However, after summarizing the cases, we also found that regardless of whether the patient received retreatment after the occurrence of DFP, the course of facial palsy was about 3 weeks. Currently, there is no evidence that immunotherapy can shorten the course of facial palsy and improve the prognosis.

CONCLUSION

In this study, we reported a case of GBS with rare features of delayed unilateral facial palsy at the same time. The facial and peripheral nerves had the same electrophysiological changes. We reviewed all previously reported cases of GBS combined with DFP and concluded that the occurrence of DFP may be related to the early subclinical demyelination of the facial nerve, the blood-nerve barrier of the facial nerve, facial movement, and descending reversible paralysis, and the occurrence of unilateral paralysis may be related to *C. jejuni*, specific anti-ganglioside antibodies, and CNS anatomical involvement. Although IVIG and PE can be used for treatment, there is no evidence that immunotherapy is related to the shortening of the DFP course and improving patients' prognosis. We hope that this study can provide references for clinical diagnosis and treatment, but the pathogenic mechanisms of such diseases need to be verified by larger studies.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of The Second Xiangya Hospital. The written consent to publish this information has been obtained from the study patient. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XH conducted the literature review and drafted the manuscript. ZL made substantial contributions to conception and interpretation of data. ZH and YZ were involved in revising the manuscript critically and have given final approval of the version to be published. All authors read and approved the manuscript.

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CASE REPORT
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Case Report: A Well-Hidden Cause for Myelopathy

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Introduction: Sarcoidosis is a rare, systemic inflammatory disease and can involve multiple organs, especially the lungs and lymph nodes. The nervous system is affected in <10 percent of patients, which is called neurosarcoidosis. Neurosarcoidosis can cause a multitude of symptoms and can mimic various diseases. A rare manifestation is bone marrow involvement. We describe a case of spinal cord syndrome due to myelopathy that was caused by sarcoidosis of the bone marrow.

Case Presentation: A male patient presented to our hospital with incomplete spinal cord syndrome. He suffered from numbness of the legs which had progressed to severe paraparesis. Magnetic resonance imaging revealed thoracic myelopathy without contrast enhancement. Thorough diagnostics found no explanation for the myelopathy, and the patient was treated symptomatically with high-dose steroids. When the patient developed non-resolving leukopenia, a bone marrow biopsy was performed. The bone marrow showed changes due to sarcoidosis. Further testing revealed myocardial involvement of the sarcoidosis. The patient was started on oral prednisolone and methotrexate. Over the course of time, his symptoms improved, but he still suffers from spastic leg paresis and needs aids to walk farther than 1 kilometre.

Conclusion: In patients presenting with neurological deficits of unknown cause, neurosarcoidosis is a potential explanation. If it manifests primarily in the bone marrow, the diagnosis can be easily overlooked. Abnormalities in a full blood count should make the treating physician consider this diagnosis, and a bone marrow biopsy should be performed.

Keywords: bone marrow sarcoidosis, neurosarcoidosis, myelopathy, case report, spinal cord syndrome

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INTRODUCTION

Sarcoidosis is a rare, systemic inflammatory disease characterised by non-caseating granulomas (1). It occurs in all ages and can involve multiple organs, especially the lungs and lymph nodes (2, 3). In <10 percent of patients, the nervous system is affected, which is called neurosarcoidosis (4–6). A rare manifestation is bone marrow involvement (7). We describe the case of a young male who presented with spinal cord syndrome caused by thoracic myelopathy. It took 8 weeks to find its cause: Sarcoidosis of the bone marrow.

CASE PRESENTATION

A male in his 40s was referred to our hospital's emergency department complaining of numbness in his lower limbs. The numbness started 3 days before in both legs and rose to the trunk over the course of time. In the days before presentation, his walking ability deteriorated, and he had problems emptying his bladder. Two days before, he perceived flu-like symptoms and shivering. Three months before, he suffered from a gastrointestinal infection. He had a past medical history of arterial hypertension and gout. His prescribed medication comprised ramipril, amlodipine, lercanidipine, and allopurinol.

The initial physical examination revealed no pareses but incomplete spinal cord syndrome with sensory loss on the level of the 9th or 10th thoracic spinal segment, slightly elevated reflexes on the left upper extremities and right lower extremities, and a distended bladder.

An MRI of the spine on the day of admission revealed myelopathy without contrast enhancement spanning from T4 to T11 (**Figure 1a**). Aortic dissection was not found on a contrast-enhanced CT-angiography scan of the thorax and abdomen. Other abnormalities were also not detected. A lumbar puncture was performed because of a suspected autoimmune or infectious cause. We found a xanthochrome cerebrospinal fluid (CSF) with pleocytosis (57/µl; normal: <5/µl) and elevated levels of protein (1.04 g/l; normal: <0.45 g/l) and lactate (2.28 mmol/l; normal: <1.9 mmol/l). Oligoclonal bands were not detected in the CSF. The patient was started on antibiotic therapy of Ceftriaxone and ampicillin and virostatic therapy of acyclovir. These therapies were stopped when microbiological and virological testing did not show any signs of bacterial or viral infections. There was no growth of bacteria in the CSF culture and viral DNA (VZV, HSV ½, EBV, CMV, Entero- and Rhinovirus) was not found using PCR. We then started the patient on a steroid pulse therapy of 1 g methylprednisolone over the course of 5 days. The symptoms slightly improved at first with this therapy, but over the next few days, the patient showed progression of the spinal cord syndrome with severe paraparesis, dysaesthesia (burning sensations), and diminished bowel function. The steroid pulse was repeated with a dosage of 2 g of methylprednisolone over the course of 5 days that id not result in any improvement of his symptoms. Therefore, the patient was treated with 7 treatment cycles of plasmapheresis that still did not lead to improvement. Due to neuropathic pain, he was started on a therapy of 200 mg of carbamazepine twice daily.

In the meantime, the patient was tested for serum-autoantibodies (ANA, ANCA, dsDNA, PR3, MPO, ß2-Glycoprotein, Cardiolipin, CCP, rheumatoid factor, mitochondrial, LKM, SLA, smooth muscles, parietal cells, AQP4, MOG) and markers for sarcoidosis (ACE, soluble IL2-receptor), which all proved negative. No evidence of HIV-infection was found. The samples were acquired prior to steroid therapy. Somatosensible and magnetic-evoked were normal from and to the upper extremities but pathologic on the lower extremities. Neuropsychological testing did not reveal any deficits but signs of reactive depression. An MRI of the brain did not show any abnormalities. Two weeks after the initial MRI of the spine, a new MRI revealed contrast enhancement on the level of T4/5 (**Figure 1b**).

Several times, the patient developed elevated inflammatory markers (fever, C-reactive protein [CRP]) and was treated for pneumonia, epididymitis, and urinary tract infections with antibiotics. 4 weeks after admission, the patient developed leukopenia (3.3 10^9/l) that further dropped over the following days and weeks (lowest: 1.2 10^9/l) and was attributed to the carbamazepine after we discussed the case with our infectious diseases department. The patient was then tested for several bacterial infections (TBC [quantiferon test], Bartonellae, Brucellae, Coxiella) and for Hepatitis A-E. As the CRP did not resolve, transesophageal echocardiography (TEE), magnetic resonance cholangiopancreatography (MRCP) and positron emission tomography computed tomography (PET-CT) were performed. The TEE and MRCP did not provide any explanation, but the PET-CT showed bilateral central pulmonary embolization as a sign of diffuse coagulopathy, and anticoagulation was initiated. The PET-CT also showed heightened activity in the bone marrow, which was attributed to the infectious state. As the leukopenia did not resolve, the patient underwent a bone marrow biopsy. The analysis of the biopsy revealed the bone marrow was low in cells, consistent with toxic damage, myelodysplastic syndrome, or regeneration, and the patient was started on granulocyte colony stimulating factor. Leukopenia resolved 2 weeks after the first occurrence. Further testing of the bone marrow finally revealed multifocal epithelioid cell granulomas with giant cells, and 8 weeks after admission, the patient was diagnosed with sarcoidosis of the bone marrow (**Figure 2**). High-resolution CT of the lungs did not show any signs of pulmonary involvement, but a cardiac-MRI displayed signs of myocardial oedema, that were attributed to sarcoidosis- related inflammation. After active CMV-infection was excluded, the patient was started on 60 mg of prednisolone. Afterwards, CMV serology showed IgM-production once, which was attributed to reactivation under immunosuppression. A new MRI of the spine did show the old lesion in the thoracic myelon (**Figure 1c**) and a new lesion spanning from C3 to C7 (**Figure 1d**).

Ten weeks after initial admission, the patient was transferred to stationary rehabilitation. On discharge, the patient was able to stand with help and wiggle his toes. We recommended retesting the CMV-status and, in the case of negative CMV-status, starting the patient on a therapy of methotrexate and folate.

Five months after initial admission, the patient presented to our outpatient clinic for a routine appointment. He reported being able to walk 500 metres with help from walking aids. The bladder and bowel dysfunction had completely resolved, but he complained of weakness of the right leg and a persisting sensory deficit starting from Th9. He reported no sequelae from the pulmonary embolism, but due to the necessary anticoagulation, haematoma evacuation was necessary after a trivial trauma

Abbreviations: CT, computed tomography; CSF, cerebrospinal fluid; ECG, electrocardiogram; MRI, magnet resonance imaging; MRCP, magnetic resonance cholangiopancreatography; PET-CT, Positron emission tomography computed tomography; TEE, transesophageal echocardiography.

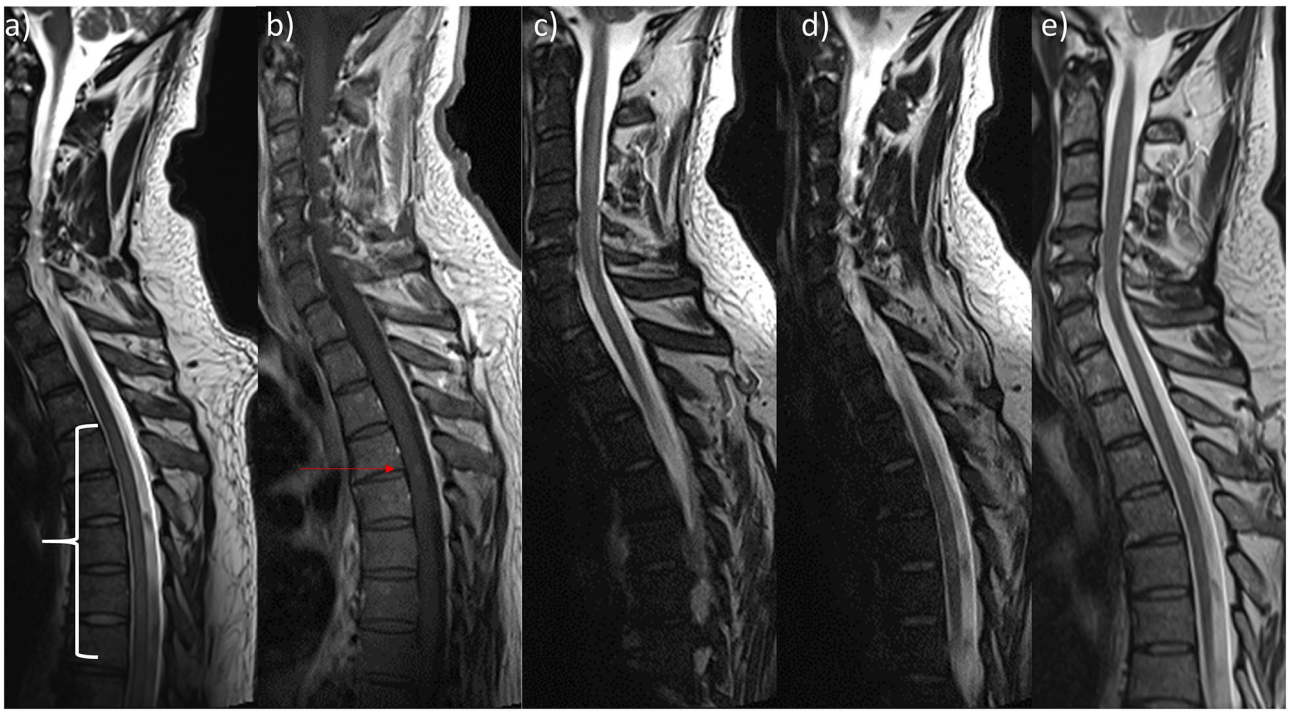

FIGURE 1 | Sagittal Magnetic resonance imaging of patient's spine. **(a)** On admission there was discrete signal enhancement spanning from T4 to T11 in T2-weighted sequences. **(b)** 2 weeks later, there was a discrete contrast enhanced signal at the height of T4/5 in T1-weighted sequences. **(c,d)** Prior to discharge, T2-weighted sequences showed **(c)** a new cervical lesion spanning from C3 to C7 and the unchanged signal enhanced thoracic lesion **(d)**. **(e)** Resolvance of myelopathic changes 1 year after initial admission.

to the right calf. Methotrexate was started as recommended, and the prednisolone was gradually reduced to a dosage of 6 mg daily (8). On examination, there was moderate paresis of foot elevation and knee flexion and paraspasticity of the legs, with emphasis on the right side. Babinski's sign was present in the left foot. We recommended further reduction of the prednisolone, physiotherapy, and a therapeutic attempt with off-label fampridine to reduce spasticity. Fampridine was prescribed due to personal preference of the treating physician. There was no evidence-based reason.

Three months later, the patient reported being able to walk one kilometre with walking aids and walking freely at home. He still complained of weakness of the right leg and unchanged sensory deficits. A clinical examination now revealed light paresis of foot elevation and knee flexion. The remaining pre-reported symptoms were unchanged. As the fampridine did not lead to any improvement of spasticity, 5 mg of baclofen daily were recommended to reduce spasticity.

Over the course of time and 4 further appointments in our outpatient clinic, the walking distance and spasticity gradually and moderately improved. When last reporting to our outpatient clinic, the patient was able to walk 1 kilometre freely. The sensory deficits did not improve. The prednisolone was further reduced. An MRI of the spine showed complete resolution of the myelopathic changes and no contrast enhancement (**Figure 1e**). He had physiotherapy weekly and planned to restart his job 17 months after his first admission to our hospital.

DISCUSSION

In patients presenting with spinal cord syndrome, the diagnosis of myelopathy is readily made with MRI. If the origin of the myelopathy is non-traumatic, a thorough diagnostic workup is required. Angiography can identify ischemic causes. Laboratory investigations including CSF can help find hypovitaminosis or autoimmune causes (Neuromyelitis optica, multiple sclerosis, sarcoidosis, etc.). In young patients, an MRI of the brain can be performed to find cerebral evidence for multiple sclerosis.

Depending on the cause of the myelopathy, treatment can be initiated. Physiotherapy is usually necessary and can help reduce the patient's disability (9).

Sarcoidosis is a rare inflammatory disease affecting about 10/100,000 people in the USA of all ages and ethnicities (5). The non-caseating granulomas that are the hallmark of the disease contain macrophages, multinucleated giant cells, and epithelioid cells. Among others, T-cells promote the cellular immune reaction, and B-cell hyperactivity leads to immunoglobulin production (10).

A comparatively benign entity is Löfgren syndrome, an acute form of sarcoidosis with polyarthritis, erythema nodosum, and

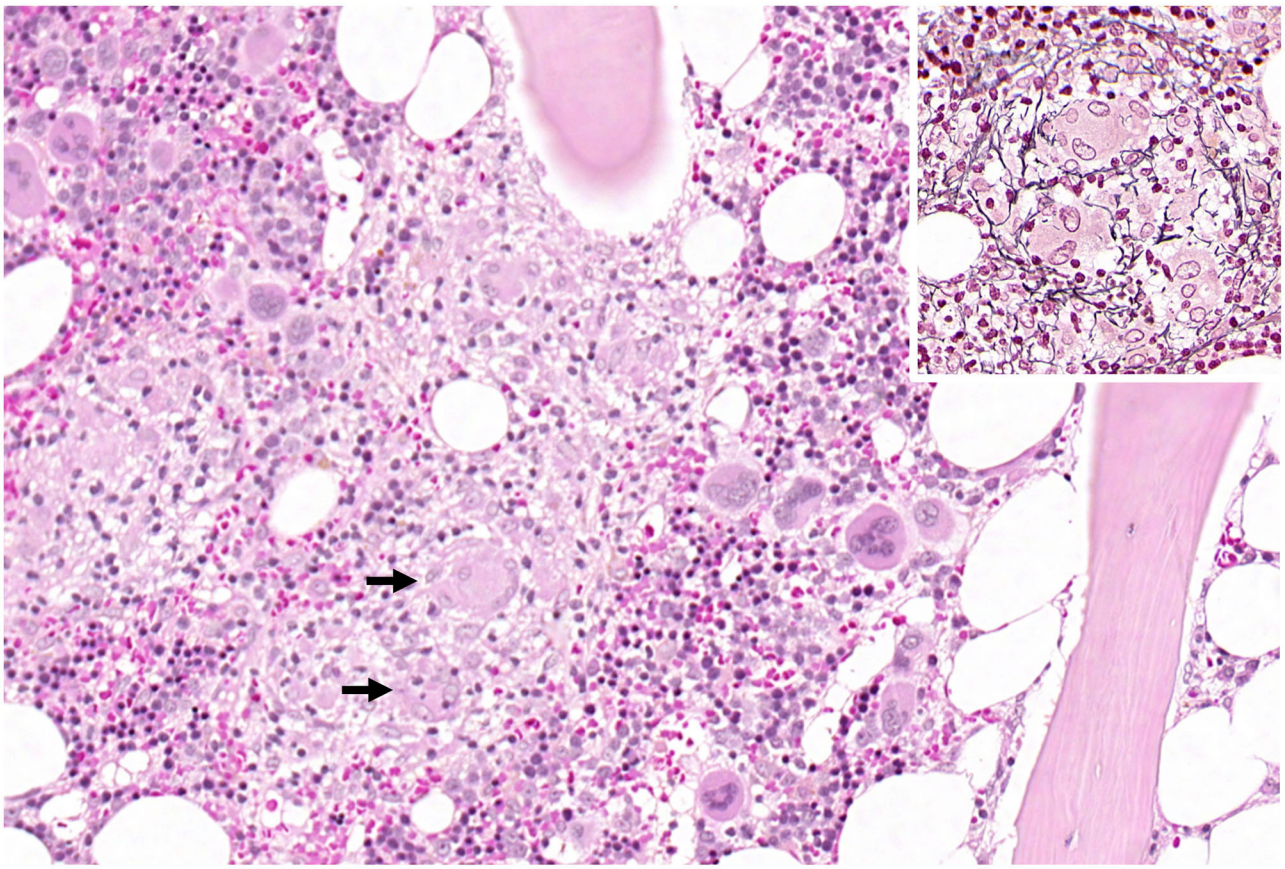

FIGURE 2 | Overview of haematopoietic bone marrow with a central granuloma. The arrows mark multinucleated giant cells. The inset shows a granuloma with the typical radially arranged fibres in the reticulin fibre stain.

bilateral hilar adenopathy of the lung, that usually resolves without sequelae (11). In chronic sarcoidosis, the lungs can be affected, but extrapulmonary manifestations can mimic various diseases. It can affect the eyes, skin, lymph nodes (most common), heart, joints and bones, liver, spleen, and kidneys (10). If the sarcoidosis manifests in the nervous system (neurosarcoidosis), patients suffer from cranial nerve dysfunction, aseptic meningitis, headaches, focal symptoms if the brain tissue is affected, and in the case of granuloma obstructing the flow of CSF, raised intracranial pressure. Myelopathy is rare in neurosarcoidosis (4). The gold-standard for diagnosis is histopathological evaluation of the affected organs (10). In isolated neurosarcoidosis, a meningeal or brain biopsy can lead to the diagnosis (citation).

Sarcoidosis of the bone marrow is very rare. The incidence of granulomas in bone marrow biopsies is low. In these cases, up to 21 percent are attributed to sarcoidosis (5). We were unable to identify other cases of myelopathy due to bone marrow sarcoidosis.

In our patient, the non-resolving leukopenia, that was attributed to toxic bone marrow damage, led to the bone marrow biopsy. Isolated leukopenia has been described as an initial presentation of sarcoidosis secondary to bone marrow infiltration (12).

Anaemia is the most common finding in a complete blood count in bone marrow sarcoidosis (13). In our patient, the lowest level of haemoglobin was 113 g/l, which was mild and would not have led to further diagnostic testing if the leukopenia had not been present. Without these findings, we probably would have missed the diagnosis.

Immunomodulatory therapy is usually initiated in sarcoidosis, and patients are usually started on a course of prednisolone. In addition, methotrexate, azathioprine, infliximab, or rituximab are used to reduce the need for prednisolone to circumvent side effects. In neurosarcoidosis, the treatment is more aggressive, as early immunosuppression is associated with better a prognosis (14).

It should be noted as a limitation, that we should have performed conventional angiography early after the patient presented to our hospital. Thereby, an arterial or venous thrombosis, venous fistula, or venous hypertension as a cause for myelopathy might have been overlooked (9).

CONCLUSION

In patients presenting with neurological deficits of unknown causes, neurosarcoidosis is a potential explanation. If it manifests primarily in the bone marrow, the diagnosis can be easily overlooked. Abnormalities in a full blood count should make the treating physician consider this diagnosis, and a bone marrow biopsy should be performed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the corresponding author.

AUTHOR CONTRIBUTIONS

TB, ES, MV, OA, MY, and MJ treated the patient. TS was responsible for the acquisition and interpretation of neuroradiologic imaging. SG was responsible for histological examinations and analyses. TB and MJ wrote the manuscript. All authors were involved in the analysis and interpretation of findings, they proved the manuscript, contributed for important intellectual content, and contributed to writing and approved the final manuscript.

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CASE REPORT
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Case Report: Longitudinal Extensive Transverse Myelitis With Novel Autoantibodies Following Two Rounds of Pembrolizumab

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A 63-year-old male with metastatic non-small cell lung cancer developed longitudinal extensive transverse myelitis (LETM) following two cycles of Pembrolizumab, an immune checkpoint inhibitor (ICI) targeting the programmed cell death receptor 1 (PD-1). Magnetic resonance imaging (MRI) showed centromedullary contrast enhancement at several levels, cerebrospinal fluid (CSF) cytology showed lymphocytic pleocytosis, and indirect immunofluorescence assay (IFA) on the primate cerebellum, pancreas, and intestine revealed strong binding of neuronal autoantibodies to unknown antigens. CSF C–X–C motif ligand 13 (CXCL13) was elevated. The patient was treated with plasma exchange (PEX) and intravenous (i.v.) methylprednisolone (MP) 1 g/day for 5 days followed by oral (p.o.) MP 100 mg/day for 10 days with clinical and radiological response. However, after discontinuation of MP, LETM relapsed and the patient developed paralytic ileus presumably due to autoimmune enteropathy and suffered a fatal gastrointestinal sepsis. Findings of novel neuronal autoantibodies and highly elevated CXCL13 in CSF suggest that the severe neurological immune-related adverse event (nirAE) was B-cell mediated contrary to the commonly assumed ICI-induced T-cell toxicity. An individual evaluation of the underlying pathophysiology behind rare nirAEs is essential for choosing treatment regimens and securing optimal outcome.

Keywords: immune checkpoint inhibitors, transverse myelitis, immune related adverse events, pembrolizumab, case report (source: MeSH NLM), neurological immune-related adverse effects, PD-1 monoclonal antibody, longitudinal extensive transverse myelitis

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have changed the way we approach cancer treatment. Instead of attacking the tumor tissue itself, ICIs enhance the endogenous antitumor response by blocking inhibitory antigens CTLA-4 (cytotoxic T-lymphocyte-associated protein) or PD-1 (programmed cell death protein 1) expressed on host immune cells or programmed cell death protein ligand (PD-L1) on some tumor cells. Pembrolizumab is an anti PD-1 antibody that has shown remarkable results in the treatment of many solid cancers including malignant melanoma and non-small cell lung cancer (NSCLC), improving the overall survival (OS) and progression-free survival (PFS) compared to conventional therapies (1, 2).

While treatment effects can be significant, ICIs can induce immune-related toxicity in almost all tissues, most commonly in the gastrointestinal tract, skin, liver, endocrine, and pulmonary organs (3). The neurological immune-related adverse events (nirAEs) are less common with an overall incidence between 3.8 and 12% from randomized trials—highest with combination therapy (4). Serious nirAEs defined as Common Terminology Criteria for Adverse Events (CTCAE) grades 3–5 are below 1%, and to our knowledge, only two case reports have been published with ICI-induced transverse myelitis (5, 6). However, many cases of myelitis are reported as encephalitis or encephalomyelitis in clinical trials, which makes accurate incidence difficult to estimate (7). A recent review of data from World Health Organization's (WHO's) pharmacovigilance database, VigiBase, found 24 cases reported as ICI-related myelitis including four cases with encephalomyelitis (8). To our knowledge, this is the third case report describing transverse myelitis following monotherapy with ICIs and the second case with evidence of autoreactive antibodies targeting unknown neural antigens.

CASE DESCRIPTION

A 63-year-old male was diagnosed with metastatic pulmonary squamous cell carcinoma, T4N3M1c, PD-L1 expression >50%. He suffered from chronic obstructive pulmonary disorder (COPD), was a former smoker with 33 pack years, and had performance status 1. Comorbidities were hypertension and hypercholesterolemia, but he had no known underlying autoimmune diseases or family history of such. Earlier the same year, he had undergone surgical excision of a malignant melanoma (T1aN0M0) with no adjuvant treatment. His pulmonary cancer was treated with two cycles of first-line treatment with Pembrolizumab (a PD-1 inhibitor) 2 mg/kg with a 3-week interval.

One day after his second treatment with Pembrolizumab, he presented with fever (38.9°C), chills, intermittent headache, and pain located to joints and lower back. During the following week, he developed constipation and urinary retention to which he was catheterized several times in the ER. After 2 weeks of urinary retention and obstipation, the patient was admitted due to progressively painful dysphagia with hoarseness and burping tendency. A gastroscopy showed no signs of pathology, symptoms relieved with fluconazole treatment, and he was discharged.

Five days later, the patient was readmitted due to lumbar fatigue, reduced muscle strength in the lower extremities, and difficulties walking. A neurological examination showed a flaccid tetraparesis with greater affection of the lower extremities, most prominently bilaterally in the hip and ankle joints. Deep tendon reflexes were normal, and sensibility was not affected. An MRI without contrast showed suspicion of LETM, and p.o. Prednisone 50 mg/day was initiated. Also, a CT scan of the lungs showed significant regression in the pulmonary cancer compared to baseline PET-CT. A few days after, the patient could not walk and was immobilized to a wheelchair or bed rest. While an MRI of the cerebrum showed no signs of pathology, a repeat MRI of the spinal column with contrast confirmed LETM (**Figure 1A**). Subsequently, treatment with bolus i.v. MP 80 mg followed by i.v. MP 1 g/day for 5 days and PEX every second day for 2 weeks was initiated.

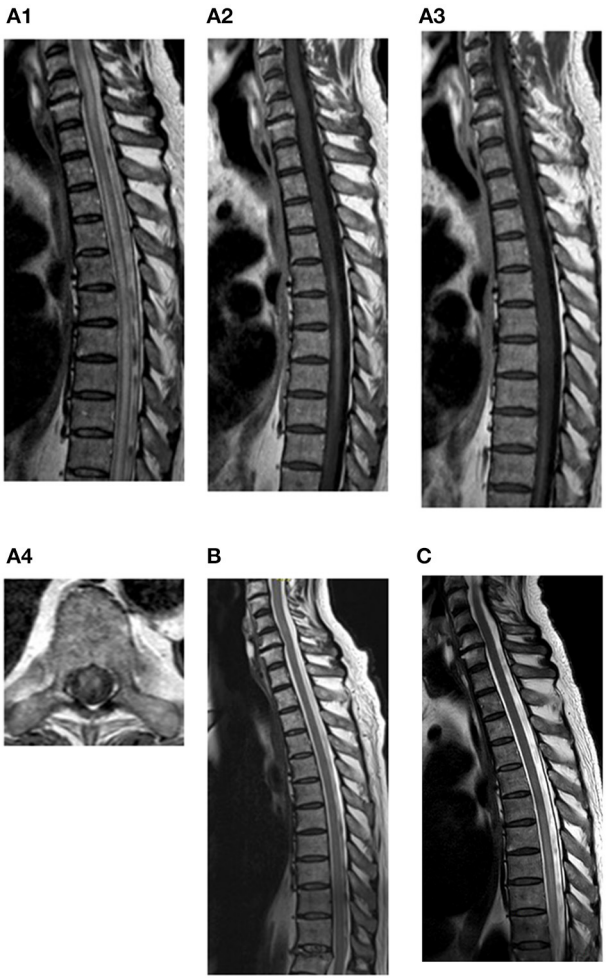

FIGURE 1 | MRI progression: at time of diagnosis **(A1–4)**, 3 days after last dose of p.o. MP **(B)** and 11 days after last dose of p.o. MP **(C)**. **(A1)** Sagittal T2-weighted MRI of columna totalis showing extensive LETM at cervical and thoracic levels. **(A2)** Sagittal T1-weighted MRI of columna totalis with contrast showing contrast enhancement at levels Th5–Th9. **(A3)** Sagittal T1-weighted MRI with contrast showing enhancement from C4-Th1. **(A4)** Axial T1-weighted MRI with contrast showing anterolateral multifocal contrast enhancement at level Th9. **(B)** Sagittal T2-weighted MRI of columna totalis showing almost complete regression of LETM. No contrast enhancement on T1 (not shown). **(C)** Sagittal T2-weighted MRI of columna totalis with relapsing LETM on levels Th5–Th11. Contrast enhancement on T1 weighted MRI (not shown).

On the second day of the initiated treatment (after two doses of i.v. MP 1 g and 12 h after first PEX), blood and CSF were drawn for analysis. Blood was tested for autoantibodies related to LETM, but both anti-aquaporin-4 (AQP4) and anti-myelin oligodendrocyte (MOG) antibodies were negative. CSF revealed that lymphocytic pleocytosis (63 cells with 50 lymphocytes) significantly elevated IgG, IgG index, and elevated CXCL13

TABLE 1 | CSF and serum findings after two doses of 1 g i.v. MP and one treatment with PEX.

CSF	Result	(Reference value)	Serum	Result	(Reference value)
Albumin	420 mg/L	(100–370)	AQP-4-Ab	Neg	(<1:10)
Glucose	5.0 mmol/L	(2.2–3.9)	MOG-Ab	Neg	(<1:10)
Protein	0.80 g/L	(0.15–0.50)	NACHRA3-Ab (IgG)	Neg	(<0.05 nmol/L)
IgG	248 mg/L	(14–52)	Calcium channel P/Q-type	Neg	(<40 pmol/L)
Cells	63 e6/L	(<5)	DPPX	Neg	(Neg)
– Lymphocytes	50 e6/L	(<5)			
– Macrophages	3 e6/L	None	*Paraneoplastic panel*		
– Neutrophils	<1 e6/L	(<1)	IFA on primate cerebellum	Pos, 1:100	(<1:10)
CXCL13	119 ng/L	(<20)	IFA on primate intestine	Pos, 1:100	(<1:10)
Oligoclonal bands	Neg	(Neg)	IFA on primate pancreas	Pos, 1:100	(<1:10)
DPPX	Neg	(Neg)	EUROLINE PNS 12 Ag® LIA	Neg	(Neg)
			GAD65 Ab	Neg	(<1:10)
Paraneoplastic panel					
IFA on primate cerebellum	Pos	(Neg)			
IFA on primate intestine	Pos	(Neg)			
IFA on primate pancreas	Pos	(Neg)			
EUROLINE PNS 12 Ag® LIA	Neg	(Neg)			
GAD65 Ab	Neg	(Neg)			
IgG index	1.64	(0.38–0.67)			

IgG, immunoglobulin G; CXCL-13, C–X–C motif chemokine ligand 13; AQP-4-IgG, Aquaporine 4 IgG; MOG-Ab, myelin oligodendrocyte glycoprotein antibodies; NACHRA3-AG, neuronal acetylcholine receptor subunit alpha-3-antibody; Anti-GFAP, anti-glial fibrillary acidic protein antibody; IFA, immunofluorescence assay; PNS 12 Ag® LIA, paraneoplastic Neurological Antigens 12 Profile line immunoassay (testing for amphiphysin, CV2, Ma/Ta, Ri, Yo, Hu, recoverin, Sox1, titin, Zic4, GAD and Tr antibodies); GAD65 Ab, glutamic acid decarboxylase-65 antibody.

in CSF (**Table 1**). CSF cultures and polymerase chain reaction (PCR) showed no signs of bacterial or fungal growth or viral activity. CSF flow cytometry showed an overall normal distribution of T- and B-cells; however, there was a population of $CD38^+$ cells, presumably plasma cells.

Indirect immunofluorescence assay (IFA) on primate cerebellar sections (Euroimmun AG, Luebeck, Germany) showed cytoplasmic and dendritic fluorescence of Purkinje cells and a granular fluorescence of the molecular and granular cerebellar layers in both serum and CSF. Euroline Paraneoplastic Neurological Antigens 12 Profile line immunoassay (LIA) (Euroimmun AG, Luebeck, Germany) was negative (testing for amphiphysin, CV2, Ma/Ta, Ri, Yo, Hu, recoverin, Sox1, titin, Zic4, GAD, and Tr antibodies). There was no indication of anti-glial fibrillary acidic protein (GFAP) antibodies on the tissue-based assay. Samples were sent to a reference laboratory for second opinion. An anti-neuronal reaction was confirmed; however, target antigen and hence clinical relevance could not be determined. Furthermore, there was a strong fluorescence of pancreatic islet cells and the cytoplasm of neurons in the intestinal plexus myentericus. Again, target antigens could not be identified, especially anti-GAD65 by enzyme-linked immunosorbent assay (ELISA) (Euroimmun AG, Luebeck, Germany) which was negative.

After 5 days of i.v. MP 1 g/day, PEX was discontinued (after two series) due to markedly improved motor function and ability to walk again with a high walking frame. Corticosteroids were changed to p.o. MP 100 mg/day for 10 days without a taper. LETM remitted during treatment and MRI confirmed LETM regression (**Figure 2B**). The patient was subsequently discharged. However, at discharge the patient still suffered from constipation and urinary retention.

A few days later, the patient was readmitted with severe constipation. CT showed signs of paralytic ileus and an MRI showed relapsing LETM (**Figure 2C**). Treatment with i.v. MP 1 g/day was reinitiated. Four days later, the patient became septic with respiratory insufficiency, hypotension, tachycardia, kidney failure, and blood cultures showing growth of Bacteroides fragilis. Broad-spectrum antibiotics was initiated, and PEX was attempted on an empiric basis. The following day, the patient died of respiratory insufficiency due to sepsis following paralytic ileus. Due to his severe paralytic ileus, a post-mortem supplementary search for autoimmune autonomic/enteric neuropathy was done, but serum neuronal acetylcholine receptor subunit alpha-3-antibody (NACHRA3-Ab) was negative. Also, dipeptidyl-peptidase-like protein 6 (DPPX) antibodies were negative. An overview of the timeline is illustrated in **Figure 3**.

DISCUSSION

Treatment with ICIs is rapidly emerging within the oncological field. Being fairly novel, not all uncommon and severe adverse events are known or thoroughly described. LETM is a very rare nirAE that can easily be overlooked in the initial phase.

There are several lines of notice that endorse that both LETM and paralytic ileus were induced by Pembrolizumab; it

evolved in close proximity to ICI treatment, and the patient did not receive any other new medications or therapies. No infectious cause was found, and known markers of LETM, i.e., anti-MOG, anti-AQP4, and anti-GFAP (the last only tested by indirect immunofluorescence in a tissue-based assay, not cell-based assay), were negative (**Table 1**). There was evidence of an antibody-mediated anti-neuronal reaction by IFA on the primate cerebellum and intestine, significant intrathecal IgG synthesis (IgG index of 1.64), and significantly elevated CXCL13, altogether suggesting B-cell/antibody-mediated disease.

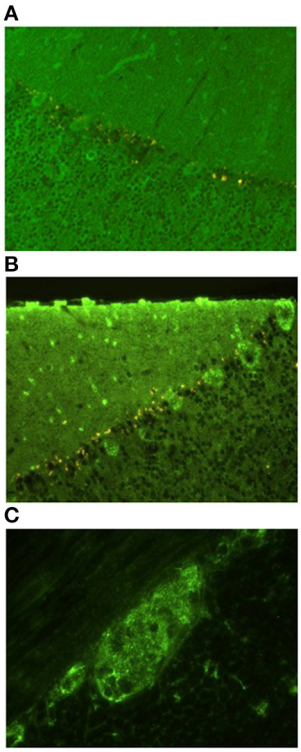

FIGURE 2 | Indirect immunofluorescence assay on primate cerebellar and intestinal sections. **(A,B)** Granular cytoplasmic and dendritic fluorescence of Purkinje cells and a granular fluorescence of the molecular and granular cerebellar layers. **(A)** Sera in dilution 1:100, **(B)** undiluted CSF. **(C)** Granular cytoplasmic fluorescens of neurons in the intestinal plexus myentericus. Undiluted CSF.

This case shares some key features with prior similar cases; Wilson et al. equally presented the finding of novel neural autoantibodies in a case of Pembrolizumab-induced LETM, which had a 4-week lag from treatment to symptom onset and responded to MP and PEX (6). A case of Pembrolizumab-induced neuromyelitis optica spectrum disorder (NMOSD) also remitted with MP and PEX (9), and a case of steroid-refractory Nivolumab-induced NMOSD improved on PEX as monotherapy (10). While a case of Ipilimumab-induced meningoencephalomyelitis did not attempt PEX treatment, they achieved remission with Infliximab and long-term Prednisone following non-response to IVIG and MP combination therapy (11).

In our case, circulating antibodies are thought to be accountable for the nirAE on two levels: the ICIs themselves (IgG antibodies) and their induction of an antibody-mediated toxicity. Therefore, depletion of antibodies by PEX should theoretically be the first-line treatment in similar cases of severe ICI-induced LETM. Our case supports this thesis, as the patient partially regained motor function after two treatments with PEX, although i.v. MP probably also contributed. While no randomized trials have confirmed the efficacy, it is increasingly apparent from other neurological antibody-mediated autoimmune diseases, e.g., NMOSD, that early PEX is an important factor in achieving a good outcome (9, 10).

Taking the American Society of Clinical Oncology's (ASCO's) guidelines for grade 3–4 irAEs into consideration, the right treatment was initiated upon diagnosis. However, it is recommended to taper corticosteroids over at least 4–6 weeks (12). Along with early discontinuation of PEX, this might explain why the LETM relapsed. ICIs are IgG antibodies with

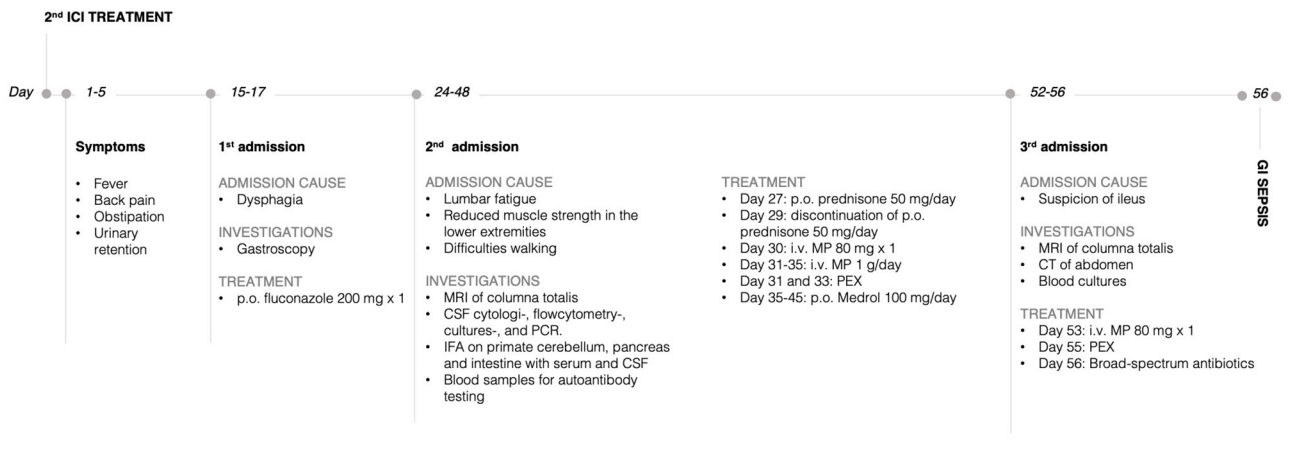

FIGURE 3 | Timeline with selected events and data. p.o., oral; i.v., intravenous; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; IFA, indirect immunofluorescence assay; MP, methylprednisolone; PEX, plasmapheresis; CT, computer tomography; GI, gastrointestinal.

long half-lives, why tapering of corticosteroids and a complete PEX series are essential to avoid a delayed inflammatory flare. This underlines that high-grade nirAEs (grades 3–4) should not be regarded and treated as their more common idiopathic autoimmune or post-infectious disease counterparts.

This case had a fatal outcome despite the initiated combination treatment. After partial remission of LETM, the patient developed paralytic ileus, presumably due to enteric neuropathy as an additional nirAE to Pembrolizumab. No specific anti-enteric neuronal antibodies could be detected; however, IFA on the primate intestine showed granular cytoplasmic fluorescence of cells in the myenteric plexus (**Figure 1**). Although the target antigen and hence the clinical relevance of this finding is unknown, it seems unlikely that this finding is merely coincidental.

ICIs are known to enhance T-cell responses; thus, irAEs are expected to be T-cell mediated. However, this case along with prior cases (6, 9, 10) suggests an ICI-induced activation of antibody-mediated toxicity. While we and Wilson et al. described a 4-week lag from treatment initiation to symptom onset, a review from 2019 described a mean lag of 94.8 days in all central nervous system nirAE case reports (13). This discrepancy suggests that the underlying mechanisms differ. A 4-week lag from ICI administration to symptom onset probably does not allow significant levels of novel neuronal IgG antibodies to be formed, suggesting that latent humoral autoimmunity was demasked by Pembrolizumab (6). Wilson et al. found anti-human-IgG antibodies bound to a specific T-regulatory cell subpopulation in peripheral blood, suggesting a potential adverse target for Pembrolizumab and a possible link between ICIs and B-cell activation. Also, a study investigating early B-cell changes in combination ICI therapy found that a B-cell subset with properties of rapid activation specifically increased and correlated with high-grade irAE, whereas changes in T-, NK-, and myeloid cells did not (14). This suggests that B-cells at least in some cases can be held accountable for autoimmunity following ICI therapy.

Therefore, we speculate that it could be feasible to use B-cell-depleting treatments, e.g., Rituximab under continuation of ICI to allow continuous T-cell-mediated antitumor activity. Indeed, an experimental study with melanoma cancer cells showed that B-cell depletion had no effect on tumor growth, response to PD-1 inhibition, or survival rates (15).

In conclusion, as ICI emerges within the field of cancer treatment,this case emphasizes the need of a dedicated and specialized team to handle the wide range of rare irAEs. Anti-neuronal antibodies with an unknown target antigen were seen, suggesting an unknown underlying pathophysiology behind this nirAE. Further studies should investigate the role of B-cells in nirAEs and confirm the optimal treatment taking the effector mechanism into consideration.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SC wrote the first draft and was the main editor of following revisions and revised all patient files and selected relevant events and data. Also, SC made **Figure 3**. CS discovered the case in clinics, made the diagnostics, and wrote the majority of sections with neurological content including **Figure 1**. AN performed the immunological testing and wrote the majority of sections with immunological content including **Figure 2**. LE-N was the primary oncologist in the terminal stage of the patient case and wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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frontiers in Neurology

CASE REPORT
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Eculizumab in the Treatment of Aquaporin-4 Seronegative Neuromyelitis Optica Spectrum Disorder: A Case Report

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Objective: To report the case of a 35-year-old woman with treatment-resistant aquaporin-4 (AQP-4) immunoglobulin G (IgG) seronegative neuromyelitis optica spectrum disorder (NMOSD) successfully treated with eculizumab (a terminal complement inhibitor).

Methods: The investigational procedures and treatment regimens the patient received were documented over 8 years [2012 (first presentation) to 2020].

Results: The patient presented with subacute onset of lower-limb weakness and numbness, gait imbalance, and urinary incontinence. Magnetic resonance imaging (MRI) showed abnormalities in the thoracic spine from T7 to T10, but brain and cervical spine scans, visual evoked potential latencies, and IgG index were normal; cerebrospinal fluid pleocytosis and oligoclonal bands were both present. After treatment with intravenous methylprednisolone 1 g/day for 5 days, the patient was discharged without medication to acute rehabilitation but experienced relapses from 2012 to 2014. She was treated with oral prednisone (initiated at 40 mg/day in 2014; the dose was halved in 2015 due to weight gain) and mycophenolate mofetil (MMF) 1 g twice daily (from June 2015), but between 2014 and 2019 experienced 4–5 relapses/year, requiring treatment with intravenous methylprednisolone, with added maintenance plasma exchange from 2018 onwards. Although the patient tested negative for antibodies to AQP-4 and myelin oligodendrocyte glycoprotein, she was diagnosed with NMOSD in February 2017, based on recurrent episodes of longitudinal extensive transverse myelitis, MRI changes, and area postrema syndrome. By 2018 the patient needed a cane to walk. Prednisone and MMF were discontinued mid-2018, and rituximab was prescribed from July 2018 (maintenance regimen two 1 g doses 2 weeks apart every 6 months) but discontinued in July 2019 owing to lack of significant improvement. From July 2019 eculizumab was prescribed for 6 months (900 mg weekly for the first four doses, then 1200 mg every 2 weeks). The patient had no relapses or adverse events during and after eculizumab treatment (as of August 2020) and was able to walk unaided; her Expanded Disability

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Status Scale score improved from 4–5 during 2015–2018 to 2 in 2020 following eculizumab treatment.

Conclusion: Eculizumab shows promise as a treatment for AQP-4 IgG-seronegative NMOSD and further studies are warranted.

Keywords: autoimmune disease, neuromyelitis optica spectrum disorder, seronegative, eculizumab, aquaporin-4, complement-inactivating agents, relapses

INTRODUCTION

Neuromyelitis optica (NMO)/NMO spectrum disorder (NMOSD) is a rare disease characterized by autoimmune demyelination and axonal damage predominantly affecting the spinal cord [longitudinal extensive transverse myelitis (LETM)] and optic nerve (optic neuritis) (1). It is preponderant in women, and the median age of onset is 39 years (2). For many years, NMOSD was considered to be a variant of multiple sclerosis, but in 2004 the identification of aquaporin-4 (AQP-4) immunoglobulin G (IgG) antibodies in a subset of patients led to the differentiation of NMOSD from multiple sclerosis (3, 4). The anti-AQP-4 antibody selectively binds the AQP-4 water-channel protein in astrocytes and is detected in up to 73% of patients with NMOSD (5). AQP-4 antibodies activate the complement cascade, leading to the breakdown of complement protein 5 (C5) to C5a and C5b, and generation of the membrane attack complex (MAC; C5b-9) (6). Of the remaining patients with NMOSD, 11% are positive for antibodies to myelin oligodendrocyte glycoprotein (MOG)—a component of myelin expressed on the surface of myelin sheaths in the central nervous system (CNS) (7)—and 16% have no detectable antibodies to either AQP-4 or MOG (4, 5).

NMOSD is characterized by unpredictable recurrent episodes of optic neuritis and myelitis. Partial recovery occurs between attacks, but neurologic disability accumulates, including blindness and paralysis (8). The conventional treatment of an acute episode of seronegative NMOSD is intravenous corticosteroids, with or without plasma exchange (PLEX). Various immunosuppressive therapeutic strategies, such as mycophenolate mofetil, azathioprine, and rituximab, are useful in the prevention of relapses.

Eculizumab is a recombinant humanized monoclonal antibody that binds to complement component C5 and prevents its conversion to C5a and C5b (9). The precise mechanism by which eculizumab exerts its therapeutic effect in NMOSD is unknown, but it is presumed to involve inhibition of AQP-4-antibody-induced MAC generation and associated astrocyte loss (9). It was approved in 2019 by the US Food and Drug Administration as the first drug for the treatment of patients with NMOSD who are anti-AQP-4 antibody positive (10). Here we report a case of a woman diagnosed with treatment-resistant AQP-4 IgG-seronegative NMOSD, who responded well to eculizumab without any adverse effects. To our knowledge, this is the first such case reported in the literature.

CASE REPORT

We describe the case of a 35-year-old white woman. She initially presented in July 2012 at the age of 27 years, when she was working as a nurse. She reported subacute onset of lower limb weakness (strength 3/5 on the Medical Research Council scale), lower limb numbness, gait imbalance, and urinary incontinence. Magnetic resonance imaging (MRI) of the thoracic spine, with and without contrast, demonstrated signal abnormality from T7 to T10 associated with post-contrast enhancement. MRI of the brain and cervical spine, with and without contrast, was normal. Visual evoked potential (pattern VEP) showed normal P100 latencies. A lumbar puncture showed cerebrospinal fluid pleocytosis (white blood cells: 20 cells/dL, with predominant lymphocytes), normal IgG index, and oligoclonal bands.

A summary of treatment regimens and timelines is shown in **Figure 1** and the clinical course is described in **Figure 2**. Following her initial presentation the patient was admitted to hospital and treated with intravenous methylprednisolone at a dose of 1 g/day for 5 days, after which she was discharged without medication to acute rehabilitation. She had a relapse in October 2012 and underwent PLEX every other day for a total of five exchanges which resolved the episode; a relapse was defined as patient-reported symptoms or any new signs consistent with CNS lesions and attributable objective changes in MRI or visual evoked potential. The patient was treated with intravenous methylprednisolone for relapses between 2012 and 2014, during which she experienced multiple episodes of lower limb weakness, urinary incontinence, and falls. During these relapses, MRI of the thoracic spine showed contrast enhancement from T6 to T10. In 2014, the patient tested negative for AQP-4 IgG and in February she was initiated on oral prednisone 40 mg/day. Her Expanded Disability Status Scale (EDSS) score was 4 at that time.

In 2015, testing for anti-AQP-4 antibodies by fluorescence-activated cell sorting (FACS) proved negative. In March of that year, the patient's oral prednisone dose was reduced to 20 mg/day because of weight gain. In June 2015, the patient was initiated on mycophenolate mofetil 1 g twice daily.

In 2016 and 2017, testing for MOG IgG (FACS assay) was negative; tests for antinuclear antibody panel, urine heavy metal screen, and paraneoplastic panel were also negative. In February 2017, following episodes of intractable nausea and vomiting with associated area postrema changes on MRI, the patient received a diagnosis of seronegative NMOSD from a National Multiple Sclerosis Society Center of Excellence, based on recurrent episodes of LETM, MRI changes, area postrema syndrome, and lack of anti-AQP-4 antibodies. The patient continued to

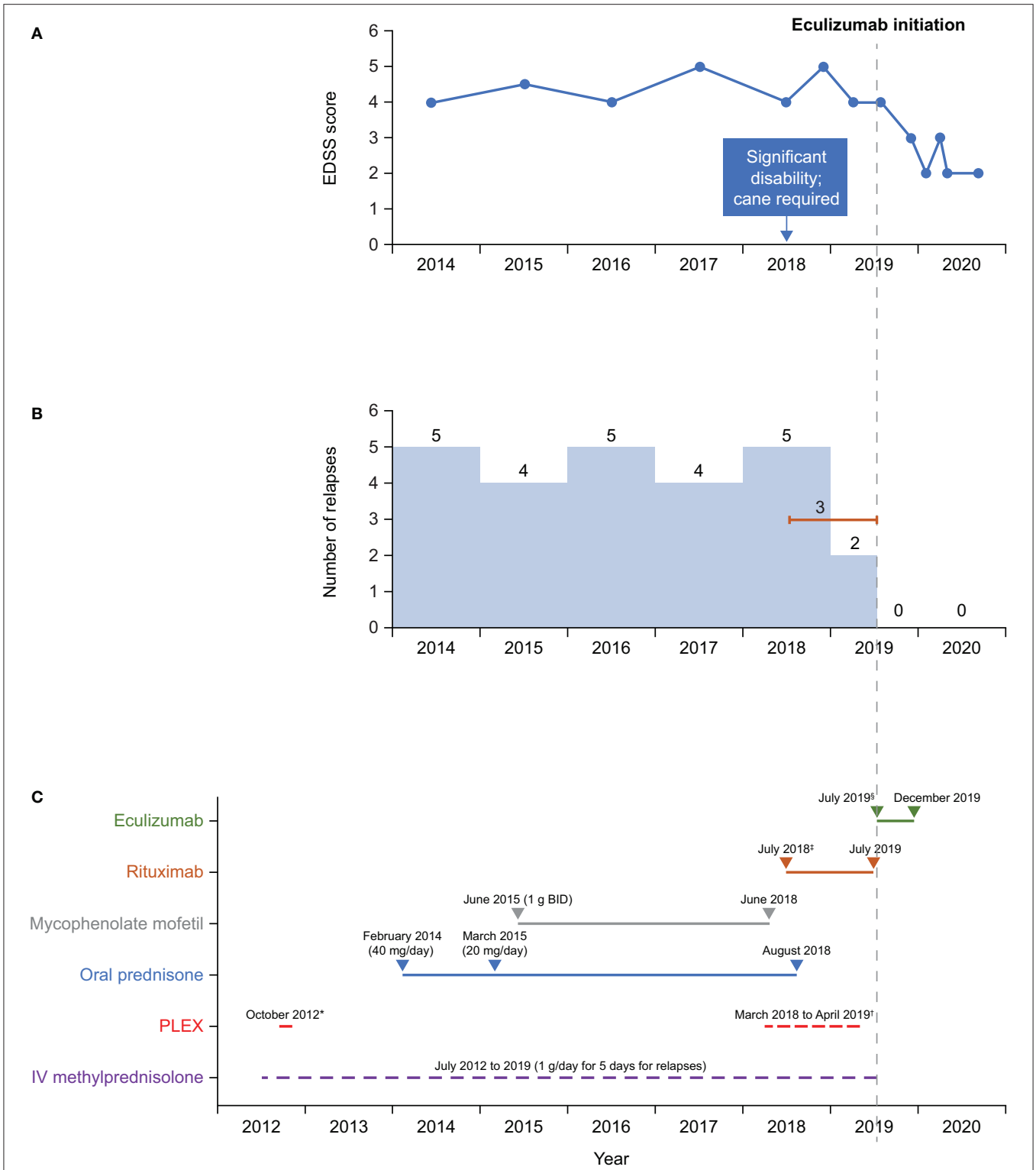

FIGURE 1 | Timeline of **(A)** EDSS scores, **(B)** relapses, and **(C)** treatment. *Rituximab dose: 2 × 1 g, 2 weeks apart, then every 6 months. †Eculizumab dose: 900 mg weekly (first four doses) then 1,200 mg every 2 weeks. ‡5 exchanges on alternate days. §3–5 exchanges on alternate days every 4 weeks. BID, twice daily; EDSS, Expanded Disability Status Scale; IV, intravenous; PLEX, plasma exchange.

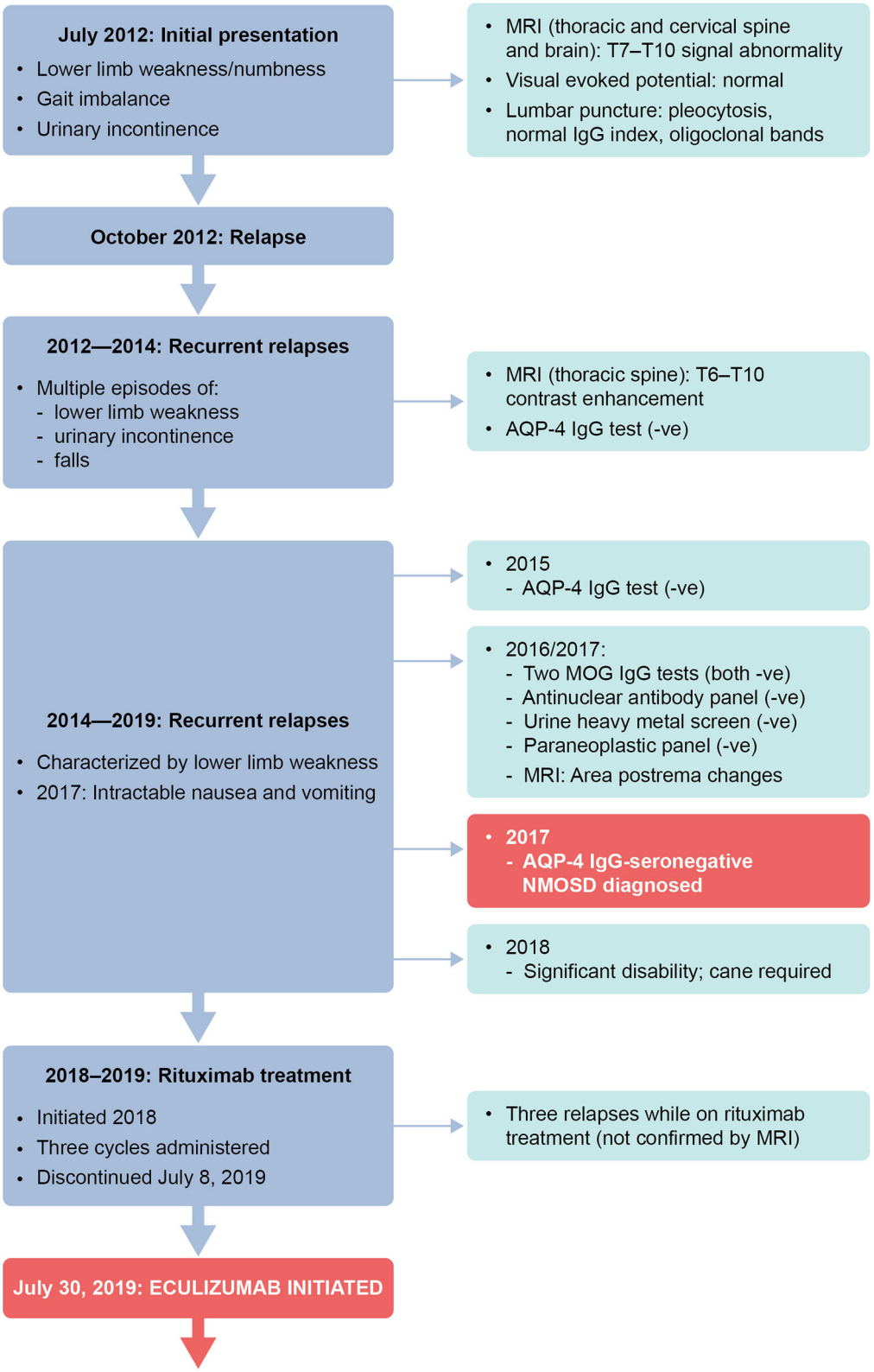

FIGURE 2 | Timeline of clinical presentation and investigations. –ve, negative; AQP-4, aquaporin-4; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging.

experience relapses between 2014 and 2019, with 4–5 relapses per year (**Figure 1**), characterized by lower limb weakness. On average, the patient was hospitalized three times a year for treatment of relapses with intravenous methylprednisolone 1 g/day for 5 days, with maintenance PLEX applied every 4 weeks from March 2018 to April 2019 as a total of 3–5 exchanges on alternate days. In June 2018, the patient stopped mycophenolate mofetil treatment as she felt it was not effective. Between 2014 and 2018, the patient's EDSS score was 4–5, and she eventually needed a cane to walk in 2018.

Starting in July 2018, rituximab 375 mg/m^2 was administered intravenously every week for 4 weeks, then as two 1 g doses, 2 weeks apart every 6 months. Rituximab has not been approved for treatment of NMOSD; this regimen is the same as that used in a Phase 3 trial in patients with NMOSD (11). In August 2018, the patient stopped oral prednisone treatment [due to weight gain of 20 lb (∼9 kg) in 2 months, acne, and mood issues]. Rituximab treatment was stopped after the second maintenance cycle was completed on July 8, 2019, as no significant improvement in relapses occurred—the patient experienced three relapses while receiving rituximab (not confirmed by MRI). CD19$^+$ B cells were depleted during rituximab therapy, with the median cell count for the last 6 months of treatment being 0.001×10^9cells/L (range 0–0.0159×10^9 cells/L). Eculizumab infusion was initiated on July 30, 2019, with the approval of the patient's insurance provider following a peer-to-peer review by one of her physicians (RG) and the provider. Two weeks before eculizumab initiation, the patient was vaccinated against *Neisseria meningitidis* with meningitis ACWY and B vaccines, according to the recommendations of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (12). She then received the recommended dose of eculizumab 900 mg weekly for the first four doses, followed by 1,200 mg every 2 weeks starting 4 weeks after initiation. While treated with eculizumab, the patient showed improvements on the EDSS (score of 2–3; lower scores indicate less disability) (**Figure 1**) and she experienced no relapses or adverse events. Eculizumab was discontinued in December 2019 when the patient's insurance provider denied continued coverage despite peer-to-peer review. At subsequent follow-up visits after eculizumab discontinuation and as of August 2020 she has remained relapse-free and symptom-free and is not taking any medication for NMOSD. The patient can walk without any aids, has an EDSS score of 2, and works full time as a physician's assistant.

DISCUSSION

The underlying cause of NMOSD is primarily humoral-mediated autoimmunity, resulting in florid demyelination and inflammation (8). Although detection of anti-AQP-4 antibodies is a critical diagnostic step in diagnosing NMOSD, a more challenging testing sequence is necessary for diagnosing NMOSD in seronegative patients in order to exclude a variety of diseases mimicking NMOSD (13).

The core clinical characteristics of NMOSD constitute acute myelitis, optic neuritis, area postrema syndrome, acute brainstem syndrome, symptomatic cerebral syndrome with NMOSD-typical brain lesions, and symptomatic narcolepsy or acute diencephalic clinical syndrome with typical NMOSD-diencephalic MRI lesions (2). To meet the criteria for the diagnosis of seronegative NMOSD, patients must have experienced at least two core characteristics and at least one of the three most common characteristics (optic neuritis, acute myelitis with LETM, or area postrema syndrome with associated MRI lesions). This patient's core clinical characteristics were recurrent LETM, area postrema syndrome, and absence of AQP-4 antibody.

There are interesting differences between patients who are seropositive and seronegative for AQP-4 antibodies: the seronegative disease population does not show the female predominance of the seropositive patients, comprises a higher proportion of white people, and is associated with a younger mean age at onset (1, 13, 14). There are also differences in disease characteristics between the two groups. Although there are few differences in the time to relapse, annualized relapse rate, recovery from relapse, annualized EDSS increase, and mortality rate, seronegative patients are more likely to present with both optic neuritis and LETM than seropositive patients (14, 15).

The crucial role of the complement cascade in NMO pathogenesis is supported by the fact that NMO-like lesions were only reproducible in an animal model when human complement was co-administered (16). The pathophysiology associated with anti-MOG antibodies is less well-characterized, but they have also been shown to activate the complement cascade (15, 17). Similar to the patient described in this report, a small proportion of patients with NMOSD are seronegative for both antibodies, with no detectable AQP-4 IgG or MOG IgG. The pathophysiology in this patient population is poorly understood (18), although complement-mediated damage can be seen in both seropositive and seronegative cases (6, 19). Although our patient might be described as being "double seronegative"—as patients who are seronegative for both AQP-4 IgG and MOG IgG are sometimes referred to in the literature—there is ongoing debate about how this subgroup should be classified and further research is required (18).

In such patients, the presence of low antibody titers or autoantibodies against aquaporin-1 (AQP-1), another water channel in CNS astrocytes, has been suggested to be associated with the development of NMOSD (20, 21). Other data suggest that seroconversion to negative status may occur with immunotherapy and that patients should be retested for AQP-4 IgG during relapses and before immunotherapy (8). There is also the possibility that there is an as yet unidentified target for complement activation (6, 19).

It follows that inhibition of complement activation should reduce damage to astrocytes in patients with AQP-4-IgG-positive NMOSD. Eculizumab prevents the cleavage of C5 to C5a and C5b, and significantly reduced the relapse risk in patients with AQP-4-IgG-positive NMOSD compared with placebo in a large Phase 3 trial, leading to its approval for this condition (22).

Eculizumab is not approved for seronegative NMOSD. Given the pathological similarities between seropositive and seronegative NMOSD, we decided to try eculizumab in our patient. A distinct improvement was seen during the 6 months of eculizumab treatment. The last dose of rituximab was given 22 days before eculizumab initiation. Although there may have been some overlap in activity between the two drugs, we believe the subsequent improvement in the patient's condition to have been associated with eculizumab treatment, given that the patient experienced three relapses while receiving rituximab. Before eculizumab initiation, the patient's EDSS score was 4–5, but it reduced to 3 during eculizumab therapy, at which point the patient was also relapse-free (**Figure 1**). There is a common misconception that damage caused during NMOSD relapse is irreversible; however, the improvements in EDSS score seen in our patient are corroborated by the findings of several studies reporting reductions in EDSS scores in response to targeted treatment (23, 24). Our patient remained relapse-free during the 12 months after stopping eculizumab therapy, even though she received no other therapy.

Although the repeated testing suggests that this patient did not have anti-AQP-4 or anti-MOG antibodies, it is possible that she harbored a low titer that may have been detectable with a more sensitive assay. Alternatively, she might have complement-activating antibodies to AQP-1 or a currently unidentified target. Outside of the research setting it may be difficult to conclusively identify the pathology; however, our experience suggests that a trial of eculizumab may be warranted in patients with AQP-4 IgG-seronegative NMOSD.

CONCLUSION

Eculizumab shows promise as a treatment for AQP-4/MOG IgG-seronegative NMOSD, and further studies are warranted to explore the possibility of using this treatment in patients with treatment-resistant seronegative NMOSD. The mechanism of action of eculizumab in seronegative NMOSD remains to be elucidated.

SUMMARY

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease that affects the spinal cord and optic nerve, causing severe disability. Despite standard treatment, including off-label oral and intravenous corticosteroids and immunosuppressants, patients often continue to have recurrent attacks. Eculizumab has been approved for patients with NMOSD who have autoantibodies to the protein aquaporin-4 (AQP-4); eculizumab blocks the damage to nervous-system cells triggered by these antibodies. The patient described in this case report belongs to a minority of patients with NMOSD who are seronegative for anti-AQP-4 antibodies and for antibodies to another protein implicated in NMOSD—myelin oligodendrocyte glycoprotein (MOG). The woman presented in 2012 (then aged 27 years) and was diagnosed with AQP-4 IgG-seronegative NMOSD in 2017. She experienced frequent relapses between 2012 and 2019, despite receiving courses of standard treatment and rituximab, and eventually needed a cane to walk. After receiving eculizumab for 6 months in 2019, the patient experienced improvements in her level of disability and no longer experienced relapses. At follow-ups after treatment discontinuation, the patient continued to be relapse-free and could walk unaided. These findings suggest that eculizumab may be a useful addition to treatment options in the subgroup of patients with AQP-4-antibody seronegative NMOSD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patient provided her written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors: conception, organization, execution of the research described in the manuscript, review, and critique of the manuscript.

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Conflict of Interest: RG has served on advisory committees for Alexion Pharmaceuticals, argenx, and Catalyst Pharmaceuticals, and is a member of the speakers' bureaux for Alexion Pharmaceuticals and Catalyst Pharmaceuticals.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
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Bilateral Meningo-Cortical Involvement in Anti-myelin Oligodendrocyte Glycoprotein-IgG Associated Disorders: A Case Report

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Cortical T2-weighted fluid-attenuated inversion recovery (FLAIR)-hyperintense lesions in anti-myelin oligodendrocyte glycoprotein (MOG)-associated encephalitis with seizures (FLAMES) are mostly unilateral and rarely spread to the bilateral cortex and meninges. We describe a case of MOG-immunoglobulin G (IgG) associated disorder (MOGAD) in a 39-year-old male with bilateral meningo-cortical involvement. The patient was hospitalized for epilepsy, fever, and headache. The initial MRI revealed abnormalities in the sulci of the bilateral frontal, temporal, and parietal lobes. He was considered to have infectious encephalitis and given empiric antibiotic and antiviral therapy, which were ineffective. His condition rapidly improved after the patient was switched to high-dose immunoglobulin therapy. No tests supported the presence of central nervous system (CNS) infections or autoimmune encephalitis. The second and third MRI scans showed reduced but still clearly observable meningo-cortical lesions. The patient was discharged without a definite diagnosis, but reported severe left vision impairment 25 days later. A fourth MRI showed signs typical of demyelinating CNS disease in addition to the original meningo-cortical lesions. The patient's symptoms were initially relieved by low-dose corticosteroid therapy, but they eventually returned, and he was re-admitted. The original lesions were diminished on the fifth MRI scan, but new lesions had developed in the deep white matter. A positive cell-based assay for MOG-IgG in serum confirmed MOGAD. The patient received high-dose corticosteroid treatment followed by an oral methylprednisolone taper, and his visual acuity gradually improved. The sixth and final MRI showed substantial decreases in the original lesions without new lesion formation. This unique case presents the complete diagnosis and treatment process for MOGAD with bilateral meningo-cortical involvement and may provide a reference for prompt diagnosis.

Keywords: anti-myelin oligodendrocyte glycoprotein-IgG associated disorders, bilateral, meningo-cortical involvement, magnetic resonance imaging feature, case report

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INTRODUCTION

Myelin oligodendrocyte glycoprotein (MOG)-immunoglobulin G (IgG) associated disorder (MOGAD) magnetic resonance imaging (MRI) findings often involve the white matter, thalamus, pons, optic nerve, and spinal cord (1, 2). Notably, the phenotype of unilateral fluid-attenuated inversion recovery (FLAIR)-hyperintense lesions in anti-myelin oligodendrocyte glycoprotein (MOG)-associated encephalitis with seizures (FLAMES) has distinct radiographic manifestations (3) that are different from other common phenotypes. To date, only a few cases of FLAMES have been reported in the literature, and there are limited longitudinal MRI data regarding this entity. This case report covers the complete trajectory of MOGAD findings from initial meningo-cortical involvement to consequent MRI changes.

CASE PRESENTATION

On June 16, 2020, a 39-year-old male patient was admitted to our hospital following 2 days of seizures that were preceded by 15 days of fever and headache. The patient denied having any prior psychiatric or other diseases. His neck was slightly stiff, and there were suspiciously positive bilateral Kernig's signs. On day 2 of hospitalization, the initial MRI examination showed FLAIR hyperintensities in the cortex and meninges of the bilateral frontal, temporal, and parietal lobes; the abnormalities were also clearly visualized on T1-weighted post-gadolinium-enhanced images (**Figure 1**). The patient was considered to have developed a central nervous system (CNS) infection and was given empiric antibiotic and antiviral therapy, but his condition steadily worsened, suggesting that there may be other underlying etiologies (e.g., autoimmune encephalitis or tuberculous meningoencephalitis). After considering the pros and cons, we administered high-dose immunoglobulin treatment, and the patient's symptoms rapidly improved. The second MRI examination on day 8 demonstrated mildly regressed meningo-cortical lesions, but abnormalities were still observed (**Figure 1**). No other test results (listed in **Table 1**) supported the existence of autoimmune encephalitis or a CNS infection. We did not prescribe corticosteroid therapy due to concern about unknown infections. After further observation, the third MRI examination conducted on day 24 showed that the meningo-cortical lesions had decreased but were still clearly observable (**Figure 2**). At that time, the patient exhibited good recovery except for mild palpitations and insomnia, and he was discharged on day 30 of hospitalization without a definite diagnosis.

On August 9, 2020, he was followed-up at our outpatient clinic and reported that the vision in his left eye was severely impaired. This symptom first manifested ∼1 month earlier, but it was mild and he did not seek medical help. A fourth MRI examination was immediately conducted and showed that the meningo-cortical lesions were reduced compared, but new lesions were present in the right parietal lobe, right cerebellar dentate nucleus, and left optic nerve (**Figure 2**). At this point, we realized that a demyelinating CNS disease was responsible for the symptoms. The patient refused hospital re-admission, further examinations, or further high-dose immunoglobulin therapy due to economic reasons, so we prescribed low-dose corticosteroid therapy. The patient's visual acuity was considerably improved after treatment, which he decided to discontinue after ∼1 month. On December 19, 2020, the patient complained that his left visual acuity had again deteriorated, and he was re-admitted to the hospital. A fifth MRI examination showed that the original lesions were diminished, but new lesions had developed around the deep white matter (**Figure 3**). A cell-based assay for serum anti-MOG-IgG was positive, and the final diagnosis was MOGAD. The patient accepted high-dose corticosteroid treatment, and his

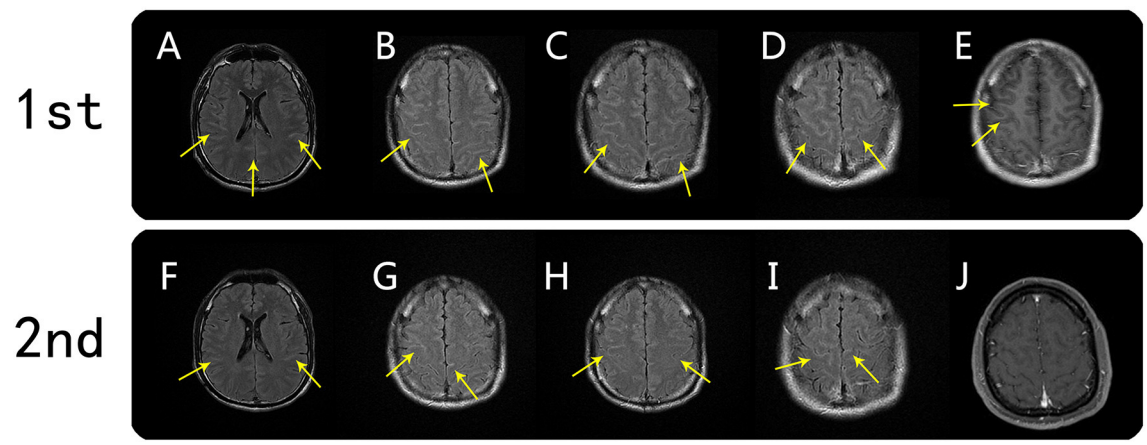
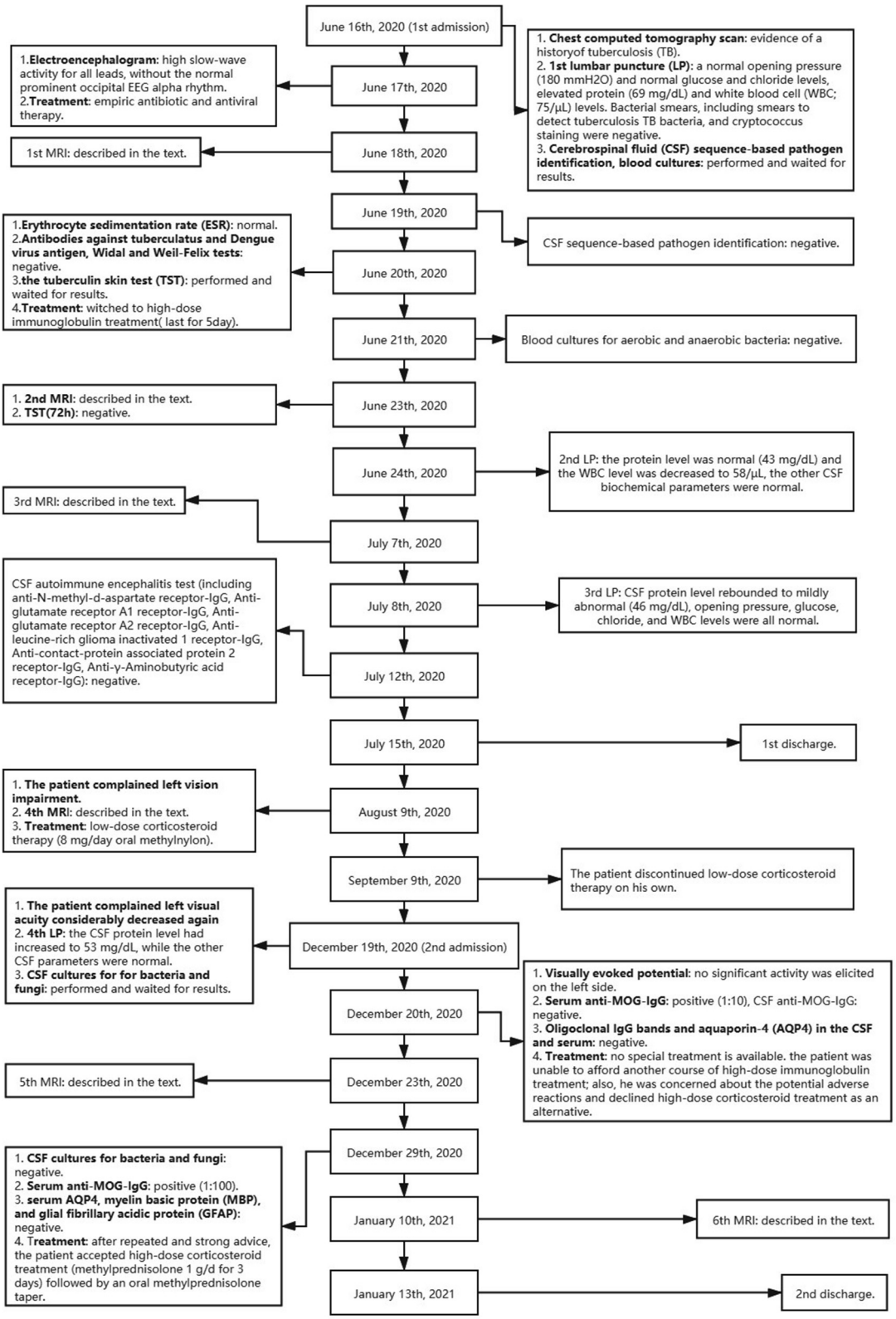


FIGURE 1 | Brain MRI findings from the first and second scans. First MRI scan (on day 2): axial FLAIR hyperintensity was seen in the sulci of the bilateral frontal, temporal, and parietal lobes (**A–D**, arrows). Corresponding meningo-cortical enhancement was also seen on axial T1-weighted postgadolinium-enhanced images (**E**, arrow). Second MRI scan (on day 7): meningo-cortical lesions on axial FLAIR were mildly regressed, but abnormalities were still observed (**F–I**, arrows). T1-weighted postgadolinium-enhanced image showed a corresponding meningo-cortical lesion with no enhancement **(J)**.

TABLE 1 | Timeline of the patient's lab data and cerebrospinal fluid results.



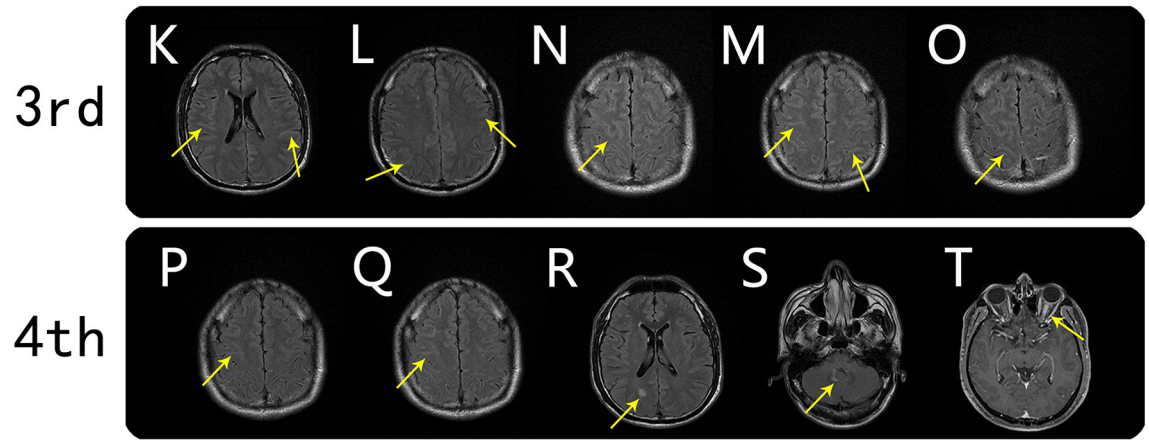


FIGURE 2 | Brain MRI findings from the third and fourth scans. Third MRI scan (on day 22): axial FLAIR showed reduced meningo-cortical lesions that were still clearly observable (**K–O**, arrows). Fourth MRI scan (on day 37): axial FLAIR showed that the meningo-cortical lesions were further resolved (**P** and **Q**, arrows), but new lesions were present in the right parietal cortex and right cerebellar dentate nucleus (**R** and **S**, arrows). T1-weighted postgadolinium-enhanced image showing left optic nerve thickening and obvious enhancement (**T**, arrow).

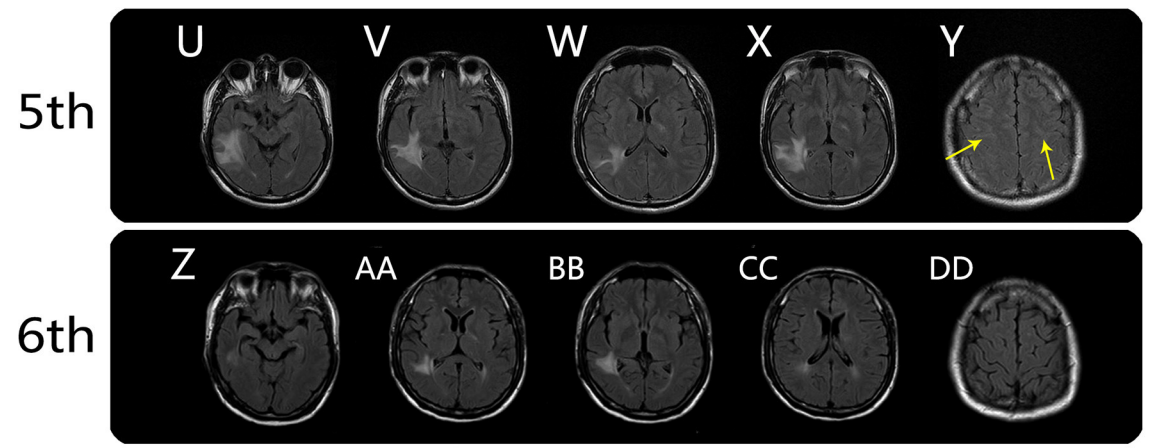


FIGURE 3 | Brain MRI findings from the fifth and sixth MRI scans. Fifth MRI scan (on day 132): axial FLAIR showed persistent meningo-cortical hyperintensity (**Y**, arrows) and new lesions around the temporal lobe, posterior limb of internal capsule (right), and left trigone of the lateral ventricle **(U–X)**. Sixth MRI scan (on day 148): axial FLAIR showed substantial reductions in the original lesions without new lesion formation (**Z**, **AA**, **BB**, and **CC**), and the meningo-cortical FLAIR hyperintensity disappeared **(DD)**.

left visual acuity gradually improved. The sixth and final MRI examination was conducted on January 8, 2021 and showed substantial reductions in the original lesions without new lesion formation (**Figure 3**). The patient was discharged on January 13, 2021. At the time of writing, he had remained in generally good condition.

In addition to the above MRI examinations, the patient also underwent a series of other tests at different time points that were crucial for diagnosis. The relevant details are listed in the timeline in **Table 1**.

DISCUSSION

In 2017, Ogawa et al. (4) first reported a rare MOGAD phenotype with unique unilateral cortical encephalitis properties. Budhram et al. (3) more thoroughly characterized these unique clinico-radiographic syndrome and referred to this entity as FLAMES. Although initially described as a unilateral cortical encephalitis, it can also manifest as bilateral cortical lesions with or without leptomeningeal involvement (3, 5) or even isolated unilateral leptomeningeal enhancement (3, 5). FLAMES is more likely to be misdiagnosed as other CNS diseases such as viral meningitis,

carcinomatous meningitis, or subarachnoid hemorrhage. In our case, the patient initially presented with fever, headache, and cerebrospinal fluid findings similar to those associated of viral meningitis. We were unaware of the possibility of bilateral meningo-cortical MOGAD manifestations, which delayed the diagnosis. Given that the FLAMES phenotype is highly steroid-responsive, increased knowledge and appreciation of these symptoms is critical to facilitate timely treatment.

Here we described a case of MOGAD presenting with the MRI feature of bilateral meningo-cortical involvement. The exact correlations between meningeal and cortical involvement are not fully clear, but there are two possible mechanisms. One suggests that primarily meningeal lesions spread to the cortex, while the other proposed that both meningeal and cortical lesions appear simultaneously (3, 8). Unlike the other common phenotype of MOGAD, cases involving cortical lesions do not exhibit distinct pathologic demyelination features and have only mild inflammatory changes (6, 7). One perspective is that MOGAD with cortical lesions should be considered as a new disease associated with anti-MOG antibodies (6). Other recent studies have indicated that anti-MOG antibodies may not be directly associated with the cortical lesion phenotype or may not even be involved in this phenotype (4, 6). Although no evidence of other auto-antibodies has been detected in FLAMES-related phenotypes so far, an unknown auto-antibody might be involved in disease pathogenesis (4, 8).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GM, YH, YX, and FC designed the diagnostic and treatment plans. GM, JH, and YL drafted the manuscript. GM and FC revised the manuscript draft. GM, JH, YH, and YX generated the figures. All authors approved the submitted version of the manuscript.

SUPPLEMENTARY MATERIAL

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CASE REPORT
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Post-COVID Opsoclonus Myoclonus Syndrome: A Case Report From Pakistan

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Background: Coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory distress syndrome–coronavirus-2 (SARS-CoV-2), is primarily a respiratory infection but has been recently associated with a variety of neurological symptoms. We present herewith a COVID-19 case manifesting as opsoclonus-myoclonus syndrome (OMS), a rare neurological disorder.

Case Presentation: A 63-year-old male diagnosed with COVID-19 infection developed behavioral changes, confusion, and insomnia followed by reduced mobility and abnormal eye movements within 48 h of recovery from respiratory symptoms associated with COVID-19. On examination, he had rapid, chaotic, involuntary saccadic, multidirectional eye movements (opsoclonus), and limb myoclonus together with truncal ataxia. CSF analysis, MRI of the brain, and screening for anti-neuronal and encephalitis related antibodies were negative. Extensive testing revealed no underlying malignancy. The patient was successfully treated with intravenous immunoglobulin (IVIG) with complete resolution of symptoms within 4 weeks of treatment.

Conclusion: COVID-19 infection can be associated with the manifestation of opsoclonus myoclonus syndrome, a rare neurological disorder that can be treated with IVIG if not responsive to corticosteroids.

Keywords: ataxia, COVID-19, movement disorder, neurological disorder, opsoclonus myoclonus syndrome, autoimmue disease

PRACTICAL IMPLICATIONS

- Following the recovery of respiratory symptoms, SARS-CoV-2 can manifest OMS, a rare neurological disorder.
- OMS manifested by SARS-CoV-2 can have a good response to IVIG in steroid-resistant cases.

INTRODUCTION

Coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory distress syndrome–coronavirus-2 (SARS-CoV-2), is primarily a respiratory infection but has been recently associated with a variety of neurological symptoms (1). Here, we present a case of post-COVID

opsoclonus-myoclonus syndrome (OMS), a rare neurological syndrome characterized by a subacute onset of opsoclonus, a disorder of involuntary saccadic eye movements, ataxia, and involuntary multifocal myoclonus mainly affecting the trunk, limbs, or craniocervical region (2, 3).

CASE DESCRIPTION

A 63-year-old male patient, with a history of hypertension and ischemic heart disease, presented with fever, diarrhea, cough, malaise, and sore throat, with high clinical suspicion of COVID-19. The PCR for SARS-CoV-2 was positive, and the patient was managed with conservative clinical care with quarantine. The patient's COVID symptoms recovered in 3 weeks that was correlated with negative a PCR result and positive serum antibody test (IgG) for COVID-19.

Following 48 h of recovery (day 23 after the onset of COVID), the patient developed mental confusion, behavioral changes, and insomnia with a gradual reduction in mobility and abnormality in eye movements. On examination, he had rapid, involuntary saccadic multidirectional eye movements (opsoclonus) (**Supplementary Video 1**). Marked truncal ataxia and limb myoclonus were also present at this point (**Supplementary Video 2**). His baseline investigations including complete blood count, urine routine examination, thyroid profile and cerebrospinal fluid (CSF) analysis were within normal limits. Hepatitis B, C, and HIV serology were negative. Chest X-ray, ultrasound of abdomen and pelvis, and MRI of the brain were normal (**Table 1**). At that point, a presumed diagnosis of OMS was made. OMS is a rare disorder that is thought to be immune mediated, with primarily para-neoplastic or para-infectious etiologies. Our investigations failed to discover any malignancy or para-neoplastic condition in the patient. Additionally, the anti-neuronal antibodies profile and auto-immune encephalitis screen were also negative. Taken together, OMS manifested by the patient appeared to be associated with COVID-19 infection.

Before admission at our neurology ward, the patient was administered with IV methylprednisolone 1 gm OD for 5 days with no response. The patient was given IVIG treatment (2 gm/kg body weight in five divided doses) following 5 days of his last dose of methylprednisolone. Interestingly, we observed gradual but substantial improvement in OMS following IVIG treatment. The patient exhibited complete recovery over the next 4 weeks following immunotherapy (**Supplementary Video 3**). Subsequent follow-up of the patient to date did not show any recurrence of signs and symptoms of OMS.

DISCUSSION

Herein we report another case of OMS following COVID-19 infection in an adult. OMS is a rare neuroinflammatory disease of paraneoplastic, parainfectious, toxic/metabolic or idiopathic origin, characterized by opsoclonus, myoclonus, ataxia, and behavioral and sleep disorders (4). The important aspect in clinical features is that opsoclonus might not be present during the time of presentation, which can lead to delay in diagnosis or misdiagnosis as cerebellar ataxia (5).

OMS has been often reported with paraneoplastic etiology such as neuroblastoma (6, 7); however, it can manifest with parainfectious etiology, that is, following viral infections (e.g., enterovirus, Epstein–Barr virus, poliovirus, Coxsackie virus, mumps, West-Nile virus, HIV) or bacterial pathogens (e.g., Salmonella species, parasitic infections like *Plasmodium falciparum* and Mycobacterium tuberculosis) (4). Additionally, it is important to rule out any toxic-metabolic states caused by cocaine intoxication, phenytoin overdose, or hyperosmolar non-ketotic coma that may lead to OMS symptoms (4, 8). The prognosis of OMS is worse with paraneoplastic etiology, which might show resistance to immunotherapy and can lead to severe encephalopathy or death (9). In contrast, parainfectious or idiopathic OMS responds well to immunotherapy (mainly intravenous immunoglobulins or corticosteroids) (10, 11). A critical aspect in the management of OMS is to rule out underlying malignancy. In our case, there was no evidence of underlying malignancy, so suspicion of a post-infectious etiology is reasonable (4).

The emergence of neurological disorders, particularly OMS following COVID-19 infection, has been recently reported in several studies (2, 3, 12–14). Interestingly, the majority of these COVID patients developing OMS were affected by mild-to-moderate respiratory symptoms as observed in our case (2). Emamikhah et al. reported seven COVID patients affected by OMS who showed normal brain MRI scans and CSF findings as in our case (2). However, none of the patients in this case series had features of encephalopathy (2). By contrast, our patient showed behavioral changes and confusion, which has been typically reported previously with paraneoplastic OMS (4).

Our patient showed complete remission of OMS following immunotherapy within 4 weeks. Previous studies also support that OMS patients showed dramatic recovery with immunotherapy (2, 15). In agreement to our case, another study showed that a patient with generalized myoclonus and ataxia (without opsoclonus) exhibited better response to IVIG compared to high-dose methylprednisolone pulse therapy (16). However, there are reports showing recovery of OMS or myoclonus patients devoid of opsoclonus symptoms patients with IV methylprednisolone (1 g/d) (3).

The exact pathophysiology of OMS is poorly understood. It is hypothesized to have autoimmune etiology because of its response to immunosuppressive therapy, but the specific autoantibodies leading to the disorder have not yet been identified. However, it is proposed that the pathogenesis involves antibodies that react against cerebellar Purkinjie cells (17) since mild cell loss has been described in Purkinjie cell layer, inferior olives, and brainstem along with mild inflammatory changes. Hence, the diagnosis of OMS is based on clinical presentation. Furthermore, there is no specific standard or guideline for treatment, but glucocorticoids with IVIG are commonly used as first-line therapy (10).

TABLE 1 | Summary of patient features.

Patient's biography	• 63 years • Male • Married
Initial Covid symptoms	• Fever • Diarrhea • Cough • Sore throat • Malaise
Subsequent neurological symptoms*	• Behavioral changes (confusion, insomnia) • Marked truncal ataxia • Myoclonus • Opsoclonus
Laboratory investigations**	• CBC–normal • Urine RE–normal • TFT–normal • Hep B, C, HIV Serology–negative • CSF examination–normal cell count, proteins and glucose • Anti-neuronal Anti-bodies (including Anti-CV2 Abs, Anti-Ri Abs, Anti-yo Abs, Anti-Hu Abs) profile–negative • Auto-immune encephalitis screen–negative
Neuroimaging**	• CT brain–normal • MRI brain–normal
Treatment and response	• *IV Methyl prednisolone (1 gm OD for 5 days)–no response • **IVIG (2 gm/Kg body weight divided over 5 days)–complete resolution of symptoms within 4 weeks

**3 weeks after initial covid-19 symptoms.*

***All of these investigations were done after 2nd admission to hospital for neurological symptoms.*

CBC, Complete Blood Count; Urine RE, Urine Routine Examination; TFT, Thyroid Function Test; Hep B, Hepatitis B; Hep C, Hepatitis C; HIV, Human Immunodeficiency Virus; CSF, Cerebrospinal Fluid; Abs, Antibodies; CT, Computerized Tomography Scan; MRI, Magnetic Resonance Imaging; IV, Intravenous; IVIG, Intravenous Immunoglobulins.

Our case provides further evidence that COVID-19 can trigger OMS irrespective of the severity of respiratory symptoms in such patients (2, 3, 12–14). Hence, further research is needed to dissect the underlying pathophysiological mechanisms associated with COVID-19-induced neurological disorders including OMS.

CONCLUSION

SARS-CoV-2 infection can lead to the manifestation of various neurological events, including a rare autoimmune OMS. This parainfectious OMS presumably caused by COVID-19 showed a dramatic response to IVIG treatment compared to corticosteroids.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HI, TD, ZU, and MU identified the patient and wrote the first draft of the paper. NK and PM contributed to revising the paper. All authors revised and commented on the final draft.

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CASE REPORT
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Case Report: Successful Stabilization of Marburg Variant Multiple Sclerosis With Ocrelizumab Following High-Dose Cyclophosphamide Rescue

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The Marburg variant of multiple sclerosis (Marburg MS) is the most aggressive form of MS, often leading to death soon after onset. Here we describe the case of a 26-year-old Marburg MS patient presenting with severe neurological deficits requiring intensive care. In spite of more than 100 gadolinium-enhancing MRI lesions, the patient recovered almost completely upon high-dose cyclophosphamide (HiCy) rescue treatment (four consecutive days with 50 mg/kg/day, cumulative absolute dose of 14 g). Following the acute treatment, her disease was stabilized by B cell depletion using ocrelizumab. Clinical amelioration was reflected by a decrease of MRI activity and a marked decline of serum neurofilament light chain levels. HiCy rescue treatment followed by ocrelizumab as a maintenance therapy prevented permanent disability and achieved an almost complete clinical and drastic radiological improvement in this Marburg MS patient.

Keywords: Marburg MS, malign MS, high dose cyclophosphamide, ocrelizumab, neurofilament

INTRODUCTION

The Marburg variant of multiple sclerosis [Marburg MS (1)] which accounts for <4% of the total incidence of MS cases mostly affects children and young adults (2). It is a fulminant form of MS, featuring an acute onset of severe neurological deficits often resulting in death within weeks to months (3). Histology usually shows extensive demyelination as well as necrosis, which often involves vital areas like the brainstem (3). Synonyms for Marburg MS, which is the most aggressive variant of the disease, include malign, acute fulminant, acute malignant, and rapidly progressive MS. Its most important differential diagnoses are acute disseminated encephalomyelitis, Balo's concentric sclerosis, and Schilder's diffuse sclerosis. Treatment has proven to be challenging, but recent reports documented positive outcomes following an administration of high-dose cyclophosphamide (4). Here we describe the case of a 26-year-old Marburg MS patient initially presenting with symptoms of a bilateral optic neuritis and no further abnormalities upon examination. In this case, we successfully used ocrelizumab as a maintenance therapy following a high-dose cyclophosphamide induction protocol and monitored the therapy response by serum neurofilament light chain (NfL) levels.

CASE PRESENTATION

A 26-year-old female patient without a history of neurological symptoms presented to our hospital with bilateral optic neuritis which had gradually developed within 5 days prior to admission. Other than hypothyreosis, her past medical history was unremarkable. The patient complained of mainly left-sided bilateral blurred vision, reduced color discrimination, and pain with eye movement. Visual acuity was impaired on both eyes (left: 20/80; right: 20/40). Ophthalmological examination yielded no retinal abnormalities, but optic coherence tomography (OCT) was not possible as the patient was unable to focus appropriately. She was unable to read letters bilaterally during low-contrast visual acuity (LCVA) testing using 2.5% low-contrast Snellen charts. Visual evoked potentials (VEPs) yielded no response for the left eye, while P100 latencies for the right eye were pathologically increased to 139.5 ms. At admission, neurological examination revealed no further abnormalities. Cerebrospinal fluid (CSF) analysis 9 days after the first occurrence of symptoms revealed a lymphomonocytic pleocytosis of 72/μl with positive oligoclonal bands (OCBs) and intrathecal IgM synthesis. The MRZ reaction (MRZR), anti-AQP4, and anti-MOG antibodies as well as vasculitis screening and virological/microbiological analyses were all negative (see **Table 1**). 1 day later, intravenous corticosteroids (1,000 mg/day for five consecutive days) were initiated, and on the following day, numerous supra- and infratentorial gadolinium (Gad)-enhancing and non-enhancing T2w as well as two Gad-enhancing spinal lesions consistent with the diagnosis of multiple sclerosis (MS) were seen on MRI (**Figure 1A**). In detail, there was Gad enhancement in both optic nerves, more than 35 dot-shaped Gad-enhancing juxtacortical/periventricular lesions with typical Dawson's finger configuration, and more than 12 active infratentorial lesions. Due to the typical presentation and the above-described paraclinical findings, we dispensed with further imaging such as magnetic resonance spectroscopy or positron emission tomography–computed tomography. As intravenous steroids resulted in no clinical improvement, five cycles of plasmapheresis and two additional cycles of immunoadsorption were performed. Following this treatment, her sight ameliorated subjectively as she regained the ability to recognize outlines, but overall improvement was poor. While LCVA yielded a score of 0 bilaterally, OCT was now possible, showing a normal peripapillary retinal nerve fiber layer thickness in both eyes (right: 102 μm; left: 103 μm). The patient was scheduled for ocrelizumab therapy within the following 2 weeks and discharged. Regarding other therapeutic options, we decided against alemtuzumab due to her known diagnosis of hypothyroidism. Moreover, the patient was opposed to natalizumab treatment due to concerns regarding progressive multifocal leukoencephalopathy even though she had a negative anti-John–Cunningham virus antibody titer. 1 day after discharge, the patient received the 13-valent pneumococcal conjugate vaccine in preparation for the planned ocrelizumab treatment. Within the next 5 days (i.e., ca. 1 month after the initial symptoms), she experienced a second relapse and was re-admitted to our hospital with a newly developed left spastic hemiplegia and progressive loss of vigilance. MRI revealed a fulminant progression of the lesion load and Gad enhancement with now more than 100 Gad-enhancing lesions (**Figure 1B**). CSF analysis prior to the following therapy showed a shift to a lymphogranulocytic pleocytosis. Serum NfL was 340 pg/ml as measured by ELISA (**Figure 1G**). After exclusion of an infectious etiology, a course of intravenous high-dosage corticosteroid (2,000 mg/day for 3 consecutive days) was administered. On the second day of corticosteroid therapy, the patient was started on an additional high-dose cyclophosphamide (HiCy) therapy for 4 consecutive days with 50 mg/kg/day, reaching a cumulative absolute dose of 14 g. Shortly after this combined therapy, serum NfL peaked at 833 pg/ml. 3 days after HiCy therapy, stem cells were mobilized with 6 mg granulocyte-colony stimulating factor. As expected, blood analysis revealed leukopenia and lymphopenia immediately after HiCy treatment. A recovery of the leukocytic population was observed at 10 days later. Circa 3 days after the last dose of cyclophosphamide, we observed both clinical and radiological improvement. While the total lesion load was stable, only 16 lesions were still active (**Figure 1C**). Peripheral CD34-positive hematopoietic stem cells (HSC) were harvested by leukapheresis 3 weeks later and cryopreserved for future transplantation, if needed. The patient was discharged with mild residual neurological deficits and was closely monitored both clinically and radiologically (**Figures 1D–F**). Serum NfL levels slowly decreased over the course of 10 weeks to 566 pg/ml.

TABLE 1 | Laboratory characteristics and differential diagnoses.

Characteristics	OCBs	Positive	Cranial lesions	Yes	Spinal lesions	Yes
	MRZ	Negative	Anti-AQP4-IgG	Negative	Anti-MOG-IgG	Negative
Differential diagnoses	Vitamin B1, B6, B12, folic acid	Normal	ANA, ANCA, ENA	Negative	ACE	16 U/l
	Vitamin D	8 ng/ml	JCV-PCR	Negative	JCV titer	0
	Anti-HIV 1/2 IgG	Negative	Borrelia and treponema IgG/IgM	Negative	Toxoplasmosis-PCR	Negative
	Anti-HHV6 IgG	Positive	Cryptococcosis antigen	Negative	Anti-toxoplasmosis IgG/IgM	Negative
	Anti-*Candida* antibodies	Negative	Anti-*Aspergillus* antibodies	Negative	Bartonella IgG/IgM	Negative

OCBs, oligoclonal bands; ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmatic antibodies; ENA, extractable nuclear antigen antibodies; ACE, angiotensin-converting enzyme; JCV, John–Cunningham virus.

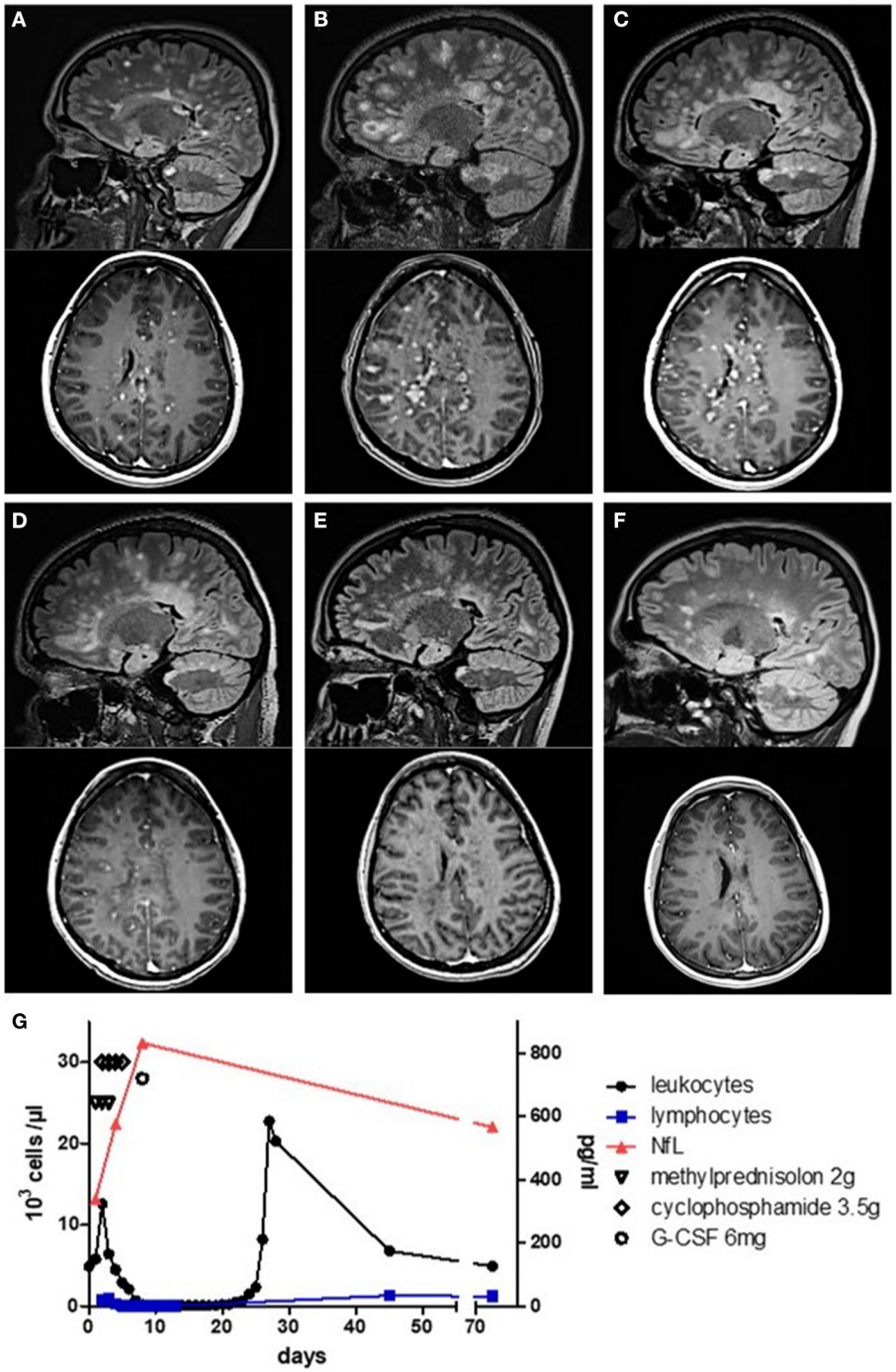

FIGURE 1 | MRI and serological monitoring of the disease course. **(A–F)** Sagittal FLAIR and axial T1 gadolinium (Gad) sequences. **(A)** Numerous lesions with Gad enhancement at first admission. **(B)** MRI at re-admission showing more than 100 Gad-enhancing lesions. **(C)** Decrease of lesion load 7 days after the first dose of cyclophosphamide. **(D)** Further decrease of lesion load mirroring clinical remission at 15 days and **(E)** at 30 days. **(F)** At 44 days after cyclophosphamide treatment, no more Gad enhancement was detectable. **(G)** Leukocyte and lymphocyte count as well as serological neurofilament light chain levels during treatment.

9 weeks after the HiCy treatment, maintenance therapy with ocrelizumab was initiated following standard dosing (i.e., loading with 300 mg i.v. twice within 2 weeks and 600 mg i.v. as maintenance). 6 months later, the patient was still clinically stable without any relapses. The only residual symptom was a slightly impaired visual acuity (left: 20/30; right: 20/30). The VEP P100 latencies had returned to normal (right, 110 ms; left, 109 ms).

DISCUSSION

The initial manifestation of MS in our patient raised several red flags, suggesting a severe disease course, such as persisting and disabling symptoms, almost no recovery after the first steroid pulse, and a high lesion load at baseline, including spinal and infratentorial Gad-enhancing lesions. In addition, intrathecal IgM synthesis is associated with an unfavorable prognosis (5). Thus, following an acute relapse treatment, we aimed at a highly effective immunodepletion therapy with ocrelizumab. However, when the mostly fatal Marburg variant of MS became evident, we were forced to take a more aggressive therapeutic approach. This decision was made since, of the 28 cases documented in the literature, only 11 (39%) survived, of whom only two (18%) had a favorable outcome. Of note is that the Marburg MS is still poorly defined as an MS variant in its own right as demonstrated by the heterogeneous nomenclature found in the literature (e.g., malign MS, acute fulminant MS, acute malignant MS, rapidly progressive MS, etc.). As a result, the clinician is faced with uncertainty regarding the potential transferability of previous therapeutic approaches. While there are cases in which mitoxantrone or alemtuzumab were successfully applied (6, 7), we advocate the use of cyclophosphamide as this agent not only effectively targets immune cells but also mobilizes HSC. These can then be harvested for later therapeutic use in the form of autologous hematopoietic stem cell transplantation, which has proven to be a potent therapy for highly active relapsing–remitting MS (8) and might therefore be effective as a long-term therapy in Marburg MS as well. Furthermore, following the high-dose cyclophosphamide protocol of Krishnan et al. (4) and using ocrelizumab as a maintenance therapy, we were able to prevent permanent disability and to achieve an almost complete clinical and drastic radiological improvement. As most other reported cases were fatal, this will provide the unique opportunity to monitor the long-term disease course. Regarding the pharmacodynamics of our treatment, we did not measure the cyclophosphamide levels in our patient. However, a case series of seven patients from 1,983 compared cyclophosphamide levels in the serum and CSF of MS patients following oral administration and showed identical levels, which demonstrated the high CNS penetration of this medication (9). As our patient had a reduced level of consciousness, we decided for intravenous administration. So far, there have been two case reports with favorable outcomes using the protocol that we applied (4, 10). Of note is that the cyclophosphamide treatment was primarily intended as a rescue therapy for the fulminant disease course and not as a means of stem cell mobilization. In general, the doses needed for effective immunosuppression are far higher than those required for stem cell mobilization (11). Beyond the Marburg MS cases, the dose that we applied was also evaluated in refractory MS patients (12). Regarding side effects, high doses of cyclophosphamide can induce hemorrhagic cystitis, hepatic damage, and cardiac necrosis (13) as well as infertility and ovarian endocrine failure (14). However, neither during the acute treatment phase nor during follow-up for 6 months were any of these side effects observed. Concerning ocrelizumab, this medication depletes CD20-positive B and T cells (15) within days but may take up to 3 months to reach its maximal effect. However, upon consultation with the patient, we decided to use it as a maintenance therapy due to her concerns described above. With regard to disease biomarkers, serum NfL levels in MS reflect ongoing disease activity and correlate with worsening of disability, lesion load (16), and risk for relapses. Accordingly, we found a rapid increase of NfL levels in our patient which doubled within a period of 7 days, reflecting the fulminant disease course. On the other hand, our data suggest that NfL may also be a suitable tool to monitor therapy response in Marburg MS, as we found it to steadily decrease following the HiCy treatment. To our knowledge, this is the first case of Marburg MS where data on this serological biomarker of CNS damage were collected during disease and recovery. Another interesting feature of our case was that, while we found positive OCBs, the MRZ reaction was negative. In MS, the MRZR, a polyspecific antiviral immune response against measles, rubella, and varicella zoster virus has a specificity of ∼97% (17). Unfortunately, the majority of the other Marburg MS case reports did not include information on this laboratory marker so that, at present, its significance in Marburg MS remains unclear. Lastly, it is an important feature of this case that the severe disease reactivation occurred shortly after anti-pneumococcus vaccination. Of note is that there have been recent studies describing a worsening of MS after the administration of live attenuated vaccines like yellow fever (18), but inactivated vaccines, like pneumococcal vaccination, are usually considered safe regarding MS activity. In summary, we trust that this report will contribute to a more successful management of Marburg MS.

CONCLUSION

In this case, we were able to prevent permanent disability and to achieve an almost complete clinical and drastic radiological improvement using ocrelizumab as a maintenance therapy following the high-dose cyclophosphamide protocol of Krishnan et al. NfL may be a suitable tool to monitor therapy response in Marburg MS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

VK, SM, and DK gave the idea of case reporting. VK and DK analyzed the case and prepared the MRI scans as well as the figure and the table. VK drafted the manuscript for intellectual content. MF, KB, MH, EA, AA, PA, OA, PK, SM, and DK critically reviewed the manuscript and were involved in patients' healthcare. All the authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Coexistence of Anti-AMPA Receptor Encephalitis and Positive Biomarkers of Alzheimer's Disease

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Anti–α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor encephalitis is a rare autoimmune disease that is characterized by acute cognitive impairment, mental symptoms, and seizures. The high comorbidity rate between anti–AMPA receptor (AMPAR) encephalitis and other somatic diseases, such as malignancy, has revealed the possibility of potential copathogenesis. However, there have not yet been reports about anti-AMPAR encephalitis with concomitant cerebrospinal fluid (CSF) biomarkers consistent with Alzheimer disease (AD). Herein, we present the case of an elderly male patient with autoimmune encephalitis (AE) presenting with anti–AMPA1-R and anti–AMPA2-R antibodies, as well as CSF biomarkers of AD. The patient was hospitalized with acute memory decline for 1 week. Anti–AMPA1-R and anti–AMPA2-R antibodies were positively detected in CSF, and the anti–AMPA2-R antibody was also present in the serum. Additionally, the biomarkers of AD were concurrently present in CSF ($A\beta_{1-42}$ = 245.70 pg/mL, t-Tau = 894.48 pg/mL, p-Tau = 78.66 pg/mL). After administering a combined treatment of intravenous immunoglobulin and glucocorticoids, the patient recovered significantly, and his cognitive function achieved a sustained remission during 2 months' follow-up. This case raises the awareness of a possible interaction between AE and changes of CSF biomarkers. We speculated that the existence of AMPAR antibodies can induce changes of CSF, and other pathological alterations. This present report highlights that a potential relationship exists among AE and provides a warning when making the diagnosis of AD.

Keywords: autoimmune encephalitis, anti-α-amino-3-hydroxy-5-methyl-4-Isoxazolepropionic acid receptor, Alzheimer's disease, cognitive impairment, cerebrospinal fluid biomarkers

BACKGROUND

Autoimmune encephalitis (AE) is defined as a group of important neurological inflammatory diseases with specific autoantibodies. The incidence of AE has increased to 1.2/100,000 person-years (2006–2015) compared to 0.4/100,000 person-years (1995–2005) (1). The rapid development of a spectrum of specific autoantibody-associated neurological disorders has

deepened our understanding in the last 30 years. As one of the specific antibodies targeting neuronal surface antigens, which are more likely to be pathogenic, anti–α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibody has rarely been seen in clinical practice. To date, ∼60 related cases have been reported (2). Anti-AMPAR encephalitis is characterized by diverse clinical manifestations, and ∼60% of patients might be associated with malignancy (3). Coexisting antibodies, such as collapsin response mediator protein 5 antibody, have also been identified (4). Nevertheless, to the best of our knowledge, no case has ever been reported, comprising two positive subtypes of anti-AMPAR antibodies and typical changes of biomarkers of Alzheimer disease (AD).

Herein, we report the case of a 79-year-old man diagnosed with anti-AMPAR encephalitis with the coexistence of antibodies targeting AMPA1 receptor (AMPA1-R) and AMPA2 receptor (AMPAR2-R) and positive cerebrospinal fluid (CSF) biomarkers of AD, manifested as rapidly progressive dementia. We aim to explore the underlying pathological mechanisms of AE and the CSF biomarkers of AD.

CASE PRESENTATION

A 79-year-old man was admitted to the Nanjing Brain Hospital with rapid memory decline for 1 week, which aggravated in the past 2 days on October 16, 2020. The patient especially had deficits in recent memory, such as forgetting what he had just done or said and occasionally did not recognize the family members. His symptoms were repetitive, with remissions and exacerbations. Two days before admission, the cognitive function had further declined, mainly manifested as failure to recognize family members and inability to take care of himself. Thus, he was admitted to the hospital, brought by his son. Five days after admission, the patient developed mental symptoms, the hallmark of which was visual hallucinations. The family members reported that the patient saw people or things that did not exist and mistook the hospital for the street. During the disease course, the patient did not undergo epileptic seizures.

The patient had a history of diabetes for 2 years, which was treated by the oral administration of metformin hydrochloride (Diaformin) tablets (1.0 g, twice a day) and acarbose tablets (50 mg, thrice a day). He also had hypertension for several years and was treated by the oral administration of telmisartan tablets (40 mg, once a day), with no history of anxiety, depression, or epilepsy. However, the blood sugar levels and blood pressure were not monitored regularly. The patient lived with his wife all year round. A week before admission, his children noticed that his memory was significantly worse than before when they visited him. His wife reported that in the last 2 years, he sometimes forgot to buy things, but their life was not affected. There were no cases with similar symptoms or related family history of autoimmune diseases and dementia.

In terms of tests, cranial magnetic resonance imaging (MRI) revealed ischemic changes in centrum semiovale and corona radiate, with no other abnormalities, particularly no signs of limbic encephalitis (i.e., hippocampal sclerosis) (**Figure 1**). Electroencephalography (EEG) showed an extensive moderate abnormality, with no epileptiform discharge. Chest computed tomography (CT) showed a nodular hyperdense shadow with a diameter of ∼4.6 mm within the upper lobe of the right lung. The patient underwent neuropsychological evaluations the day after admission, in which he scored 2/30 on the Mini-Mental State Examination (MMSE), 1/30 on the Montreal Cognitive Assessment (MoCA), and 4.5/32.5 on the Hasegawa Dementia Scale. The patient also underwent laboratory tests. His hemoglobin A_{1c} level was 6.30%. Furthermore, his CSF exhibited increased protein levels (0.52 g/L, normal range = 0.20–0.40 g/L) and immunoglobulin G (46.1 mg/L, normal range = 0–34 mg/L). Routine blood and other CSF analyses (cell counts, glucose, chlorine level, and pathology) were normal. CSF polymerase chain reaction for herpes simplex viruses 1 and 2 was unremarkable. Anti–AMPA1-R and anti–AMPA2-R antibodies were detected in the CSF (titer: 1:3.2 and 1:320), and anti–AMPA2-R antibody was also present in the serum (titer: 1:100). Simultaneously, AD biomarkers were present in the CSF: $A\beta_{1-42}$ = 245.70 pg/mL, t-Tau = 894.48 pg/mL, and p-Tau = 78.66 pg/mL (**Table 1**). Besides, urinary AD-associated neuronal thread protein, tumor markers, paraneoplastic neuronal antibodies, and other common antineuronal and antineuropil antibodies did not exhibit significant changes. Other laboratory tests, such as thyroid hormone combination, the spectrum of antinuclear antibodies, and anticardiolipin antibodies, were normal. During the hospitalization, the patient's blood pressure and blood glucose were well-controlled, with an average blood pressure of 136/92 mm Hg and fasting blood glucose of ∼5.89 mmol/L. All the serum and CSF antibodies were measured using a fixed cell-based assay, and the quantitative determination of CSF biomarkers was carried out using an enzyme-linked immunosorbent assay. All the tests were carried out twice.

Because of the history of diabetes and hypertension, cerebrovascular diseases had to be considered. However, the results of brain MRI and CT excluded any possibility. Although a nodular high-density shadow was seen in the right lung, the patient had no cough, coughing sputum, hemoptysis, and no enlargement of superficial lymph nodes throughout the body. Tumor markers were all normal. After consultation with a respiratory specialist, the tumor possibility was considered unlikely, and regular follow-up was recommended.

The results of autoimmune antibodies were available 5 days after admission; the patient was diagnosed with anti-AMPAR encephalitis. The sign of the tumor was ruled out, and immunotherapy was initiated with intravenous methylprednisolone (500 mg/d) and immunoglobulin 0.4 g/kg per day for 5 days, and then methylprednisolone dose was gradually reduced. Two days later, an analysis of the CSF biomarkers showed amyloid and Tau abnormalities. Uncertain whether AE caused changes in the CSF biomarkers or whether there existed concomitant chronic cognitive decline, we planned to treat the patient with immunotherapy first and then determine the need for other drugs such as cholinesterase inhibitors based on the patient's subsequent recovery. Ten days after treatment, he recovered significantly but still suffered from mild memory impairment. Finally, he was discharged with 60 mg/d prednisone,

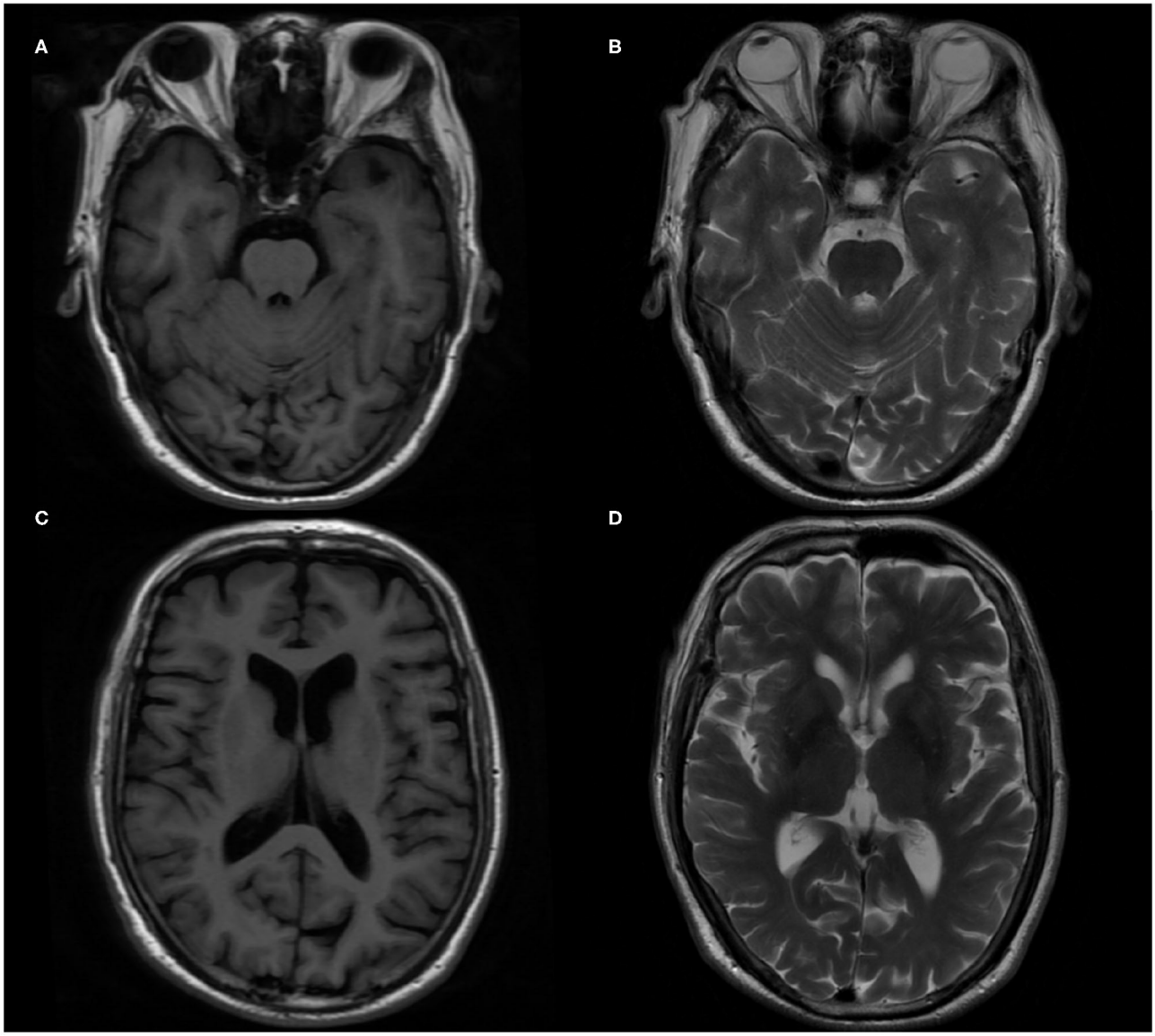

FIGURE 1 | Brain magnetic resonance imaging (MRI) in the patient. **(A,C)** T1-weighted imaging axial image. **(B,D)** T2-weighted imaging axial image.

Caltrate, and potassium chloride sustained-release tablets to prevent the side effects of the glucocorticoid. Thirty days later, the patient's cognitive function improved as he scored 10/30 on MMSE and 7/30 on MoCA. During the 2-month follow-up, his prednisolone acetate tablets had been adjusted to 20 mg/d with cognitive scale assessment: MMSE: 15/30 and MoCA: 12/30. Five months after discharge, the patient stopped taking oral prednisolone and the related medications used to prevent the side effects of the glucocorticoid and scored 22/30 on MMSE, 20/30 on MoCA, and 0.5 on the clinical dementia rating. Confirmed by his son, the patient could live alone and forgot things occasionally. We recommended that the patient should still perform appropriate cognitive function exercises daily and be followed regularly, with additional pharmacological interventions if necessary. **Figure 2** summarizes the clinical course. Details about the laboratory evaluations are presented in the **Supplementary Material**.

DISCUSSION AND CONCLUSION

Since the characterization of anti-NMDAR encephalitis in 2007, more types of AE have been explored. However, anti-AMPAR encephalitis is a relatively rare type. Because of a lack of relevant case reports and large-scale studies, the clinical manifestations and treatments have not been consistent (5). Although the core symptoms of anti-AMPAR encephalitis include cognitive impairment, mental symptoms, and seizures, some patients might present motor–sensory disturbances, ataxic gait, or

TABLE 1 | Test results of CSF biomarkers of AD.

Test method		Results	Reference interval	
ELISA	$A\beta_{1-42}$	↓245.70 pg/mL	<550 pg/mL	Aggregated Aβ
			551–650 pg/mL	Suspicious
			≥651 pg/mL	Normal
ELISA	$A\beta_{1-40}$	8,046.11 pg/mL	≥7,000 pg/mL	Normal
			<7,000 pg/mL	Aggregated Aβ
ELISA	$A\beta_{1-42}/A\beta_{1-40}$	↓0.031	≤0.05	Positive
			>0.05	Negative
ELISA	t-Tau	↑894.48 pg/mL	≤399 pg/mL	Normal
			>399 pg/mL	Neurodegeneration or neuronal injury
ELISA	p-Tau	↑78.66 pg/mL	≤50 pg/mL	Normal
			>50 pg/mL	Neurofibrillary tangles

CSF, cerebrospinal fluid; AD, Alzheimer disease; ELISA, enzyme-linked immunosorbent assay; Aβ, amyloid β-protein; t-Tau, total-Tau protein; p-Tau, phosphorylated-Tau protein. The method of the ELISA determinations can be seen in the ***Supplementary Material****.*
↓: decreased; ↑: increased.

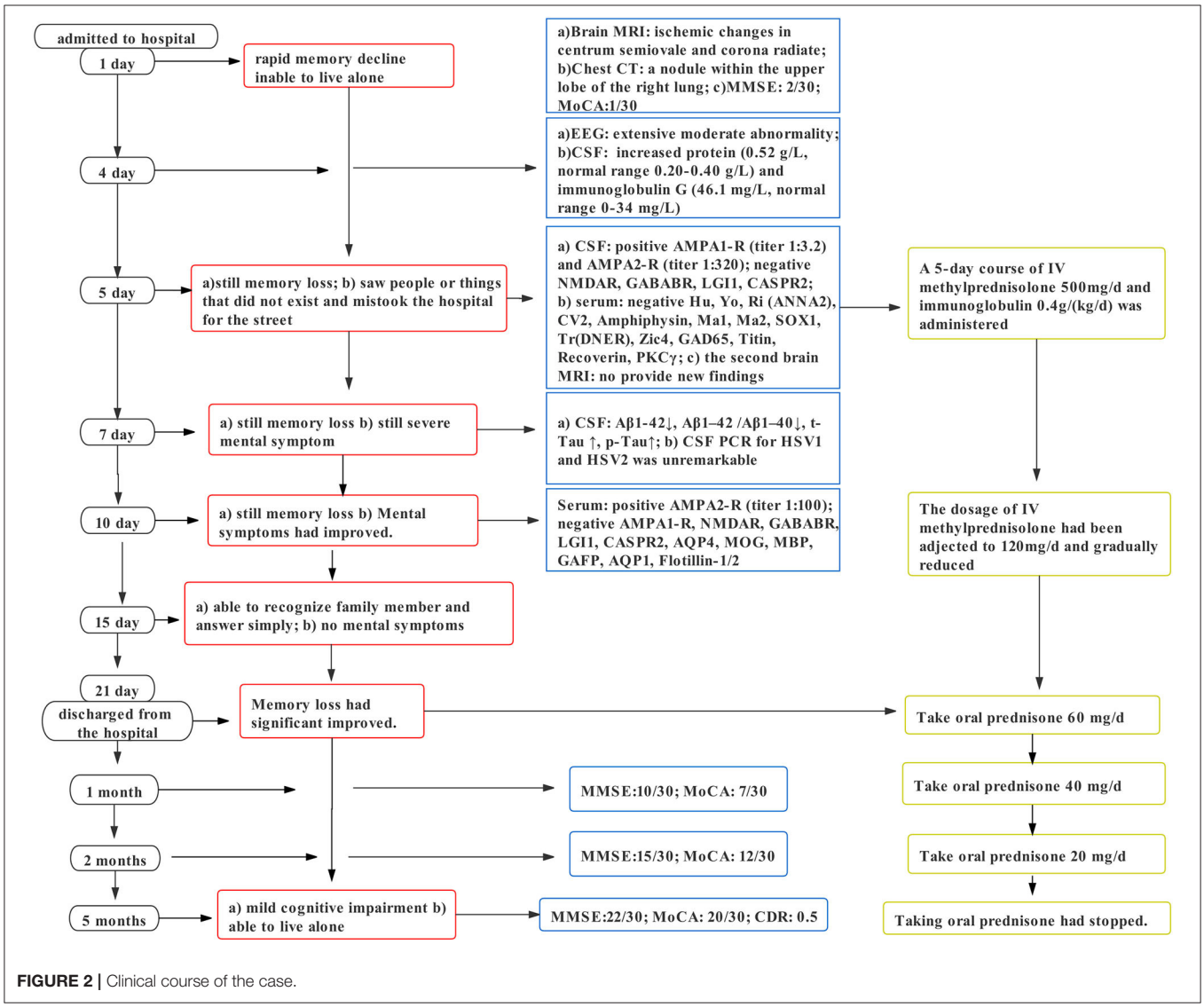

FIGURE 2 | Clinical course of the case.

dizziness (6). Currently, immunocytochemistry on HEK 293 cells transfected with GluA1 and / or GluA2 subunits is mainly used to diagnose anti-AMPAR encephalitis (7). The main treatment includes first-line therapies, such as corticosteroids, intravenous immunoglobulin, and plasma exchange or immunoadsorption, and second-line regimens, such as mycophenolate, rituximab, and cyclophosphamide. For patients with tumor-associated AE, tumor-targeting treatment should be initially considered (8). A systematic review on anti-AMPAR antibody encephalitis suggested that 84% of patients achieved sustained improvement of symptoms, whereas several other studies reported high rates of neurological relapse (9). The patient in this case report had antibodies targeting AMPA1-R and AMPA2-R in the CSF, with AMPA2-R in the serum. After immunotherapy, the symptoms improved significantly.

AMPARs are heterotetramers composed of GluA1-A4 and mediate most of the fast excitatory synaptic transmission in the brain (2). AMPAR trafficking is a key mechanism that induces nascent synaptic development. The type, threshold, and extent of synaptic plasticity at any synapse are determined by the characteristics and properties of AMPAR (10). GluA1/A2 is primarily located in the limbic system and hippocampus, indicating that GluA1/A2 is closely associated with learning, memory, personality, and epilepsy. A study investigating the effect of AMPAR antibodies on the cultures of live rat hippocampal neurons revealed that the antibodies from patients could lead to a selective decrease in total surface area and synaptic localization of AMPARs, resulting in decreased inhibitory synaptic transmission and increased intrinsic excitability. Furthermore, these changes might be attributed to memory deficits and epilepsy (11). However, interestingly, more than half of the cases have been admitted to the hospital with an initial symptom of memory decline or cognitive impairment (5).

The patient only had rapid memory loss as the first symptom. Because of living separately from their parents, his children were not very aware of the patient's condition in recent years. His wife reported that the patient forgot to buy things occasionally in the last 2 years, but their life was not affected. Thus, AE was the tentative diagnosis; however, there was the possibility of AD or preclinical AD, with some factors leading to an acute exacerbation of the disease process. Testing CSF biomarkers is the main diagnostic tool for detecting AD, as positron emission tomography is expensive (12). Surprisingly, the patient had biomarkers suggestive of AD within the CSF ($A\beta_{1-42}\downarrow$, $A\beta_{1-42}$ /$A\beta_{1-40}\downarrow$, t-Tau↑, and p-Tau↑). According to the AT(N) system proposed by the 2018 National Institute on Aging and Alzheimer's Association workgroup, the results were consistent with the biomarker category of AD (A+: aggregated Aβ, T+: neurofibrillary tangles, N+: neurodegeneration, or neuronal injury) (13).

Accumulating data suggest that AD is a continuous process, and the progression of biomarkers is also a continuum that begins before the onset of symptoms (13). AMPAR and AMPA signaling pathway disorders have been demonstrated to be particularly prominent in the pathogenesis of this continuous process. Changes in actin cytoskeleton integrity and the structure and number of dendritic spines, which occur early in AD, are associated with a decline in AMPA signaling. In addition, AMPA dysfunction correlates with the presence of soluble, but not insoluble, Aβ and Tau species (14). At the same time, anti-AMPAR antibodies can reduce the expression of AMPARs (11). It seems that the pathologic processes of AE and AD might affect each other. One previous study reported that the concentration of progranulin could be a CSF biomarker of NMDAR-AE, and high levels of t-Tau might suggest a risk for hippocampal sclerosis (15). However, the available evidence can only demonstrate that either the presence of antibodies or neurodegeneration might be associated with AE; nevertheless, it is still necessary to show whether anti-AMPAR antibodies could cause a typical change in the CSF biomarkers of AD. Moreover, it should be noted that diabetes and hypertension are associated with neurodegeneration. Insulin resistance and decreased insulin activity can suppress protein kinase B signaling, leading to dephosphorylation and activation activity of glucose synthase kinase-3β, which is involved in Tau phosphorylation and formation of Aβ1–40 and $A\beta_{1-42}$ (16). Cerebral ischemia can stimulate the expression of presenilin, which is involved in Aβ synthesis, leading to the accumulation of Aβ (17). Therefore, further investigations are necessary to determine whether there is a direct link between anti-AMPAR antibodies and alterations in AD pathologic changes or whether the presence of Aβ and p-Tau is a potential predisposing factor for AE.

Besides, it should be noted that patients with AE, who are associated with anti-AMPAR, usually exhibit limbic system involvement or temporomesial abnormality in brain MRI and slow waves or epileptic waves in EEG. Approximately 64% of cases are associated with tumors, while the current case exhibited normal brain MRI. A few cases with short memory loss or confusion as initial symptoms were reported to have normal MRI with normal or general slowing in EEG (3, 5). In this group of patients, especially those with subacute onset or longer duration of disease, the diagnosis seems to be confirmed only by determining autoimmune antibodies. The cognitive impairment in patients with AE or autoimmune dementia is manifested with a rapid disease process, whereas symptoms in patients with AD have a gradual on set over months to years (8). It is generally accepted that the pathogenesis of dementia, and AD, in particular, is associated with autoimmunity, including classic autoantibodies and functional autoantibodies (18). Therefore, we suggest that irrespective of whether anti-AMPAR antibodies are involved in pathologic changes of AD and whether patients with AE exhibit cognitive impairment, they could suffer from AD pathologic changes. However, limited reports are available on anti-AMPAR–associated autoimmune dementia, as well as the relationship between anti-AMPAR antibodies and the changes of CSF. Thanarajah et al. reported an atypical AE case with neuropil antibodies against an unknown epitope, increased Tau level, decreased level of amyloid ratio, and temporoparietal atrophy; however, they did not explore the potential correlation between them (19). Because of a lack of clear-cut history of cognition and typical imaging presentation, whether the case presented here really suffers from AD or pre-clinical AD is uncertain. During 5 months of follow-up, the patient exhibited continuous improvements in cognitive function and was in the stage of mild

cognitive impairment. His son confirmed that his father was only more likely to forget things than the period before the onset of the disease. Based on the patient's recovery, we believe that his symptoms of severe cognitive decline were caused by AE and multiple factors that induced amyloid and Tau abnormalities. At the same time, we hypothesize that the patient might have a chronic mild cognitive dysfunction that was exacerbated by the antibodies. Therefore, we have planned to follow up the patient for a long time, including repeated neuropsychological evaluation, analysis of CSF biomarkers half a year later, and brain MRI examinations at least once a year, to observe changes in the patient's condition and any changes toward AD.

In conclusion, we discussed the clinical characteristics and molecular mechanisms of anti-AMPAR encephalitis and its potential interaction with changes in CSF biomarkers of AD, which need to be further investigated. This case provides us with the insight that two pathological processes might coexist. Given the possibility of reversibility and preventing disability, clinicians should be aware of the likelihood of AE when dealing with patients with rapid cognitive decline. However, in these patients and the elderly subjects, in particular, with the possibility of concomitant chronic and progressive cognitive decline, preclinical AD should not be ignored.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YS and SC: wrote the manuscript and made table and figures. YS, SC, JG, and WX: reviewed the literature. YS, SC, JG, JL, WX, XL, and JC: performed final manuscript review and editing. All authors contributed to the article and approved the submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.673347/full#supplementary-material

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frontiers in Neurology

CASE REPORT
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Progressive Tumefactive Demyelination as the Only Result of Extensive Diagnostic Work-Up: A Case Report

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Tumefactive demyelinating lesions belong to the rare variants of multiple sclerosis, posing a diagnostic challenge since it is difficult to distinguish them from a neoplasm or other brain lesions and they require a careful differential diagnosis. This contribution presents the case report of a young female with progressive tumefactive demyelinating brain and spinal cord lesions. An extensive diagnostic process including two brain biopsies and an autopsy did not reveal any explanatory diagnosis other than multiple sclerosis. The patient was treated by various disease-modifying treatments without significant effect and died from ascendent infection via ventriculoperitoneal shunt resulting in *Staphylococcus aureus* meningitis.

Keywords: demyelinating diseases, multiple sclerosis, neuropathology, neuroradiology, case report

INTRODUCTION

Tumefactive demyelination belongs to the rare variants of multiple sclerosis (MS), posing a diagnostic challenge and therapeutic enigma as they can mimic other pathologies such as brain neoplasm, abscess, vasculitis, or granulomatous disease.

Atypical features of MS plaques on MRI include size >2 cm, mass effect, edema, and/or the presence of ringlike or open-ring enhancement. Lesions with these characteristics are often described as tumefactive demyelinating lesions (TDLs) (1).

The prevalence of TDLs is estimated to be one to three per 1,000 cases of MS (2), although Sánchez et al. report the prevalence of 21 per 1,000 cases of MS (3). Neuroimaging is necessary to confirm the diagnosis, and a biopsy may be warranted if imaging is not precise (4). The clinical presentation of patients with TDLs is variable and could be atypical for the demyelinating disease. The mass effect is usually the cause of symptoms due to the displacement of the surrounding tissue, is present in about half of TDL cases, and may lead to increased intracranial pressure and cerebral herniation (1). This contribution presents the case report of a young female with TDLs. Such a case report of a patient exhibiting similar TDLs has not been reported before.

CASE REPORT

A 23-year-old female was admitted to the neurological department of a major university hospital presenting with a mild central paraparesis of the lower extremities; an MRI indicated T2-hyperintense lesions in a periventricular, infratentorial, and intramedullary localization; both contrast-enhancing and non-enhancing lesions were found (**Figure 1**). Five oligoclonal bands (OCBs) appeared in the cerebrospinal fluid (CSF), but no OCB appeared in the serum; no signs of neuro-infection were found in the CSF. The patient's medical and family history was unremarkable, without any chronic disease, neoplasm, or autoimmune disease.

The MS diagnosis was determined according to the McDonald 2010 criteria (5). The patient was treated with high-dose steroids resulting in a slight reduction of complaints. Chronic treatment with interferon beta-1b commenced, and the patient was relapse-free for 4 years; no MRI progression appeared.

At the age of 27, the patient exhibited a mild central paraparesis of the lower extremities (treated with high-dose steroids), and the chronic treatment began with dimethyl-fumarate. An MRI of the brain and spinal cord showed multiple TDLs (**Figure 2**). An extensive diagnostic process was made, including positron emission tomography (PET) demonstrating high accumulation of 18F-fluoroethyl-L-thyrosine (FLT) within the lesions and MRI spectroscopy revealing elevation of choline peak and choline/creatine ratio. The histopathological findings from stereotactic brain biopsy of the lesion in the left occipital lobe confirmed demyelination; no neoplasm signs were found.

A broad range of tests was undertaken during follow-up (**Table 1**), all with negative results. The patient did not exhibit any other autoimmune disease or any other non-neurological manifestation over the whole follow-up period. She underwent a second CSF examination: no signs of infection or neoplasm were found, one OCB appeared in the CSF, and no OCB appeared in the serum.

At the age of 28, the patient exhibited left-sided negative sensitive symptoms and was treated with high-dose steroids. An MRI of the brain and cervical spinal cord showed significant progression of TDLs, and the treatment with natalizumab commenced.

At the age of 29, cognitive and gait problems together with a headache and papilledema occurred, and a diagnosis of obstructive hydrocephalus (**Figure 2**) was established. Thus, a ventriculoperitoneal shunt was inserted. Brain MRI revealed further progression of TDLs, and the patient underwent another brain lesion biopsy. Histopathological findings revealed demyelination (**Figures 3**, **4**).

At the age of 30, left-sided hemiparesis together with further progression of TDLs appeared. The patient was treated with high-dose steroids and an immunomodulatory dose of intravenous immunoglobulins resulting in a slight reduction of complaints to mild central paraparesis of the lower extremities and mild left-sided hemiparesis. From a chronic treatment point of view, hematopoietic stem-cell transplantation was considered.

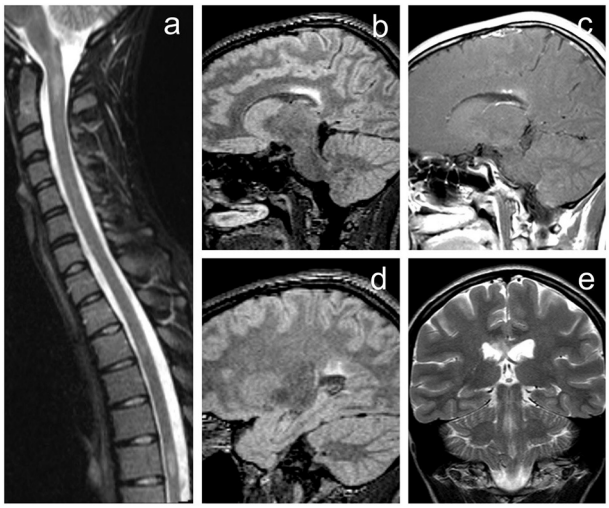

FIGURE 1 | Initial MRI of the brain demonstrating rather typical finding of demyelinating disease fulfilling McDonald diagnostic criteria for multiple sclerosis. **(a)** Short-tau inversion recovery (STIR) image of the cervical and upper thoracic spine in sagittal plane revealing several hyperintense lesions (level C1/2, Th3/4, and Th6). **(b,d)** 3D fluid-attenuated inversion recovery (FLAIR) images of the brain in the sagittal plane. **(e)** T2-weighted image in the coronal plane. **(c)** Contrast-enhanced T1-weighted image with magnetization transfer in sagittal plane. Brain MRI revealed several periventricular white matter lesions including the largest FLAIR hyperintense plaque within the corpus callosum **(b,e)** with punctate enhancement **(c)**. Image **(d)** shows some of the other smaller lesions near the trigone of the left lateral ventricle.

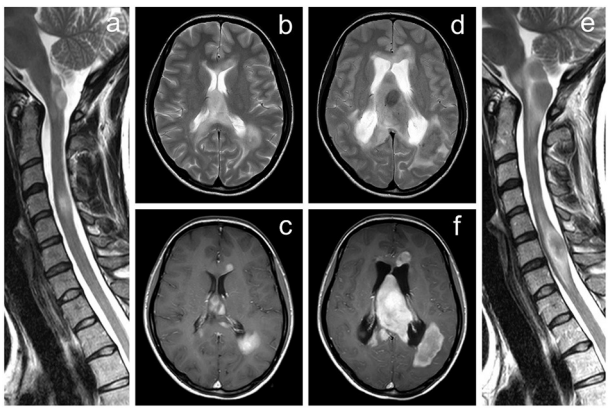

FIGURE 2 | MRI of the brain and cervical spine documenting a significant progression of the tumefactive lesions. **(a–c)** Examination performed ~5 years after the initial diagnosis of multiple sclerosis, **(d–f)** follow-up examination after further 22 months. Several tumor-like enhancing lesions located around the lateral ventricles are visible on axial T2-weighted images **(b,d)** and contrast-enhanced axial T1-weighted images **(c,f)**. Extensive mass lesion located within the septum pellucidum finally caused the hydrocephalus by obstruction of the interventricular foramina; a significant dilatation of the lateral ventricles is seen on follow-up examination **(d,f)**. The progressive course of the disease is also demonstrated by T2-weighted images of the cervical spine in the sagittal plane **(a,e)**.

However, the patient died from circumscribed peritonitis complicated by ascendent infection via ventriculoperitoneal shunt resulting in *Staphylococcus aureus* meningitis. The autopsy

TABLE 1 | Laboratory tests undertaken during follow-up.

Laboratory test categories	Detailed description	Result
Autoimmune antibodies	Anti-aquaporin-4 antibodies, anti-myelin oligodendrocyte glycoprotein antibodies, anti-nuclear antibodies, antibodies against extractable nuclear antigens, anti-double- and single-stranded DNA, anti-neutrophil cytoplasmic antibodies, anticardiolipin antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibodies	Negative
Paraneoplastic antibodies (serum and CSF)	Anti-NMDAR, AMPA1, AMPA2, CASPR2, LGI1, GABAR B1, GABAR B2, anti-Hu, anti-Ri, anti-Yo, anti-CV2, anti-amphiphysin, anti-Ma1, anti-Ma2	Negative
Infectious diseases	John Cunningham virus (CSF), HIV, syphilis, toxoplasmosis, cryptococcal antigen (CSF), panfungal antigen	Negative
Metabolic disorders	Plasma amino acids analysis, urine amino acids analysis, plasma acylcarnitine analysis, urine sulfatides, plasma chitotriosidase, urine organic acids analysis, urinary acylglycines, serum very long-chain fatty acids analysis, serum carnitine quantification, serum purines and pyrimidines, serum homocysteine quantification, plasma creatine kinase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, CSF lactate	Normal levels

DNA, deoxyribonucleic acid; CSF, cerebrospinal fluid; NMDAR, N-methyl-D-aspartate receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CASPR2, contactin associated protein 2; LGI, leucine-rich glioma-inactivated; GABAR, gamma-aminobutyric acid receptor.

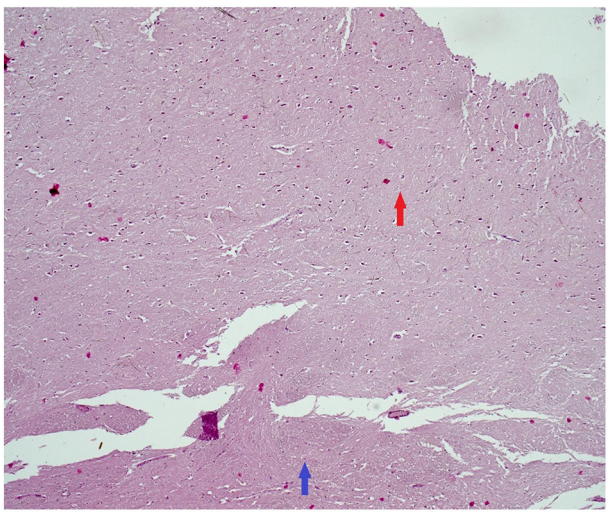

FIGURE 3 | Histopathological findings (tumefactive lesion in the left occipital lobe). Hematoxylin–eosin. Red arrow: plaque with loosing of neuropil and reactive gliosis. Blue arrow: normal myelinated CNS tissue (50× magnification). CNS, central nervous system.

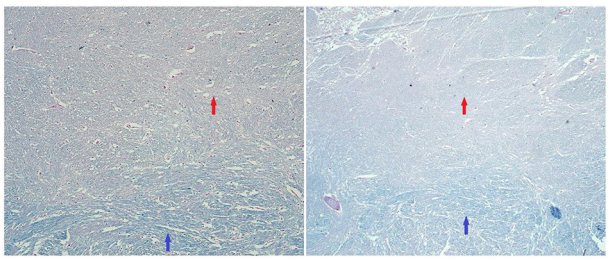

FIGURE 4 | Histopathological findings (tumefactive lesion in the left occipital lobe). Luxol fast blue/periodic acid–Schiff (PAS) staining. Red arrows: area of demyelination in plaque (pinkish color of PAS). Blue arrows: areas of normal myelination (bluish staining of myelin by luxol fast blue) (100× magnification/50× magnification).

confirmed the central nervous system demyelination without any evidence of neoplasm or other chronic disease.

DISCUSSION

This contribution presents the case report of a young female with TDLs. An extensive diagnostic work-up, including two biopsies and an autopsy, did not reveal any other explanatory diagnosis other than tumefactive MS. The report is unique due to subacute progressive TDLs of the brain and spinal cord, non-responsiveness to the high-efficacy drugs, and high diagnostic certainty due to multiple brain biopsies and an autopsy. Such a case report of a patient exhibiting similar TDLs has not been reported before.

In distinguishing between TDLs and other pathologies on MRI, the features listed above can be helpful along with follow-up imaging since TDLs tend to resolve in response to steroid therapy (6). However, the differentiation between TDLs and brain tumors by MRI alone may be difficult. One of the pathologies to be considered as a differential diagnosis of TDLs is primary central nervous system lymphoma (PCNSL) as cases of either concurrence of MS and PCNSL or demyelinating lesions preceding the development of PCNSL have been reported (7).

The value of advanced MRI techniques such as diffusion, perfusion imaging, or magnetic resonance spectroscopy has been studied in distinguishing between TDLs and brain tumors; however, it appears that those techniques still cannot provide definite diagnosis, and further studies are required to determine their additional value (8).

PET may also play some role in distinguishing TDLs from brain tumors (9). FLT tracer, which has been used in the diagnostic work-up in our patient, is generally referred to as a marker of proliferation in brain tumors; however, it should not be considered entirely specific as its increased uptake had also been observed in demyelinating lesions (10).

In the presented case, we observed several imaging features considerably atypical for TDLs like mostly homogenous enhancement, spectroscopy, and FLT-PET findings. Also, considering the constant progression of the mass lesions during the therapy leading finally to the development of obstructive hydrocephalus, the coincidence of tumor infiltration was suspected, and the brain biopsy was required to provide a definite diagnosis.

There is little comment on the effect of disease-modifying therapy on the evolution of TDLs. Some evidence supports that fingolimod should be avoided in MS patients with TDLs due to possible exacerbation (4). Patients with TDLs may have a better prognosis compared to MS patients without such lesions, especially when there is a good recovery from a tumefactive lesion (11, 12); however, there is a dearth of information on untreated TDLs in the literature.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because The manuscript presents a case report study. Written informed consent was not provided because According to the local ethics committees, the written informed consent is not necessary for a post-mortem case report study. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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CASE REPORT
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Case Report: *In Situ* Expression of a Proliferation-Inducing Ligand in Neuromyelitis Optica

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A proliferation inducing ligand (APRIL) mediates a key role in the generation and survival of antibody-inducing plasmocytes. Based on this, APRIL has been targeted in autoimmune diseases including multiple sclerosis (MS) and optic neuritis (ON). In MS lesions, APRIL has a new cellular target, the reactive astrocyte and mediates an immunosuppressive activity. Here, we analyzed APRIL expression in a case of neuromyelitis optica (NMO), another autoimmune neurodegenerative disease, showing selective aquaporin-4 depletion in the spinal cord, complement deposition and infiltration of polymorphonuclear cells. We analyzed by immunohistochemistry the presence of APRIL-producing cells, plasmocytes, astrocytes and the localization of secreted APRIL in a lesion from NMO. Plasmocytes were present close to APRIL-producing cells in meninges. However, our main observation was that APRIL targets reactive astrocytes in this lesion of NMO similarly to MS.

Keywords: neuromyelitis optica, TACI, astrocytes, B cells, APRIL (TNFSF13)

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INTRODUCTION

B cells are currently targeted with success in autoimmune diseases (1). The B-cell activation factor from the TNF family (BAFF, TNFSF13b) and a proliferation inducing ligand (APRIL, TNFSF13) are two related members from the TNF superfamily that play non-redundant role in humoral immunity (2). BAFF mostly acts on naive mature B cells, while APRIL acts on more differentiated B cells, the antibody-producing plasmocytes. These two molecules may be antagonized by the single agent atacicept, a soluble form of one of their common receptors, the transmembrane activator and CAML interactor (TACI, TNFRSF13b) (3). The completion of a recent phase II clinical trial in systemic lupus erythematosus revealed that atacicept reduces disease activity and flares with an acceptable safety profile (4). Atacicept was also tested in relapsing multiple sclerosis (MS) with the ATAMS trial (5). Consistent with a combined BAFF/APRIL blockade, the mature B-cell count and total immunoglobulins dropped in sera, indicative of an appropriate biological response. However and quite unexpectedly, an increased relapse rate was observed leading to an early trial halt. This suggested an alternative role for the BAFF/APRIL axis in the central nervous system (CNS). We recently showed that APRIL was selectively expressed in MS lesions, and induces an anti-inflammatory response by binding to reactive astrocytes (6). In an animal model of MS, we further observed disease worsening in the absence of APRIL, demonstrating an overall neuroprotective role for APRIL in the CNS. Such a new role for APRIL is a likely explanation, at least in part, for

the ATAMS trial failure observed in MS.

Concomitant to ATAMS was the trial ATON testing atacicept in optic neuritis (ON) with the exclusion of NMO (7). For safety reason, ATON was also halted once the increased relapsing events were noted in ATAMS. ATON premature analysis also revealed disease worsening with an extension to a relapsing-remitting MS-like syndrome in a significant fraction of treated patients. Contrary to MS, there is the strong association of NMO with a specific humoral immune response directed against aquaporin 4 (AQP4) expressed at the surface of astrocytes (8). Thus, atacicept might have a pronounced protective effect in principle in this disease. Based on this, a new form of soluble TACI, telitacicept, is currently tested in recurrent NMO (9). We analyzed APRIL expression in lesions present in the spinal cord from a NMO patient.

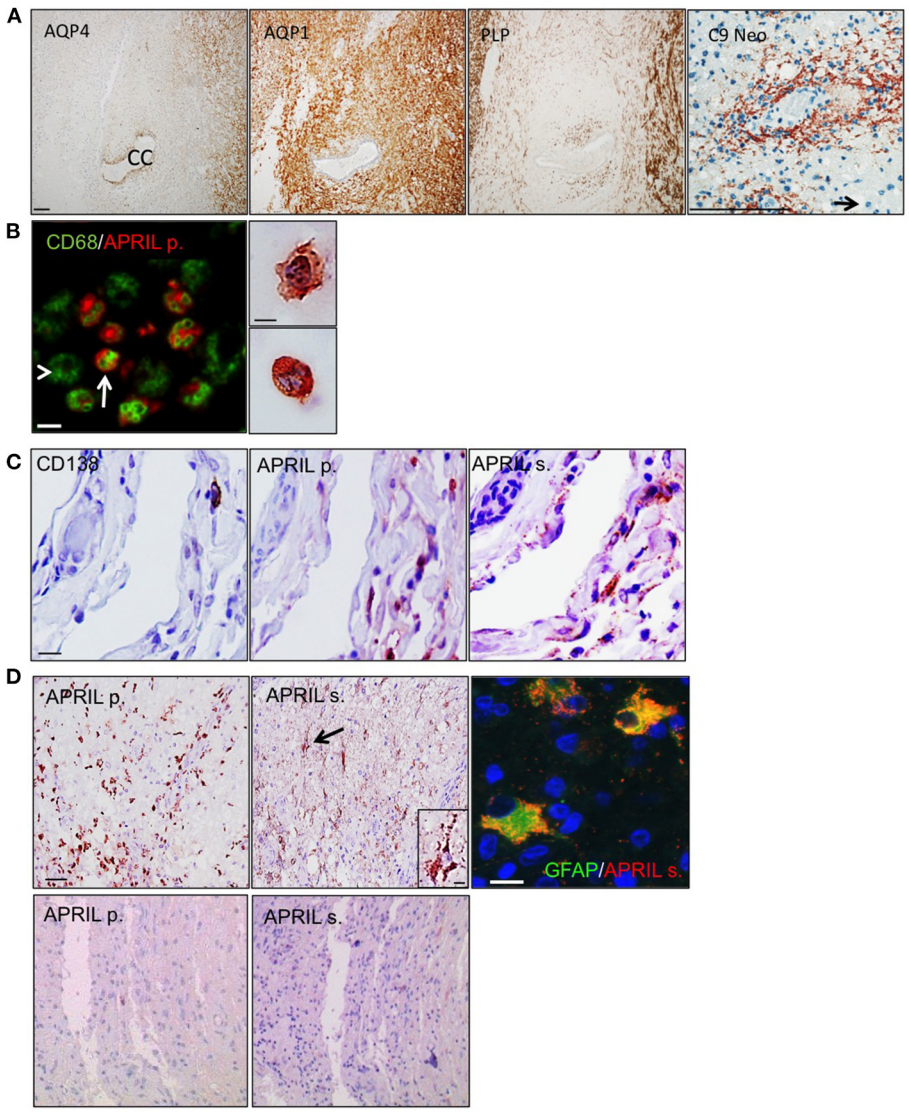

FIGURE 1 | APRIL targets reactive astrocytes in NMO lesions. Serial sections of a NMO biopsy harboring an active lesion were immunostained. **(A)** shows a widespread loss of aquaporin 4 (AQP4) associated to preservation of aquaporin 1 (AQP1), and proteolipid protein (PLP)-positive myelin sheaths. A vasculocentric (rosette-like) deposition of activated complement (C9 neo) is observed in an active lesion area rich in polymorphonuclear cells (scale bar = 100 μm). The central canal (CC) of the spinal cord and a polymorphonuclear cell (arrow) are indicated. **(B)** shows merge stainings for $CD68^+$ myeloid cells and APRIL-producing cells (APRIL p.) (scale bar = 10 μm). Arrow and arrowhead mark $APRIL^+$ and $APRIL^-$ $CD68^+$ myeloid cells, respectively. Right panel shows a high magnification of APRIL-producing cells with a macrophage (top figure) and polymorphonuclear (bottom figure) morphology (scale bar = 5 μm). **(C)** shows in meninges associated to the lesion stainings for plasmocytes (CD138), APRIL p. and secreted APRIL (APRIL s.) (scale bar = 10 μm). Upper panels **(D)** show in the parenchyma stainings for APRIL p. and APRIL s. (scale bar = 100 μm). Cells binding APRIL with a morphology of astrocytes are arrowed, showed in the high magnification insert (scale bar, 5 μm), and identified by GFAP costaining (scale bar = 5 μm). Lower panels **(D)** show an area outside lesions of the spinal cord stainings for APRIL p. and APRIL s. (scale bar 100 μm).

CASE REPORT

The patient was a female of 20 years harboring the clinical criteria for the diagnosis of a definite NMO, although at the time of her death AQP4 antibody testing was not yet established. Two weeks before her death, she experienced a massive relapse of myelitis, which broadly progressed and conducted the patient into coma. She had a disease duration of four years, and died from pulmonary embolism. The patient did not receive any immunosuppressive treatment. Autopsy demonstrated extensive lesions in the spinal cord, the brain stem and also large lesions in the forebrain hemispheres, which had been described previously by Misu et al., for the case 499 (10). At the spinal cord level, typical pathological features of NMO were seen with a widespread loss of AQP4 within and around the lesions, while AQP1 reactivity was partially spared (**Figure 1A**). Myelin sheaths assessed by proteolipid protein (PLP) immunoreactivity were preserved indicative of an early stage active lesion. Finally, a profound rosette-like perivascular complement activation (C9 neo reactivity) combined with an infiltration of polymorphonuclear granulocytes was also evidenced. To analyze APRIL expression, we used the pair of antibodies identifying APRIL-producing cells and secreted APRIL in tissues (11). APRIL-producing cells were part of the $CD68^+$ myeloid cell pool (**Figure 1B**). We identified these cells by morphology as macrophages/microglia and polymorphonuclear cells. The common APRIL target cells, $CD138^+$ plasmocytes, were sparsely distributed within meninges adjacent to lesions (**Figure 1C**). They were in close vicinity to APRIL-producing cells. We could also detect tissue retention of secreted APRIL in this area. This indicates that APRIL may sustain the survival of plasmocytes present in the CNS of NMO patients. In the parenchyma, APRIL-producing cells were highly abundant, representing as much as 50% of the total cellularity in some area (**Figure 1D** upper panels). There, plasmocytes were absent, but secreted APRIL targeted another cell type identified by staining for the glial fibrillary acidic protein (GFAP) as reactive astrocytes. Accumulation of secreted APRIL in astrocytes was quite high, filling up the entire cytoplasmic space of the cells. APRIL-producing cells and secreted APRIL were absent outside lesions from this spinal cord (**Figure 1D** lower panels). Hence, APRIL also targets astrocytes in NMO lesions.

DISCUSSION

Based on this study, APRIL may provide a favorable environment for plasmocytes in NMO lesions, due to the close vicinity between APRIL-producing cells and plasmocytes within meninges. An APRIL-targeting agent may reduce the number of CNS-infiltrated plasmocytes in NMO. However, the targeting of reactive astrocytes by secreted APRIL also indicates that APRIL may induce an anti-inflammatory response in NMO lesions. Taken together, our data highlight that trials targeting APRIL in the CNS have to be conducted with extreme cautiousness.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethics comittee, university of Vienna, Austria. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LB performed experimentation. HL provided the case. HL and RM analyzed the data. BH designed the study, analyzed the data, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: BH has received speaker bureau honoraria from Merck Serono who is developing atacicept.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Neurology

CASE REPORT
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Severe Multiple Sclerosis Relapse After COVID-19 Vaccination: A Case Report

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We describe a case of acute relapse in a woman with Multiple Sclerosis (MS) shortly after the mRNA COVID-19 vaccination. The patient received a diagnosis of MS in November 2016 at the MS Centre of the A. Cardarelli Hospital (South of Italy). Since that moment, her clinical conditions and pharmacological therapies have been managed at this MS centre where, according to national recommendations, in April 2021, the patient received the BNT162b2 vaccine. Almost 48 h after receiving the vaccine, the patient developed paraesthesia and weakness in her left arm and limbs. The neurological examination revealed walking difficulties while the MRI showed three new voluminous enhancing lesions. After having received methylprednisolone iv for 5 days, the patient's neurological symptoms fully recovered. Along with the implementation of COVID-19 vaccination programmes among vulnerable population, further studies are needed in order to improve our knowledge on the benefit/risk ratio of COVID-19 vaccines.

Keywords: COVID-19 vaccine, multiple sclerosis, acute relapse, cladribine, case report

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INTRODUCTION

Following the approval of COVID-19 vaccines across EU countries, vaccination programmes have been started in order to identify vulnerable people at highest risk from serious illness or death from COVID-19. According to recent recommendations from the Italian Ministry of Health and an Italian expert consensus, people with Multiple Sclerosis (MS), especially those with disabilities, progressive forms of the disease, older age, and comorbidities, were considered to be the category with the highest priority during the second phase of the Italian immunization programme (1, 2).

At this moment, very limited data on the effectiveness and safety profile of COVID-19 vaccines are available for MS patients. In this report, we describe a case of severe relapse occurred in a MS patient who had received COVID-19 vaccine. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

CASE PRESENTATION

In November 2016, a 26-year-old woman presented to the MS Centre of the A. Cardarelli Hospital (Italy) with tinnitus and dizziness. The MRI showed multiple periventricular, brain stem, and spinal cord hyperintense T2/FLAIR lesions, some of which were active. She was diagnosed with MS and started the treatment with fingolimod. In June 2018, after experiencing a clinical relapse,

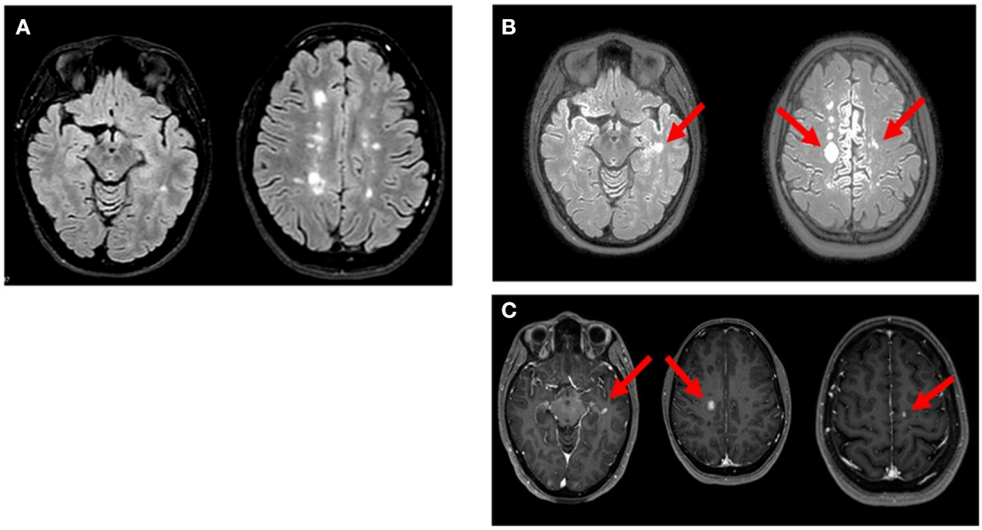

FIGURE 1 | Axial MRI images of reported patient. (**A**; Oct 2020)**:** multiple hyperintense white matter lesions were observed in T2/FLAIR weighted scan. (**B**; Apr 2021)**:** T2/FLAIR weighted scan showed new three lesions in left temporal lobe and bilateral precentral cortex (arrows). (**C**; Apr 2021)**:** gadolinium-enhancing lesions (arrow) corresponding to the new hyperintense lesions on FLAIR were noted in T1 weighted postcontrast images.

she started the first cycle of cladribine, which was well-tolerated. At 6-month, the MRI showed two new periventricular T2/FLAIR lesions with enhancement. No new lesions were present in the 1-year follow-up brain MRI. In June 2019, the patient was treated with a second cycle of cladribine tablets. Until March 2021 she showed neither clinical nor radiological progression of disease.

On April 8th, 2021, she received COVID-19 BNT162b2 vaccine. Approximately 48 h after receiving the first dose of BNT162b2, the patient developed paraesthesia in her left arm followed by weakness in her left upper and lower limbs. Five days after the onset of symptoms, the neurological examination revealed walking difficulties and strength of 3/5 in the left upper limb and 2/5 in the left lower limb, left hyperreflexia in deep tendon reflexes and loss of vibrations in the left hemisome. The MRI showed three new voluminous enhancing lesions: left (11.5 × 8 × 8.5 mm) and right (17 × 14 × 13 mm) frontal cortical lesions and left temporal lesion (**Figure 1**). Blood tests before and after the vaccination were performed (**Tables 1, 2**). The patient received methylprednisolone iv for 5 days with full recovery of neurological symptoms. Due to the new relapse and the steroid treatment, we decided not to adhere to the vaccination schedule as the patient did not take the second dose of BNT162b2.

DISCUSSION

We described a case of severe acute relapse occurred in a young patient after mRNA-based COVID-19 vaccine. Among MS patients, relapses still represent one of the most unpredictable aspects to be managed. Indeed, their prompt recognition and treatment are essential in order to achieve good clinical outcomes. Many risk factors for acute relapse were identified, including female sex (women are more likely to experience relapses throughout the course of the disease), smoking status and the discontinuation of highly effective therapy (3–5).

Adverse events following mRNA-based COVID-19 vaccines are generally mild and consist in injection site reactions, headache and asthenia (6). However, data on the efficacy and safety of these vaccines in MS patients are rather limited (7). To our knowledge, only one observational study was carried out among 555 MS patients. The study was conducted in one clinical Centre in Israel where all patients received the BNT162b2 vaccine. The safety profile of COVID-19 vaccine resembled that observed in patients enrolled in premarketing clinical trials. Indeed, the most common AEFIs were injection site reactions, fatigue, and headache. Acute relapses were detected in 2.1% of patients after the first vaccine dose and in 1.6% of patients after the second dose. The comparison of these rates with those of previous years highlighted no differences, although the short follow-up period could have resulted in lower relapses' rate (8). In our case, the early onset of neurological symptoms after the vaccination questioned the causal association with the vaccine but the presence of multiple active lesions on brain MRI undoubtedly represents a recent activation of MS. In addition, mRNA-based COVID-19 vaccines might elicit a strong T and B cells response (9), which in turn could underpin the development of autoimmune processes (10). The immunophenotype performed during the relapse showed a mild lymphopenia, mainly affecting the activated T cell compartment, both CD4 and CD8 T cells (**Table 1**). This phenomenon could be secondary to increased migration and localization of autoreactive T cell into CNS during the relapse. After 4 weeks from vaccination antibodies against Spike-SARS-COV-2 protein were present, although at low titer (**Table 2**). As a pulse therapy, cladribine may not be able to contain a strong inflammatory

TABLE 1 | Lymphocytes subsets before and after the vaccination and during the relapse.

	Before the vaccine	During relapse	After 4 week the vaccine
WBC	4.79 × 10^3/ul	5.170 × 10^3/ul	5.40 × 10^3/ul
Lymphocytes	1.520 cell/ul	960 cell/ul	1.34 cell/ul
CD3	979.2 cell/ul	691.2 cell/ul	951.4 cell/ul
CD8	164.16 cell/ml	112.8 cell/ul	151.956 cell/ul
CD4	547.2 cell/ul	403.2 cell/ul	562.8 cell/ul
CD19	115.2 cell/ul	105.6 cell/ul	134 cell/ul
CD20	115.2 cell/ul	105.6 cell/ul	134 cell/ul
CD3/HLA-DR (activated lymphocytes)	60.8 cell/ul	19.2 cell/ul	53.6 cell/ul

TABLE 2 | Ig anti-Spike SARS COV2 before and after the vaccination (range < 0.80).

	Before the vaccine	After 4° week the vaccine
Ig against Spike SARS-COV-2	0.40 U/ml	17.14 U/ml

response triggered by the vaccine, leading to a relapse. On the other hand, among DMTs, cladribine is associated with a low risk of infection and severe lymphopenia (11). In addition, since systemic infections, such as COVID-19, can worsen MS, the vaccination can be able to reduce the risk of relapses by dropping the risk of infections (8). Thus, at this moment, currently available data show that COVID-19 vaccines seem to be not associated with an increased risk of acute relapses.

To our knowledge this is the first case describing the occurrence of a severe acute relapse in a young patient after mRNA-based COVID-19 vaccine, even though cases of MS relapses occurred shortly after other COVID-19 vaccines can be found in the literature. Indeed, Etemadifar et al. described the case of a 34-year-old woman suffering from RRMS and treated with rituximab, who had received her first dose of adenovirus-vectored COVID-19 vaccine Gam-COVID-Vac (Sputnik V) 3 days before experiencing her latest MS relapse episode, preceded by mild symptoms (fatigue, myalgia, generalized weakness, etc.). As for our patient, the woman received corticosteroid therapy for five consecutive days, and her neurological deficits slightly improved. However, differently from the decision made by our neurologists, this woman received also her second dose of Gam-COVID-Vac after discontinuation of oral steroid taper (12). On the other hand, data from an interim analysis of the efficacy and safety of the ChAdOx1 nCoV-19 vaccine from four ongoing blinded, randomized, controlled trials (COV001, COV002, COV003, and COV005) reported a case of transverse myelitis occurred 10 days after the first dose of ChAdOx1 nCoV-19 in a patient with MS, that was determined to be unlikely to be related to vaccination by an independent committee of neurological experts (13). We are aware that further studies are necessary in order to better define the efficacy and safety profile of COVID-19 vaccines among MS patients, also in terms of risk of acute relapse.

CONCLUSION

To our knowledge, this is the first report of acute relapse following COVID-19 vaccine in a patient with a long-standing history of MS. Current knowledge seems to suggest that MS patients had similar rates of AEFIs to the general population following BNT162b2 vaccination. Our case provides new evidence on COVID-19 vaccination in MS patients but new knowledge in this field is strongly needed. Thus, the strict monitoring of MS patients who are receiving now COVID-19 vaccination should be taken into account by neurologists during their routine clinical practice.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GM, VM, MDB, SS, OM, CS, and AC: drafting the work and revising it for important intellectual content. GM, CS, and AC: substantial contributions to the acquisition, analysis, or interpretation of data for the work. GM, VM, MDB, SS, OM, CS, and AC: final approval of the version to be published. GM, VM, MDB, SS, OM, CS, and AC: agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GM and AC: developed the concept. GM, CS, and AC: wrote the paper. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Neurology

CASE REPORT
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Case Report: Paraneoplastic Hashimoto's Encephalopathy Associated With Lymphomatosis Cerebri With Periodic Synchronous Discharges Resembling Creutzfeldt–Jakob Disease

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Hashimoto's encephalopathy (HE) is an autoimmune encephalopathy that presents with various clinical symptoms, including cognitive deterioration, convulsive seizures, and personality changes. HE is associated with thyroid autoimmunity; however, few cases have been reported to develop as paraneoplastic syndrome. Herein, we report the case of a 73-year-old woman with onset of rapidly progressive dementia. Brain magnetic resonance imaging showed diffuse T2 hyperintensity areas involving the bilateral cerebral white matter, right midbrain tegmental area, left cerebral peduncle, and right middle cerebellar peduncle without clear diffusion hyperintensities and gadolinium enhancement. Her neurological symptoms worsened rapidly, and she presented with the apallic syndrome. Electroencephalogram showed periodic synchronous discharge, suggestive of Creutzfeldt–Jakob disease. However, a brain biopsy revealed infiltration of atypical lymphoid cells expressing CD20, and the anti-NH2 terminal of the α-enolase antibody was detected, diagnosing the complication with lymphomatosis cerebri and HE. High-dose intravenous methylprednisolone therapy and oral prednisolone with whole cranial irradiation enabled her to have simple conversations and consume food orally; however, severe cognitive impairment persisted. Although HE is a rare complication of malignant lymphoma, clinicians should be aware that it could be strongly suspected if the clinical symptoms worsen in the absence of imaging changes.

Keywords: Hashimoto's encephalopathy, lymphomatosis cerebri, anti-NH2-terminal of α-enolase antibody, periodic synchronous discharge, Creutzfeldt–Jakob disease

INTRODUCTION

Hashimoto's encephalopathy (HE), a steroid-responsive disorder, is an autoimmune encephalopathy associated with Hashimoto's thyroiditis in the euthyroid state (1, 2). As HE presents a variety of clinical symptoms, clinicians sometimes misdiagnose it as other neurological diseases, such as seizures, Alzheimer's disease, limbic encephalitis, psychiatric diseases, or

Creutzfeldt–Jakob disease (CJD) (3–6). At present, elevation of serum anti-thyroid autoantibodies, such as the anti-thyroid peroxidase (TPO) antibody and/or anti-thyroglobulin (Tg) antibody, is useful and essential for the diagnosis of HE; however, the anti-TPO antibody or anti-Tg antibody is known to be detected in approximately 10% of normal adults (7–9). The specificity of serum diagnosis of HE by anti-thyroid autoantibodies is low. However, Yoneda et al. reported that the serum anti-NH2 terminal of the α-enolase (NAE) antibody is a specific biomarker for HE (with specificity of 91% and sensitivity of 50%) (10, 11). Therefore, serum diagnosis of HE has recently become easier.

Lymphomatosis cerebri (LC), a rare variant of primary central nervous system lymphoma (PCNSL) that represents 2–3% of all brain tumors (12), was initially described in 1999 (13). Only less than 50 LC cases have been reported by 2019 (14). PCNSL is generally easy to diagnose with the mass formation in the brain with homogeneous contrast effects on gadolinium-enhanced MRI (15). In contrast, diagnosing LC is challenging as it shows diffuse T2 high-intensity signals without obvious contrast effect or mass formation even if a contrast effect is present (16).

As HE sometimes shows diffuse non-specific T2 high-intensity signals in the bilateral cerebral white matter on brain MRI (3), it is often impossible to discriminate between HE and LC using only image findings. However, HE is an autoimmune disease, whereas LC is a malignant neoplastic disease; therefore, HE and LC are completely different diseases, and to the best of our knowledge, LC-related HE has not been reported before. Herein, we report a case of paraneoplastic encephalopathy with anti-NAE antibody complicated with LC, which was diagnosed using brain biopsy. The clinical presentation was similar to that of CJD and responded to steroid therapy. We believe that, similar to this case, HE develops as a paraneoplastic neurological syndrome of LC.

CASE PRESENTATION

A 73-year-old woman with a history of type 2 diabetes and non-tuberculous mycobacterial infection presented to our hospital with subacute progressive dementia characterized by nausea, dizziness, headaches, loss of recent memory, and behavioral changes for 3 months. On admission, her vital signs were within the normal range. Neurological examinations confirmed disturbance of consciousness [Glasgow Coma Scale (GCS) score of 14 (E4V4M6)], increased deep tendon reflex in the left upper limb and bilateral lower limbs, positive pathological reflexes (Babinski and Chaddock reflexes), cerebellar ataxia in the right upper limb, apathy, perseveration, acalculia, and finger agnosia. We did not observe cranial nerve palsies, muscle weakness, or sensory disturbances.

Initial laboratory tests did not reveal any specific abnormalities. Complete blood count, liver function, and renal function were within the reference range (RR). Thyroid function was in a euthyroid state, and no elevation of serum anti-TPO antibody and anti-Tg antibody was observed in electrochemiluminescence immunoassay (<9.0 and <10.8 IU/ml, respectively; RR < 16.0 and <28.0 IU/ml, respectively). The concentrations of lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) were not elevated (134 IU/L and 206 U/ml, respectively; RR = 100–220 IU/L and 121–613 U/ml, respectively), and human immunodeficiency virus was negative. Cerebrospinal fluid (CSF) analyses showed elevated total protein levels (TP = 52 mg/dl, RR = 10–40 mg/dl) and slightly high levels of sIL-2R (61 U/ml, RR < 60.4 U/ml); however, the LDH concentration was 42 U/ml (RR = 8–50 U/ml). CSF analyses also demonstrated normal cell counts (1 leucocyte/μl) without atypia and no amplification of polymerase chain reaction for the John Cunningham (JC) virus. Brain MRI on initial presentation revealed diffuse non-enhancing T2/fluid-attenuated inversion recovery hyperintense lesions in the bilateral cerebral white matter, left temporal pole, and right middle cerebellar peduncle (**Figures 1A–F**). On diffusion-weighted imaging (DWI), these lesions showed faintly high intensities; however, they could be explained by T2 shine-through (**Figures 1G–I**).

Her cognitive impairments progressively worsened 1 month after admission. She simultaneously presented with a GCS score of E1M1V4 and the apallic syndrome. Despite our best efforts, we could not obtain any specific findings to confirm the diagnosis. One and a half months after admission, her electroencephalogram (EEG) showed bilateral periodic synchronous discharge (PSD), typically suggestive of CJD (**Figure 2**). To confirm the diagnosis as "CJD," we measured the CSF total tau protein and 14-3-3 protein levels. However, no elevation of the concentrations of these proteins in the CSF was observed (total tau = 708 pg/ml, RR < 1,300 pg/ml; 14-3-3 protein < 500 μg/ml, RR < 500 μg/ml). Only a half-day after initiating high-dose methylprednisolone (mPSL) therapy (1,000 mg/day), her consciousness improved rapidly; therefore, we treated her with an additional 2 days of high-dose mPSL therapy. She maintained a good state of consciousness during the 3 days of therapy. However, her consciousness worsened soon after high-dose mPSL therapy. These clinical characteristics suggest a lower possibility of CJD.

To pathologically evaluate the abnormalities seen on MRI, we performed a brain biopsy of the left frontal lobe. Pathological findings revealed infiltration of atypical lymphoid cells with large and irregularly shaped nuclei (**Figure 3A**). These atypical lymphoid cells were positive for cluster differentiation (CD) 20, with 80–90% of the Ki-67 proliferation index (**Figures 3B,C**). A few CD3-positive reactive T cells were also observed and did not show irregularities (**Figure 3D**). Moreover, the CSF data were reexamined when the brain biopsy showed clearer abnormalities (cell count = 10 leucocytes/μl, TP = 68 mg/dl, sIL-2R = 121 U/ml, LDH = 66 U/ml) than before. Based on these pathological findings, CSF abnormalities, and the distribution of white matter lesions on MRI, we diagnosed her with primary central nervous system B cell lymphoma of the LC type.

To treat LC, we administered two courses of high-dose mPSL (1,000 mg/day for 3 days), followed by 60 mg (2 mg/kg) prednisolone (PSL) for 63 days with a taper of every 5 mg for 7 days and whole cranial irradiation. Contrast-enhanced MRI performed 1 month after brain biopsy revealed a spotty gadolinium enhancement in the left periventricular

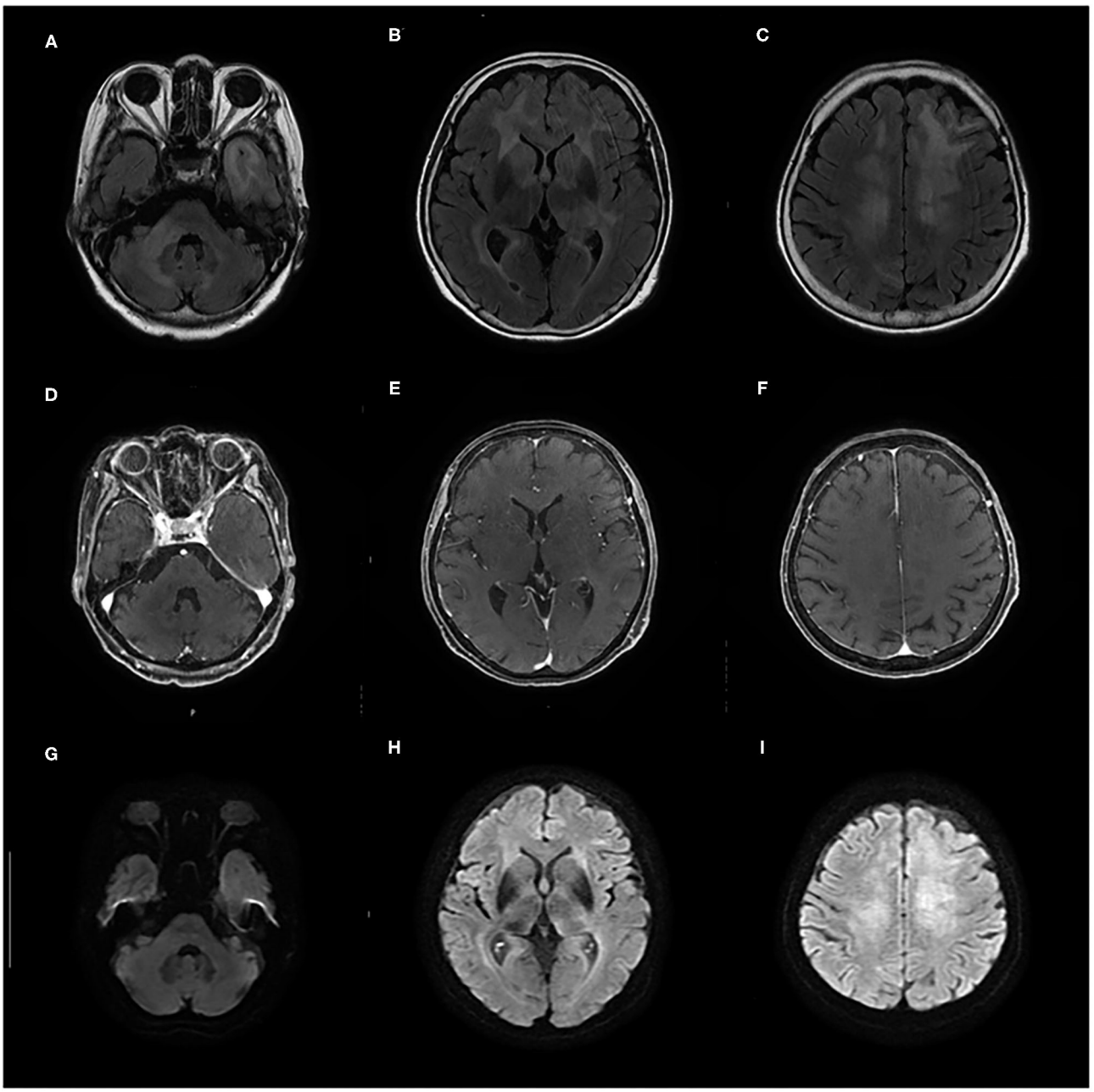

FIGURE 1 | (A–F) Contrast-enhanced brain MRI taken on admission shows diffuse T2/fluid-attenuated inversion recovery (FLAIR) hyperintense lesions in bilateral cerebral white matter, left temporal pole, and right middle cerebellar peduncle without gadolinium enhancement. **(G–I)** On diffusion-weighted imaging (DWI), these lesions show faintly high intensities that can be explained by T2 shine-through.

white matter without high intensity on DWI (**Figures 4A–C**). Two months after the treatment initiation, the anti-NAE antibody was detected in the serum before mPSL treatment, revealing the presence of HE. We performed thyroid sonography, and it was characterized by isoechogenicity, very slightly internal heterogeneity, no diffuse goiter, and a few cysts (**Supplementary Figure 1**). Moreover, a second check showed the serum anti-TPO antibody and anti-Tg antibody to be within the RR in chemiluminescent immunoassay (0.72 and <0.50 IU/ml, respectively; RR < 4.11 and <5.61 IU/ml, respectively). At that time, she recovered from the apallic syndrome, had simple conversations, and consumed food orally. However, her consciousness worsened again when PSL was reduced to 15 mg/day. No evident new abnormality, including aggravation of LC, was found on the re-performed contrast-enhanced MRI. After another high-dose mPSL therapy, her consciousness

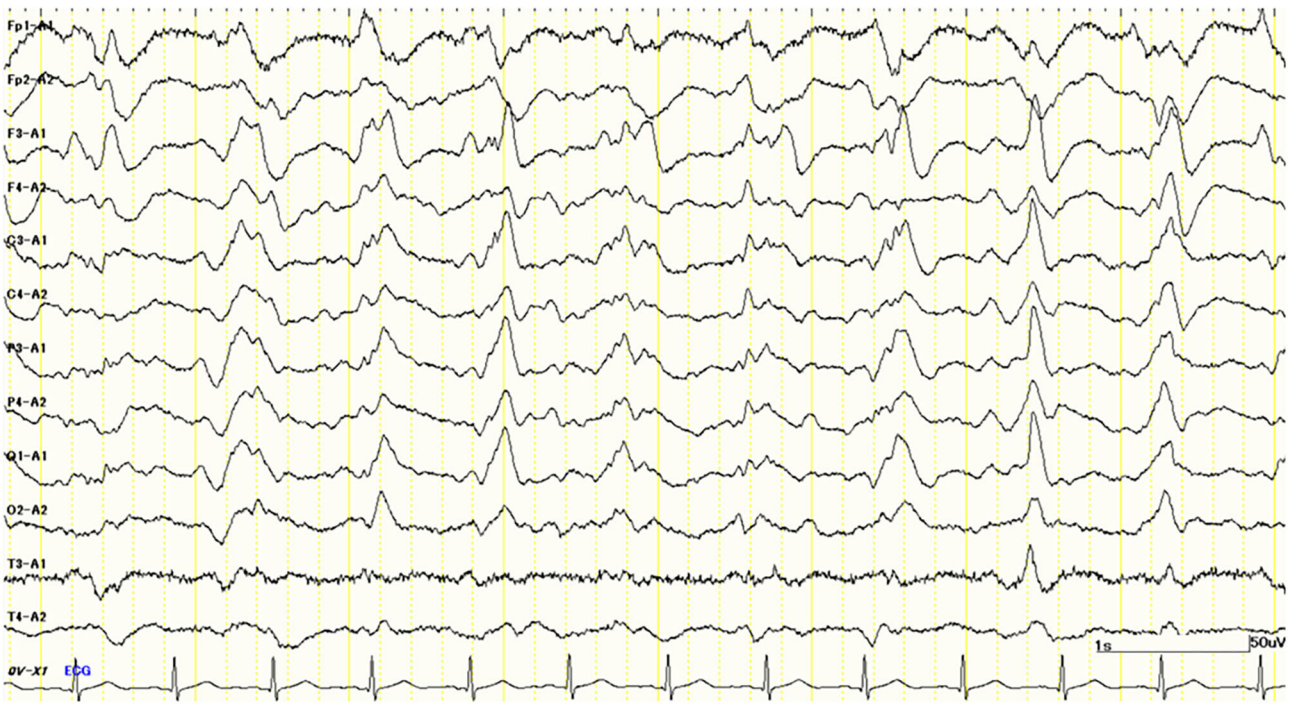

FIGURE 2 | Electroencephalography (EEG) study 1.5 months after admission shows periodic synchronous discharge (PSD) suggesting Creutzfeldt–Jakob disease (CJD).

improved; therefore, we considered the re-exacerbation of her consciousness as due to HE relapse, even though we performed a third check of the serum anti-TPO and anti-Tg antibodies, which were within the RR in chemiluminescent immunoassay (0.44 and <0.50 IU/ml, respectively). Although her consciousness improved, severe cognitive impairment persisted, and she still needed careful assistance for all her daily living activities. The clinical timeline is shown in **Supplementary Figure 2**.

DISCUSSION

We present a case of a rare complication of the anti-NAE antibody-related autoimmune encephalopathy and LC showing a CJD-like clinical presentation and PSD on EEG. Since the detection of the anti-NAE antibody and the presence of PSD on EEG suggested the same mechanisms of encephalopathy as HE, we diagnosed this anti-NAE antibody-related autoimmune encephalopathy as that.

EEG is occasionally used in neurological disorders associated with convulsive seizures and impaired consciousness. PSD on EEG can be observed particularly in diseases such as CJD, subacute sclerosing panencephalitis (SSPE), and Alzheimer's disease (17, 18). The EEG of HE shows a variety of abnormal findings in ∼90% of cases, and the basal waves tend to slow activities. However, some HE cases present PSD on EEG and require differentiation from CJD, similar to our case (6, 19, 20).

As LC has been recently reported as a new disease concept, a variant type of PCNSL, as reported by Bakshi et al., it is often overlooked as another disease (13). As far as we investigated in PubMed using the term "lymphomatosis cerebri," only 71 cases in 43 articles were reported until 2020, and no complications with HE were found (13, 14, 16, 21–60).

In these reports, seven mentioned the use of EEG for LC (13, 27, 32, 48). Most of these cases have reported generalized diffuse slowing activities with non-specific abnormalities (13, 27, 32). Deutsch et al. reported that four cases of LC on EEG were observed only with diffuse slowing without PSD, and they described that the presence of PSD could be an important differential point between LC and CJD (27). However, Revero et al. reported a case showing PSD in the "T" cell type of LC (48). In the present case, although the possibility of the B cell type of LC-derived PSD could not be ruled out, it was appropriate that PSD was derived from the anti-NAE antibody-related autoimmune encephalopathy diagnosed as HE.

At present, it is said that the positive serum levels of the anti-thyroid antibodies are essential for HE diagnosis (61). In our case, although repetitive measurements of the anti-thyroid autoantibodies in different ways were performed three times, all of these were negative. Admittedly, the presence of Hashimoto's thyroiditis could not be denied from the slight heterogeneity based on the thyroid ultrasonographic findings, but, to our knowledge, no report has made the diagnosis of HE only from the ultrasonographic findings without positive anti-thyroid autoantibodies. Moreover, unless the paraneoplastic syndrome exists, the neoplasm and autoimmune encephalopathy rarely co-occur. Therefore, the possibility of the thyroid autoimmunity

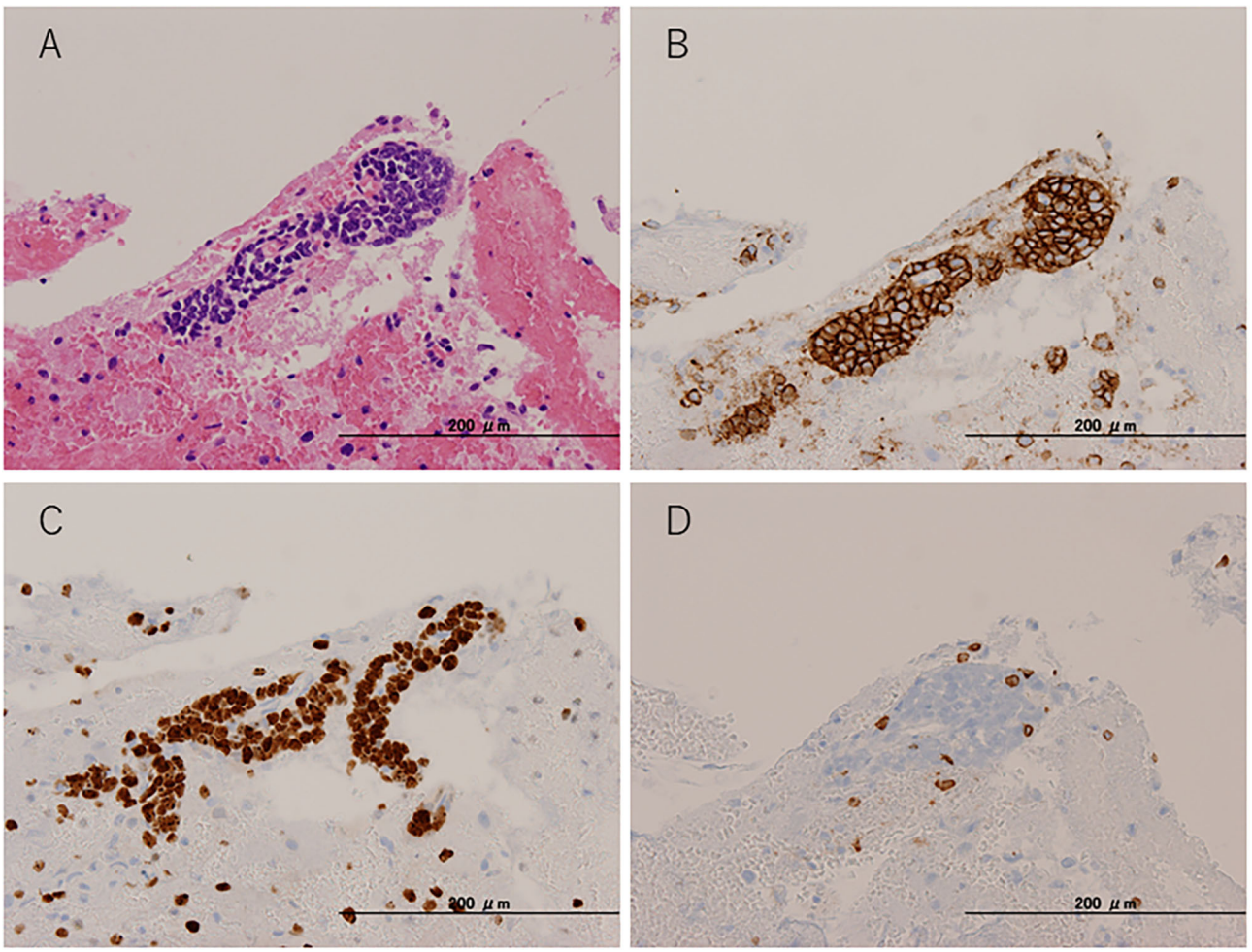

FIGURE 3 | Pathological findings. Brain biopsy from the left frontal lobe. **(A)** Hematoxylin and eosin staining. **(B)** CD20 immunohistochemical staining. **(C)** Ki-67 immunohistochemical staining. **(D)** CD3 immunohistochemical staining.

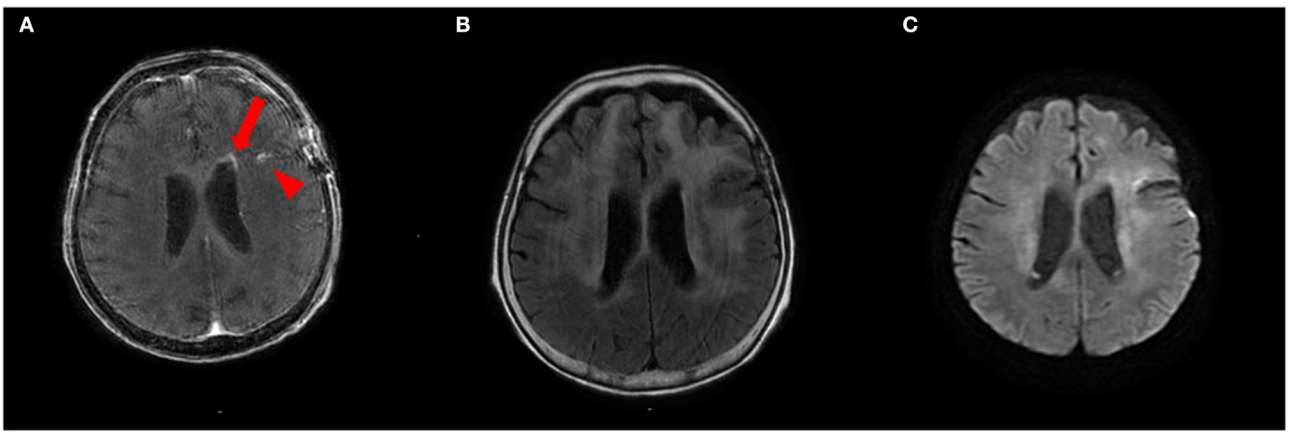

FIGURE 4 | (A,B) Contrast-enhanced brain MRI recorded 1 month after brain biopsy shows a spotty gadolinium enhancement in the left periventricular white matter (*arrow*) and post-biopsy scar (*arrowhead*) **(A)** with T2 hyperintensities **(B)**. **(C)** This lesion does not show abnormal hyperintensities on diffusion-weighted imaging (DWI).

causing the autoimmune encephalopathy was very low. Strictly speaking, the term HE might not be used for this case. At present, paraneoplastic encephalopathy with anti-NAE antibody may be more appropriate. However, the presence of anti-NAE antibodies has high specificity (∼90%) for the serum diagnosis of HE (10, 11). Hence, because of the detection of the anti-NAE antibody and PSD on EEG, the same mechanisms of autoimmune encephalopathy were suspected as the anti-thyroid autoantibody-positive "normal" HE. Although anti-thyroid autoantibodies were not detected, the detection of anti-NAE antibodies permitted the diagnosis of HE or some autoimmune encephalopathy extremely similar to HE, and continued steroid treatment led to the improvement of clinical symptoms.

In our case, the possibility that the primary intracerebral inflammation by HE caused secondary oncogenesis of lymphocytes was low. If HE caused malignant lymphoma, the anti-thyroid autoantibodies should have been detected similar to normal HEs. Patients with malignant lymphomas have a potential risk of various autoimmune diseases (62, 63). Furthermore, the clinical presentation of malignant lymphoma sometimes develops from complicated autoimmune disorders before the tumor itself (64). Although the mechanisms of anti-NAE antibody production are not clear, our case might have developed as a paraneoplastic neurological syndrome of LC.

The elevation of sIL-2R levels in PCNSL is well-known. For diffuse large B cell lymphoma of PCNSL, Sasagawa et al. reported that the cutoff value of sIL-2R in the CSF was 60.4 U/ml (sensitivity = 94.7%, specificity = 84.6%) (65). It might not have been typical that the concentrations of initial sIL-2R in the CSF in our case were only slightly high; although, its elevation may be observed non-specifically in neurosarcoidosis and meningitis (66). Currently, the levels of IL-10 in the CSF have been reported as a more useful biomarker for the initial screening of PCNSL (cutoff = 3 pg/ml, sensitivity = 94.7%, specificity = 100%) (65). If the levels of IL-10 in the CSF were measured during the first screening, LC could have been diagnosed earlier.

CONCLUSION

In conclusion, we report a case of a rare complication of HE and LC presenting with CJD-like clinical presentation and PSD. Although the initial presentation of subacute progressive dementia and EEG features was consistent with CJD, the CSF abnormalities, particularly total tau protein and 14-3-3 protein, and steroid responsiveness were not typical of CJD. Physicians should be aware of the possibility of PCNSLs and assess the total tau protein, 14-3-3 protein, sIL-2R, and IL-10 in the CSF at the first screening. Moreover, when the clinical presentation worsens without the aggravation of image findings, physicians should consider the complications of HE. Accurate and early diagnosis and appropriate treatment can improve the clinical outcomes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fujiyoshida Municipal Medical Center. The patient provided their written informed consent to participate in this study. Written informed consent was obtained from the individual's next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

RA, ST, SK, SY, and KO were the attending physicians of the patient, collected the patient data, and decided on a treatment policy. MY measured the anti-NAE antibody levels. KT assessed thyroidal function and proposed critical opinion regarding thyroid disease. RA and KT wrote the first version of this manuscript and played major roles in the conception of the manuscript. All authors have read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.701178/full#supplementary-material

Supplementary Figure 1 | B-mode of ultrasonographic image of the thyroid gland.

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CASE REPORT
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Case Report: The Use of Rituximab in Antibody-Negative Autoimmune Encephalitis

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Antibody-negative autoimmune encephalitis (AE) is challenging to diagnose because clinically suspected antibody-negative AE cases are difficult to confirm. If not treated properly, like antibody-positive AE, antibody-negative AE can cause irreparable damage to patients. Previously, immunotherapy was effective in treating patients with antibody-negative AE. We present the case of a 63-year-old man who was admitted to our hospital with altered cognition. He was diagnosed with antibody-negative AE based on CSF, brain MRI, and B-cell counts; autoimmune diseases with similar clinical symptoms were ruled out. He was treated with immunotherapy, especially rituximab, for antibody-negative AE. After 3 weeks of treatment, his mental state and brain MRI results, concomitant with a decrease in CD19+/CD20+ B-cell counts. This case report shows that patients with antibody-negative AE may respond to rituximab, similar to those with antibody-positive AE. Thus, potentially undetected antibodies could be responsible for the treatment outcome.

Keywords: autoimmune encephalitis, antibody-negative, brain MRI, CD19+/CD20+, rituximab, treatment

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INTRODUCTION

Autoimmune encephalitis (AE) has recently emerged as a major cause of non-infectious encephalitis (1, 2). Because it is difficult to diagnose AE with only the clinical presentations, it is challenging to discern whether the symptoms are due to the underlying disease or triggered by auto-antibodies. Although AE diagnostic methods are advanced, the knowledge on antibody-based diagnosis is limited (1, 3). Moreover, cases of clinically suspected antibody-negative AE are difficult to confirm. Untreated, AE can cause irreversible neurological deficits. The management of antibody-negative AE is still not substantiated (1). However, immunotherapy was successful in 50% of antibody-negative AE patients suggesting that potentially undetected antibodies could be responsible for the treatment outcome (4). The repression of autoantibody production by long-lived plasma cells (half-life of > 6 months) was a key component of treatment. The efficacy of rituximab, an anti-CD20 B cell-targeting monoclonal antibody, was demonstrated by improving neurological symptoms and brain MRI findings (5). Mechanistically, rituximab lowered the systemic humoral immune response (6). Herein, we present a rare case of antibody-negative AE treated with rituximab, showing a correlation between the improved brain MRI results and decreased CD19+/CD20+ B-cell counts.

CASE REPORT

A 63-year-old man was admitted to our hospital with altered cognition for the previous 4 months. He was disoriented in time and space and unable to recall any words after 3 min; in addition, he had a progressive headache with nausea and vomiting for 1 week. He had no history of underlying diseases. The day after admission, he entered a state of stupor [Glasgow Coma Scale (GCS): E2V2M2] with respiratory failure.

Laboratory tests, including malignancy workup [i.e., Ri, Yo, Hu, Ma2/Ta (PNMA2), LGI1, CV2/CRMP5, amphiphysin, NMDAR, GABAR, recoverin, CASPR2, and AMPAR2] and vasculitis workup (i.e., ESR, CRP, RF, ANA, C3, C4, CH 50, ANCA, RPR/VDRL, protein electrophoresis) yielded negative results. Brain MRI (T2-FLAIR) revealed abnormal hyperintensity with expansion in the hippocampi, temporal cortex, medial thalami, right insular cortex, left pulvinar, and left parietal lobe, without restricted diffusion (not shown) or contrast enhancement (**Figures 1A,B**). Brain MRI (T2-FLAIR) demonstrates the disappearance of hyperintense and expansion lesions after treatment for autoimmune encephalitis, especially in the medial thalami, right insular cortex, and left pulvinar. Brain MRI (T2-FLAIR) also shows T2-FLAIR hyperintensity with atrophy in the left medial temporal lobe (white arrow), right medial temporal lobe (white arrowhead), and left parietal lobe (**Figures 1C–F**).

A lumbar puncture showed no evidence of infection (white blood cells: 0 cells/μL) or malignant cells. Blood culture, urine culture, and CSF were negative for HSV-1, HSV-2, HHV-3, HHV-6, HHV-7, HHV-8, Epstein-Barr virus, cytomegalovirus, Enterovirus, HBV, HIV, HTLV, *Treponema pallidum*, human polyomavirus 2, *Mycobacterium tuberculosis*, *Borrelia burgdorferi*, *Anaplasma phagocytophilum*, tick-borne encephalitis virus, and polyomavirus BK. The CSF was also negative for antibodies, including Ri, Yo, Hu, Ma2/Ta (PNMA2), LGI1, CASPR2, recoverin, Sox1, Titin, Zic4, DNER/Tr, amphiphysin, CV2/CRMP5, GAD65, NMDAR, GABAR, IgLON5, AMPAR2, DPPX, glycine receptor, and mGluR5. Finally, additional auto-antibody detecting tests were performed to check for an AE with the patient's serum (7). A tissue-based assay was initially performed to screen for AE. Then, cell-based immunoassay and immunoblotting were performed to detect synaptic and intracellular auto-antibodies. In cases of an unknown auto-antibody being identified in the tissue-based assay, further tests were performed by staining cultured neuronal cells with the patients' serum. In addition, immunoprecipitation and mass spectrometry were performed to identify novel specific antigens. Despite this extensive testing of AE, no auto-antibodies were identified.

We suspected antibody-negative AE and started first-line treatment with high-dose intravenous methylprednisolone (1,000 mg) for 5 days, followed by oral prednisolone (**Figure 1G**).

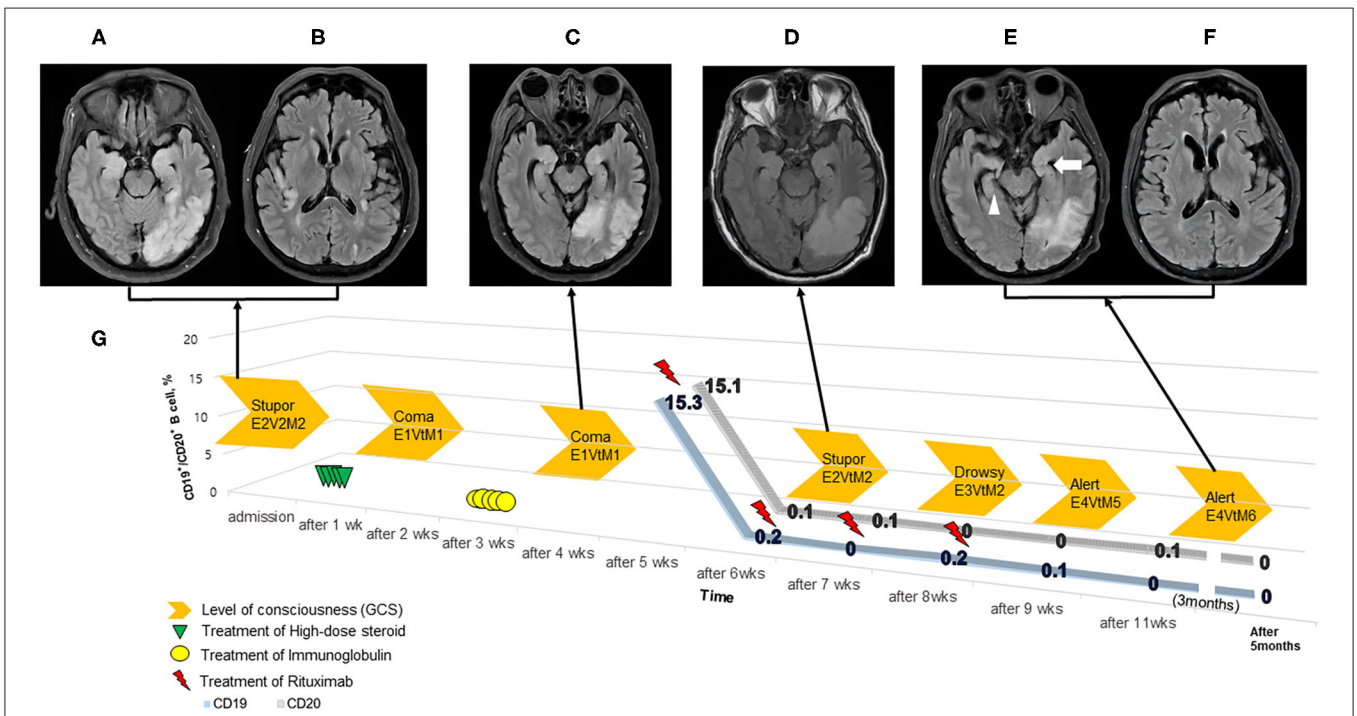

FIGURE 1 | Timeline of the patient treatment. **(A–F)** Brain MRI (T2-FLAIR) demonstrates autoimmune encephalitis. The patient's level of consciousness (orange arrows, GCS) improved following treatment with high dose steroid (green triangle), intravenous immunoglobulin (yellow circle), and rituximab (red thunderbolt) **(G)**. The $CD19^+/CD20^+$ B-cell counts were present during the 5-week to 5-month follow-up after admission. There was the depletion of $CD19^+/CD20^+$ B-cell counts within 1 week after an initial infusion of rituximab.

However, the patient's status deteriorated; he presented with episodes of right facial grimacing and right upper limb contraction, consistent with faciobrachial dystonic seizures. Continuous electroencephalogram demonstrated rhythmic sharp-and-waves arising from the left temporo-occipital lobe. These alterations were controlled with levetiracetam, valproic acid, and lacosamide.

The patient further deteriorated to a comatose state (GCS: E1VtM1) with generalized tonic-clonic seizures, requiring intravenous immunoglobulin (IVIg, 1 mg/kg for 5 days) on hospital day 16. His arousal level plateaued (GCS: E1VtM1) after receiving IVIg for 2 weeks. We then administered a second-line treatment, rituximab (IV, 375 mg/m^2, once weekly × 4 doses); before rituximab administration, we checked the patient's B-cell counts (CD19+/CD20+) on hospital day 28. CD19+/CD20+ counts of total lymphocytes in the peripheral blood were 15.3 and 15.1%, respectively (**Figure 1G**). After receiving rituximab for 3 weeks, the patient's mental status started improving (GCS: E4VtM5), and follow-up brain MRI findings were markedly improved (**Figures 1C–F**). The patient was discharged to a rehabilitation center (GCS: E4VtM6). At the last follow-up 5 months later, CD19+/CD20+ B-cells both remained at 0% (GCS: E4V5M6).

DISCUSSION

We reported a case of antibody-negative AE, with an association among clinical symptoms, CD19+/CD20+, and brain MRI findings, and treatment response. Moreover, we propose that rituximab could be considered a crucial treatment for antibody-negative AE when a patient exhibits unexplained symptoms. As antibody-negative AE is rare, we will establish a registry to collect data on its symptoms, treatments, and outcomes.

Clinical presentation-based diagnosis is more robust when considered with CSF, EEG, and MRI findings to guide antibody-negative AE treatment and ensure good response with immunotherapy (7). Owing to the overlapping clinical features, ruling out diseases that mimic AE in patients with severe neurological deficits is critical before initiating immunotherapy. Crucially, more than half of AEs are antibody-negative; nonetheless, some suspicion is required to reach the diagnosis of antibody-negative AE, and prompt management is needed to treat a potentially irreversible condition (7). The appropriate therapy should treat autoimmune phenomena against cell membranes, synapses, or intracellular antigens in the brain, similar to those with antibody-positive AE (1, 8).

Treatment options for antibody-negative AE, similar to antibody-positive AE, are broadly immune-suppressing agents for various specific steps in the pathogenesis of AE (9). As in other autoimmune disorders, corticosteroids are used in the treatment of antibody-negative AE to inhibit the inflammatory process. However, corticosteroids might have less specificity with several systemic side effects, and their efficacy is limited in AE (9). Other therapeutic approaches include various auto-antibodies and diverse immune mediators (e.g., IVIg, plasma exchange), B cells and short-lived plasma cells (e.g., rituximab), and specific cytokines (e.g., tocilizumab); anti-proliferative agents (e.g., cyclophosphamide, azathioprine, mycophenolate mofetil) are also used therapeutically (9).

B cells, in particular, present the main mechanism in autoimmune etiology (10), as demonstrated by the clinical success of B cell depletion therapies (BCDT). BCDTs such as the targeting CD20+, CD19+, and BAFF are used to treat autoimmune diseases. Although antibody-secretion is a negative consequence in autoimmune disease, BCDT impacts these cells and associated antibody levels. Therefore, in our case, it might be appropriate to evaluate B-cell counts to assess the treatment response to rituximab and formulate a prognosis. The improvements in consciousness level, MRI findings, and CD19+/CD20+ counts seemed related; however, they were independent of the antibody status.

This case report considered an AE etiology since the patient's differential diagnosis presenting with clinical symptoms, and MRI results suggested probable AE, even though the patient was antibody-negative. We speculate that rituximab played a crucial role in controlling the adverse autoimmune event before the end of the half-life of the first-line treatment, preventing the maturation of pre-B cells and B-cell depletion (7). Also, AE may require regular follow-up to evaluate symptoms or other diseases that may change the management strategy.

A limitation of our study is that antibody-negative AE, like other autoimmune diseases, has few biomarkers to identify the underlying mechanisms. Therefore, we cannot rule out the possibility of yet unknown antibodies that may be undetectable with the techniques used here. In addition, it can be difficult to distinguish between AEs because the patient's symptoms are similar to the other antibody-positive AEs such as LGI AE. Moreover, the improvement of the patient's symptoms may be attributed to the effects of IVIg rather than rituximab. Nevertheless, we proceeded with treatment by following the treatment guideline as much as possible. Therefore, our experience could be helpful to clinicians for real-life information on the use of rituximab for AE. In particular, our results and others could be useful for planning future comparative effectiveness studies with rituximab.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by this case report was conducted according

to the tenets of the Declaration of Helsinki and approved by the Institutional Review Board of Inha University Hospital (2021-01-025). Our patient's family provided informed written consent. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

S-HP and Y-CK: conception and organization of the research project, analysis and interpretation, and writing of the first draft of the manuscript. S-HP: execution of the research project and review and critique of the manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Neurology

CASE REPORT
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Ornidazole-Induced Recurrent Encephalopathy in a Chinese Man: A Rare Case Report and Literature Review

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Ornidazole-induced encephalopathy (OIE) is seldom seen in the clinic. In this study, we report a new case of a patient who had taken 1,000 mg ornidazole daily for nearly 4 years because of suspected diarrhea and proctitis and presented with subacute symptoms such as unsteady gait, slurred speech, and psychiatric disorder. These symptoms were significantly relieved 3 days after the patient stopped taking ornidazole. When he took this medicine again, however, similar symptoms occurred 4 months later, which were again reduced after 4 days of drug discontinuation. After the second onset, abnormal signals were identified around the aqueduct of the midbrain, around the fourth ventricle, and in the dentate nuclei of the cerebellum bilaterally. After 9 days of drug discontinuation, lesions disappeared in the magnetic resonance imaging (MRI) results. According to the clinical manifestations, imaging features, and the reduced symptoms after drug withdrawal, we clinically diagnosed the patient with OIE. This paper also reviews the literature on OIE. Only five cases (including our case) have been reported, all of whom presented with cerebellar ataxia and dysarthria and three with additional mental symptoms such as agitation and irritability. All five patients had abnormal lesions in the dentate nucleus of the cerebellum bilaterally, among whom four also had lesions in the corpus callosum and three around the periaqueduct of the midbrain. After withdrawal of ornidazole, the symptoms in all patients vanished or were alleviated, and three of them showed reduced or disappeared lesions in a head MRI reexamination. Overall, OIE has rarely been reported. Our case report and literature review show that the lesions in the cerebellum, corpus callosum, and brainstem can be reversed. The main manifestations of the lesions—cerebellar ataxia, dysarthria, and mental symptoms—quickly weaken or disappear after drug withdrawal, with good prognosis. Nevertheless, clear pathogenesis has yet to be further investigated.

Keywords: ornidazole-induced encephalopathy, ataxia, dentate nucleus, MRI, toxicity

INTRODUCTION

Nitroimidazole drugs, mainly including metronidazole, tinidazole, and ornidazole, with anti-anaerobic and antiprotozoal effects, are generally used for peptic ulcers. The common adverse reactions of nitroimidazoles include gastrointestinal symptoms such as nausea, vomiting, metallic taste, and abdominal discomfort. The adverse reactions of the nervous system are mostly manifested as peripheral nerve damage, especially sensory nerve damage (1). Metronidazole-induced encephalopathy (MIE) is a serious adverse reaction of the central nervous system that is mainly manifested as ataxia, dysarthria, and abnormal mental behaviors (2). Ornidazole, the third generation of novel nitroimidazole derivatives, is widely used, thanks to its fast onset, long half-life, strong antimicrobial activity, and fewer side effects (3, 4). Ornidazole-induced encephalopathy (OIE) is hard to diagnose at its initial stage due to its rarity and secretiveness and may lead to serious complications. Combining with a literature review, we report a case of a delayed diagnosis of encephalopathy induced by prolonged use of ornidazole and summarize the clinical characteristics of OIE to improve the clinical identification of such symptoms.

CASE REPORT

A 62-year-old man was first admitted to our hospital on October 1, 2020 for several days of unsteady gait, unclear speech, and abnormal mental behaviors. He denied having symptoms of weakness, dizziness, nausea, vomiting, and coughing when drinking water, nor did he have any family history of neurological disease, central nervous system dysfunction, or genetic disorders. He also denied chronic alcohol abuse, gastrointestinal surgical procedures, recurrent vomiting, chronic diarrhea, or nutritional imbalance. He had suffered from hypertension for several years without any other diseases.

On admission, the patient was irritable and easily agitated. His height was 1.75 m and weight was 75 kg. His body temperature was 36.6°C, pulse rate 80/min, respiratory rate 18/min, and blood pressure 145/78 mmHg. Neurological examination showed that he had cerebellar signs such as unsteady gait, dysarthria, and nystagmus. He failed to accurately perform the finger–nose and heel–knee–tibia tests. His Romberg sign was positive and the sensation in the upper and lower limbs decreased slightly. Other neurological and medical examinations showed no abnormalities.

The magnetic resonance imaging (MRI) results only showed mild abnormal signals around the midbrain aqueduct in T2/fluid-attenuated inversion recovery (FLAIR) (**Figure 1**). Needle electromyographic (EMG) examination was normal. There was no abnormality in the motor and sensory nerve conduction velocity. The compound muscle action potential (CMAP) amplitude of motor nerves was normal, but the sensory nerve action potential (SNAP) amplitude of the sensory nerves decreased in the upper and lower limbs, which indicated damage to the sensory nerves. Laboratory investigations revealed normal levels of routine blood, liver and kidney function, blood glucose, blood ammonia, serum electrolytes, blood clotting function, serum creatine phosphokinase, thyroid function, rheumatologic antibodies, tumor biomarkers, folate, vitamins B1 and B12, and homocysteine.

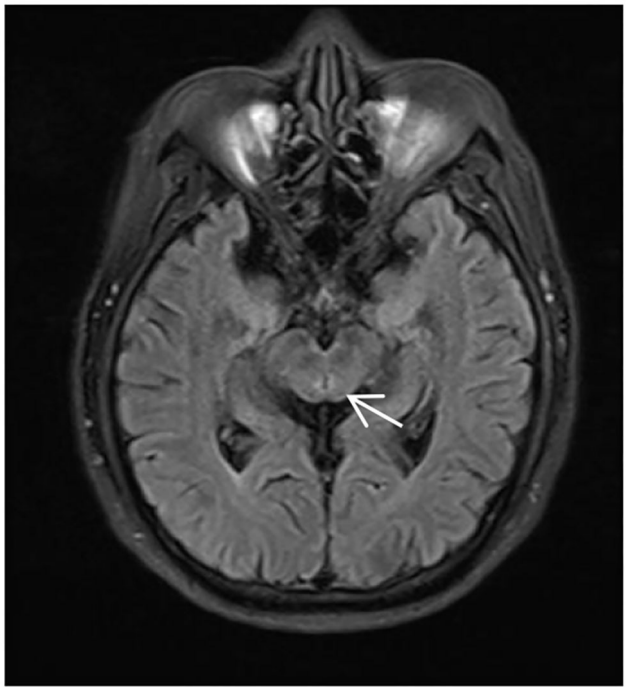

FIGURE 1 | MRI of the patient during his first time in the hospital, T2/fluid-attenuated inversion recovery (FLAIR) showing abnormally high signals around the midbrain aqueduct (*arrow*).

After 3 days of general supportive treatment and administration of vitamins B1 (25 mg, p.o. t.i.d.) and B12 (0.5 mg, p.o. t.i.d.), all of his symptoms almost completely disappeared. He was then discharged from our hospital with unclear diagnosis. On January 26, 2021, he was once again hospitalized, exhibiting much worse symptoms. Neurological examination results were the same as before. A second MRI examination showed abnormal signals around the midbrain aqueduct, around the fourth ventricle, and in the dentate nuclei of the cerebellum bilaterally in T2/FLAIR (**Figure 2**). Cervical, thoracic, and lumbar MRI examination results were normal. Other negative results included routine cerebrospinal fluid, biochemistry, and etiology, serum anti-intrinsic factor antibodies, and anti-parietal cell antibodies. The serum and cerebrospinal fluid tests were also negative, including central nerve demyelinating antibodies (AQP4, MOG, GFAP, and MBP), peripheral neuropathy antibodies (GM1, GM2, GM3, GM4, GD1a, GD1b, GT1a, GT1b, GQ1b, and sulfatide), paraneoplastic antibodies (CV2, Ri, Yo, Hu, GAD 65, SOX1, and Titin), and oligoclonal bands.

This time, the patient reported a medical history of taking ornidazole (1,000 mg/day) since the end of 2016 to treat proctitis and diarrhea. To prevent the recurrence of the latter disease, he kept taking this medicine even after the symptoms were

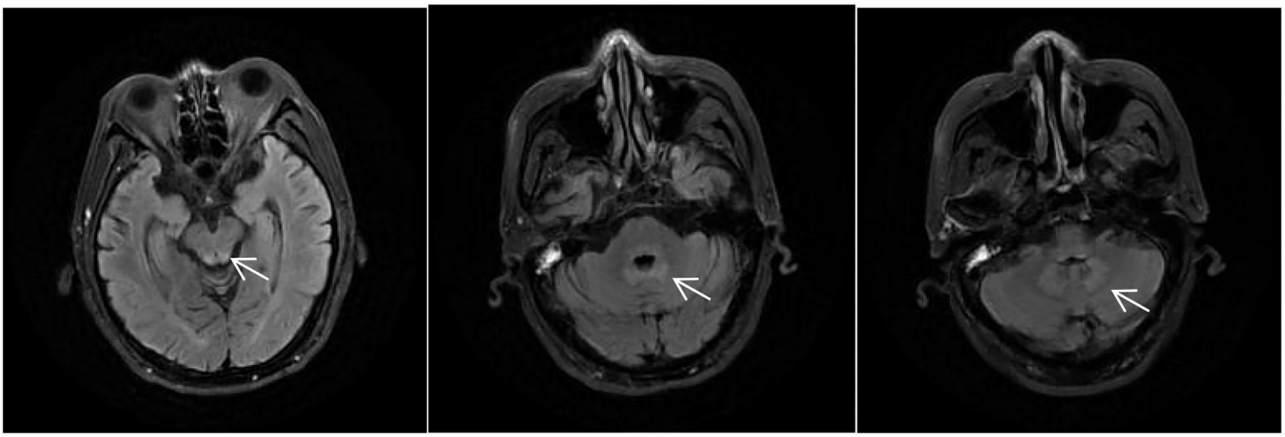

FIGURE 2 | MRI of the patient during his second time in the hospital, T2/fluid-attenuated inversion recovery (FLAIR) showing abnormally high signals around the midbrain aqueduct, around the fourth ventricle, and in the dentate nuclei of the cerebellum bilaterally (*arrows*).

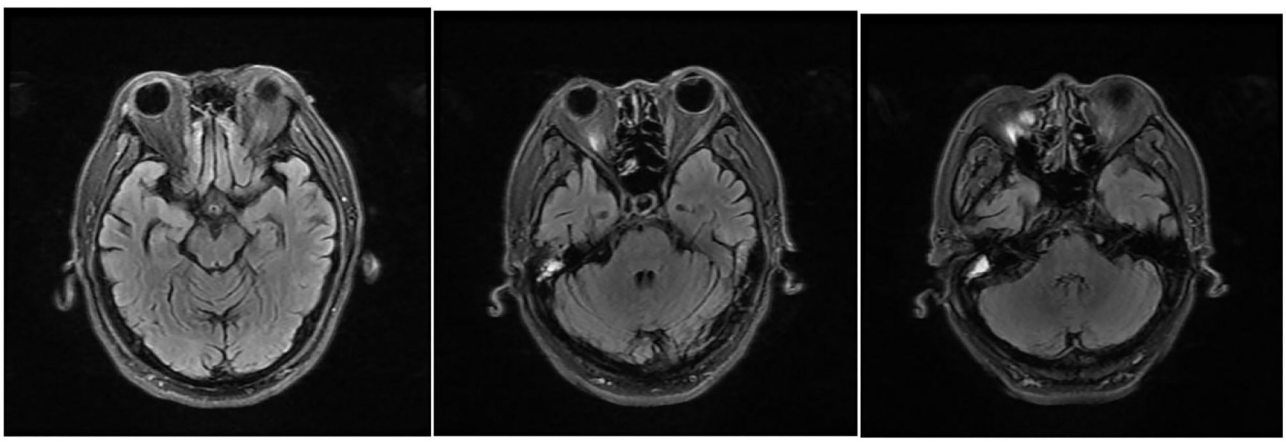

FIGURE 3 | MRI reexamination of the patient after drug withdrawal during his second time in the hospital, T2/fluid-attenuated inversion recovery (FLAIR) showing abnormally high signals around the midbrain aqueduct, around the fourth ventricle, and in the dentate nuclei of the cerebellum bilaterally, which disappeared 9 days after drug withdrawal.

relieved. During his first time in the hospital, he stopped taking the drug because he failed to bring it, and he did not disclose his medication history of taking ornidazole to the doctor. He resumed taking it after being discharged from our hospital. After the second admission, he was stopped from taking ornidazole and was treated with vitamins B1 (0.1 g, q.d. i.m.) and B12 (0.5 mg, q.d. i.m.). Four days later, his symptoms were significantly alleviated. After 9 days, MRI showed the absence of intracranial lesions (**Figure 3**) and the main symptoms completely disappeared, except alleviated irritability.

DISCUSSION

Here, we report the case of a 62-year-old man presenting with cerebellar ataxia and mental symptoms. The man had taken ornidazole for over 4 years, and his symptoms improved after withdrawal of the medicine. After resumption, however, the symptoms recurred. Magnetic resonance imaging showed reversible abnormal lesions that could explain his symptoms, and laboratory tests ruled out other causes. On this basis, he was clinically diagnosed with OIE and was subsequently fully informed of the clear diagnosis and he agreed to the treatment.

The world's first case of OIE was reported from Turkey in 2010, and another three cases from India. All four previously reported patients were females, while this is the first report of a male patient. Below is a summary of the clinical characteristics of the five patients (including our case; see **Table 1**). The patients were between 23 and 62 years old. The duration of OIE ranged from 35 days to 4 years. Cerebellar ataxia was the common symptom of all five patients, and in three of them, this was accompanied by mental behavior abnormalities such as agitation and irritability. All of them had abnormal lesions in the dentate nucleus of the cerebellum bilaterally, among whom four also had lesions in the corpus callosum and three

TABLE 1 | Literature review on ornidazole-induced encephalopathy (OIE).

Authors	Sex	Age	Duration of medication	Daily dosage	Clinical manifestations	Location of MRI lesions	Time for symptom improvement after drug withdrawal	Follow-up MRI	Prognosis
Taskapilioglu et al. (5)	Female	23	35 days	1,000 mg/day	Ataxia Dysarthria Emotionally labile	Dentate nucleus Corpus callosum	2 days	Lesions disappeared	Good
Gopinath et al. (6)	Female	61	365 days	500 mg/day	Ataxia Dysarthria	Dentate nucleus Corpus callosum Midbrain aqueduct	14 days	Not mentioned	Good
Sekhar K et al. (7)	Female	51	365 days	Not mentioned	Ataxia Dysarthria	Dentate nucleus Corpus callosum Pons dorsal	Not mentioned	Not mentioned	Good
Chouksey et al. (8)	Female	34	3–4 years	Not mentioned	Ataxia Dysarthria Mental disorder	Dentate nucleus Corpus callosum Midbrain aqueduct	60 days	Lesions disappeared	Good
The case reported here	Male	62	4 years	1,000 mg/day	Ataxia Dysarthria Mental disorder	Dentate nucleus Midbrain aqueduct Around the fourth ventricle	4 days	Lesions disappeared	Good

around the periaqueduct of the midbrain. After discontinuation of ornidazole, the symptoms of all patients improved or vanished, and the lesions of three patients disappeared or were mitigated in the MRI reexamination results. All patients had good prognosis without obvious sequelae.

Ornidazole is chiefly metabolized in the liver, and most of it is excreted in the urine as metabolites, with <4% being prototype drugs. *In vivo*, it mainly acts on the DNA of anaerobic bacteria and protozoa, such as amoeba, giardia, and trichomonas, *via* cytotoxic original drugs and intermediate metabolic active products. These drugs and products kill anaerobic bacteria and protozoa by breaking the helical structure or preventing the transcription or replication of their DNA, thus achieving antibacterial and antiprotozoal purposes. Ornidazole is easily absorbed through the gastrointestinal tract, and its plasma elimination half-life is 10.8 ± 1.4 h (9). Ornidazole is widely distributed in human tissues and body fluids and can easily penetrate the blood–brain barrier with high lipid solubility. In most tissues, including the central nervous system, the concentration of ornidazole can reach 60–100% that of the plasma (10). As a result, it will cause adverse neurological reactions. Compared with MIE, however, OIE is exceptionally rare, and only a few cases have been reported worldwide. Sørensen et al. (11) retrospectively analyzed the clinical data of 136 MIE patients averaging 56.8 years old. These patients took metronidazole against gastrointestinal infection or for other reasons. The duration of taking metronidazole ranged from 2 days to 8 years, with an average of 101.6 days, a lower quartile of 19.5 days, a median of 35 days, and an upper quartile of 63 days. The duration of treatment was longer than 1 year for 3.9% of patients. The cumulative dosage ranged from 5 to 2,000 g, with an average of 125.7 g, a lower quartile of 36 g, a median of 65.4 g, and an upper quartile of 110.8 g. The average daily dosage was about 1.24 g. The average duration of treatment before the onset of the first symptoms from the central nervous system was 47.2 days. Our case had taken ornidazole for nearly 4 years before developing neurological symptoms. Patients with OIE were reported to have taken the drug for at least 35 days before symptom onset, with a cumulative dosage of 35 g. Because only a few cases of OIE have been reported, a statistical comparison with MIE in terms of duration and dosage for treatment is quite challenging. Ornidazole can be converted into levornidazole *in vivo*. Levornidazole shows similar clinical therapeutic effects to, and fewer adverse reactions than those of metronidazole in the central nervous system (12). These might be the reasons for the low incidence of OIE.

Sørensen et al. (11) retrospectively analyzed the clinical manifestations of patients with MIE and found that dysarthria was the most common, followed by unsteady gait, limb disharmony, mental state change, multiple peripheral neuropathies, and eye movement disorders. The clinical manifestations of OIE resemble those of MIE, mainly cerebellar ataxia such as slurred speech, unsteady gait, and uncoordinated limb movements. In some patients, the symptoms are also accompanied by emotional agitation, irritability, and abnormal mental behaviors such as gibberish, and a few have peripheral nerve damage such as limb numbness. Magnetic resonance imaging plays an important role in diagnosing diseases. T2-weighted imaging (T2WI) and FLAIR sequences often show abnormally high intracranial signals (13). In MIE, lesions in the dentate nucleus of the cerebellum bilaterally are the most common, accounting for 90%. Fewer than that are the lesions in the corpus callosum mostly found in the splenium, accounting for 44%. Other lesions are in the brainstem, such as the midbrain, pons, and medulla oblongata, while a few lesions are located in the basal ganglia and white matter (11). The distribution of

OIE is similar to that of MIE. All the reported OIE cases had cerebellar dentate nucleus lesions, which can be reversed after drug withdrawal.

The pathogenesis of OIE is unclear at present. The mechanisms of metronidazole and ornidazole are similar as they both belong to nitroimidazole drugs. Both MIE and OIE belong to the type 3 antibiotic-associated encephalopathy (AAE) (14). Since the MRI result of nitroimidazole-induced encephalopathy (NIE) is similar to that of non-alcoholic Wernicke encephalopathy (WE), most patients with NIE have gastrointestinal diseases and abnormal liver function, which may lead to vitamin B1 deficiency or malabsorption in the body (15). The metabolites of nitroimidazole drugs may be converted into analogs of thiamine and may be antagonistic to vitamin B1 in the body, also resulting in vitamin B1 malabsorption (16). Some scholars, therefore, believe that there may be an overlapping pathophysiological mechanism between NIE and WE. Nevertheless, other lesions with the characteristics of WE, such as medial thalamic lesions and papillary body lesions, are rarely found in NIE, indicating differences between the two. Ornidazole-induced encephalopathy can lead to abnormal mental behaviors. Some scholars hold that a possible reason is that nitroimidazole drugs can inhibit monoamine oxidase, thereby reducing the decomposition of dopamine and causing accumulative dopamine in the body, further resulting in mental disorders (17).

The main differential diagnoses of OIE include WE, toxic encephalopathy, metabolic encephalopathy, and demyelinating disease of the central nervous system. The patient denied having a history of chronic alcohol abuse, gastrointestinal surgical procedures, recurrent vomiting, chronic diarrhea, or nutritional imbalance that may cause WE, and the serum vitamin B1 level was normal and the serum anti-intrinsic factor antibodies and anti-parietal cell antibodies were negative. None of these support the diagnosis of WE. Demyelinating diseases of the nervous system such as neuromyelitis optica (NMO) and myelin oligodendrocyte glycoprotein (MOG)-associated ones should be considered, but they can be excluded based on the negative results of aquaporin 4 (AQP4), MOG, and spinal MRI. Sensory nerve damage in the upper and lower limbs can be explained by the toxicity of ornidazole, which is the main adverse reaction of the nervous system induced by nitroimidazoles (1).

In this case, OIE was not difficult to identify according to the clinical manifestations, previous medication history, imaging features, and outcomes after drug withdrawal. Like other previously reported cases, the symptoms and intracranial lesions were abated rapidly after the timely withdrawal of medication. This patient was treated with vitamins B1 and B12. Therefore, this also might have contributed to his recovery. The general prognosis for him was good without obvious neurological sequelae.

CONCLUSION

Ornidazole is widely used in clinical practice, yet the encephalopathy induced by ornidazole is easily missed and misdiagnosed because it is rather rare. For correct diagnosis, a clear drug use history can be of help. In terms of treatment, the lesions in the cerebellum, corpus callosum, and brainstem, mainly manifested by cerebellar ataxia, dysarthria, and mental symptoms, are reversible. After drug withdrawal, these clinical symptoms recover quickly, with good prognosis. For clear pathogenesis, however, further investigations are required.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XL designed the case report. RT wrote the article. JL, YL, and TW collected data's. XL, YZ, and YM revised the manuscript. All authors contributed to the manuscript revision and approved the final manuscript.

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frontiers in Neurology

CASE REPORT
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Case Report: Multiple Sclerosis Relapses After Vaccination Against SARS-CoV2: A Series of Clinical Cases

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Objective: To describe a temporal association between COVID-19 vaccine administration and multiple sclerosis (MS) relapses.

Methods: This case series study was collected in four MS Centres in Central Italy, using data from 16 MS patients who received COVID-19 vaccination and presented both clinically and radiologically confirmed relapses between March and June 2021. We collected patients' relevant medical history, including demographics, MS clinical course, disease-modifying treatment (DMT) received (if applicable), and data from MRI scans obtained after the COVID-19 vaccination.

Results: Three out of 16 patients received a diagnosis of MS with a first episode occurring after COVID-19 vaccination; 13 had already a diagnosis of MS and, among them, 9 were on treatment with DMTs. Ten patients received BNT162b2/Pfizer-BioNTech, 2 patients mRNA-1273/Moderna, and 4 patients ChAdOx1 nCoV-19/AstraZeneca. All MS relapses occurred from 3 days to 3 weeks after receiving the first dose of the COVID-19 vaccination or the booster. All patients had evidence of radiological activity on MRI.

Discussion: Clinical and radiological findings in these cohort of MS patients confirmed disease re/activation and suggested a temporal association between disease activity and COVID-19 vaccination. The nature of this temporal association, whether causative or incidental, remains to be established.

Keywords: SARS-CoV2 infection, COVID-19 vaccine, multiple sclerosis relapse, MRI activity, lesions, adverse event

INTRODUCTION

Patients with multiple sclerosis (MS) have an increased risk of respiratory infections, especially patients presenting severe disability and on disease-modifying treatments (DMTs) (1). Infections can trigger MS relapses (2), and thus, vaccination in MS patients should be pursued as a general policy in order to reduce the risk of infections (3). Despite the long-standing debate over an

increased risk of relapse occurrence after vaccination, the existence of this phenomenon has not been confirmed (4).

The ongoing coronavirus pandemic led to an unprecedented vaccination campaign that included MS patients. In Italy, two types of vaccines were available: (i) mRNA-vaccines (BNT162b2 Pfizer/BioNTech and mRNA-1273 Moderna) (5); (ii) adenovirus-vectored vaccine (ChsdOx1 nCoV-19, AZD12222, AstraZeneca) (6).

Here, we describe 16 cases of clinically and radiologically confirmed MS re/activation that occurred after the administration of COVID-19 vaccines in MS patients regularly followed in four MS Centres in Central Italy from March to June 2021 (**Table 1**).

CASE SERIES

Case 1

A 45-year-old man received a diagnosis of MS (7) in 2012 and was started on teriflunomide and then from April 2020 with Ocrelizumab with radiological and clinical stability, as confirmed in November 2020. He received his first ChAdOx1 nCoV-19 on February 19, 2021. He experienced dysesthesia in both legs 3 weeks later. He underwent a scan on April 30, 2021 which showed two new lesions in the temporal gyri and a new spinal cord lesion at T3 level (**Figure 1A**).

Case 2

A 48-year-old woman received on March 5 her first dose of ChAdOx1 nCoV-19. 8 days later, she developed visual acuity deficit from her right eye. She underwent MRI scan on March 31, where an enhancing lesion in the corpus callosum, multiple white matter unenhanced lesions, and lesions in the occipital lobe were detected (**Figure 1B**). Diagnosis of MS was made, and she was treated with high dose of intravenous methylprednisolone (IVMP), with marked improvement of the visual deficit.

Case 3

A 54-year-old woman was diagnosed with MS in 1993. She remained clinically stable without any therapy up to 2021. On

TABLE 1 | Demographic and clinical baseline characteristics of the MS patients.

No. cases	Age	Sex	EDSS	DMT	Year of last relapse	Disease duration	Type of vaccine	Dose	Time of symptom onset after vaccine	Steroids use	No. new MRI lesions	Timing of MRI after symptom onset
1	45	M	2.5	Ocrelizumab	2020	9 years	ChAdOx1 nCoV-19	1	21 days	Yes	2 brain Gd-, 1 spine Gd-	50 days
2	48	F	2.0	None	New diagnosis	ND	ChAdOx1 nCoV-19	1	8 days	Yes	1 brain Gd+	18 days
3	54	F	2.5	None	2014	28 years	ChAdOx1 nCoV-19	1	3 days	No	1 spine Gd+	17 days
4	66	F	2.5	None	New diagnosis	ND	ChAdOx1 nCoV-19	1	7 days	Yes	4 brain Gd+	17 days
5	42	f	4.0	Ocrelizumab	2019	2 years	mRNA-1273	1	14 days	No	1 brain Gd+	17 days
6	57	F	6.0	None	2015	20 years	mRNA-1273	2	14 days	Yes	1 brain Gd+	13 days
7	49	F	1.5	DMF	2013	8 years	BNT162b2/Pfizer-BioNTech	1	5 days	Yes	1 brain Gd+, 1 spine Gd+	7 days
8	39	M	2.0	DMF	2018	7 years	BNT162b2/Pfizer-BioNTech	1	10 days	Yes	2 brain Gd+, 1 spine Gd-	7 days
9	39	F	1.0	None	new diagnosis	ND	BNT162b2/Pfizer-BioNTech	1	3 days	Yes	1 brain Gd+	9 days
10	60	F	3.5	DMF	2014	23 years	BNT162b2/Pfizer-BioNTech	1	2 days	No	1 brain Gd+	3 days
11	30	F	1.5	Cladribine	2020	3 years	BNT162b2/Pfizer-BioNTech	2	20 days	Yes	2 brain Gd+	36 days
12	58	F	5.0	None	2018	21 years	BNT162b2/Pfizer-BioNTech	1	3 days	Yes	1 brain ring Gd+	38 days
13	34	F	2.5	None	2021	3 months	BNT162b2/Pfizer-BioNTech	2	4 days	Yes	3 brain Gd+, 1 spine Gd-	16 days
14	35	F	2.0	DMF	2019	16 years	BNT162b2/Pfizer-BioNTech	2	1 day	Yes	3 brain Gd+	13 days
15	54	M	2.0	Teriflunomide	2020	18 years	BNT162b2/Pfizer-BioNTech	1	7 days	Yes	2 brain Gd+	4 days
16	37	M	1.5	DMF	2019	2 years	BNT162b2/Pfizer-BioNTech	2	10 days	Yes	1 brain Gd+	9 days

No., number of; EDSS, expanded disability status scale; M, male; F, female; DMT, disease modifying treatment; DMF, dimethyl fumarate; ND, new diagnosis; Gd, gadolinium-enhancing lesion; MRI, magnetic resonance imaging.

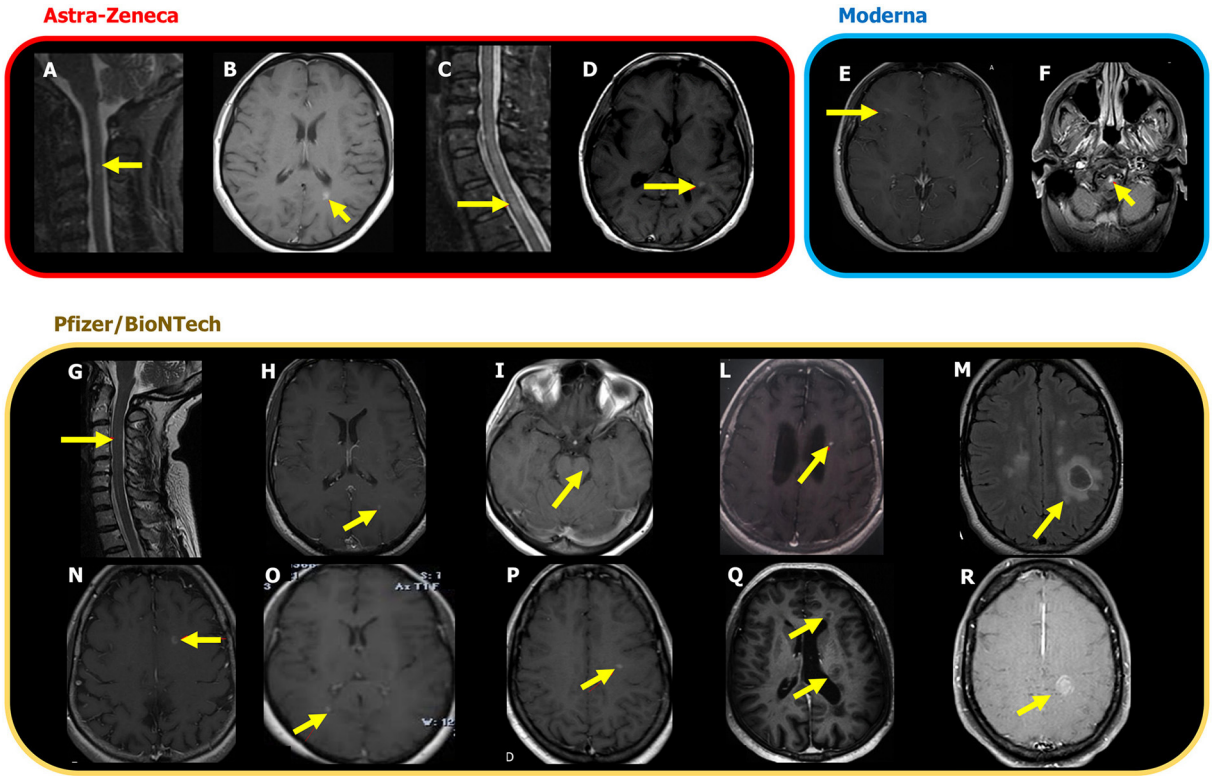

FIGURE 1 | New MRI lesions associated with the MS episodes occurred after ChAdOx1 nCoV-19 (AZD12222), mRNA-1273, Moderna and BNT162b2, Pfizer/BioNTech vaccine. The lesions are shown on T2 weighted images or on post-contrast T1 weighted images and are indicated by yellow arrows. **(A)** Case 1: C3 lesion; **(B)** Case 2: new enhancing lesion in corpus callosum and multiple white matter unenhanced lesions in periventricular areas and in the mesial occipital lobe; **(C)** Case 3: new enhancing lesion in the thoracic cord; **(D)** Case 4: multiple hyperintense lesions in the supra and infratentorial white matter, four of which are with contrast enhancement; **(E)** Case 5: new brain lesion with contrast enhancement. **(F)** Case 6: enhancing bulbar lesion; **(G)** Case 7: C3 lesion with contrast enhancement; **(H)** Case 8: new brain enhancing lesion; **(I)** Case 9: a new contrast enhancing lesion in the mesencephalon. **(L)** Case 10: new enhancing brain lesion. **(M)** Case 11: enhancing brain lesion with conspicuous oedema; **(N)** Case 12: a new active lesion with ring enhancement in the left frontal white matter. **(O)** Case 13: three new brain enhancing lesions, one of which is indicated by the arrow; **(P)** Case 14: three new enhancing lesions in the left temporal lobe and one, indicated here, in the left centrum semiovale; **(Q)** Case 15: two ring-enhancing lesions localized in the white matter adjacent to the left frontal horn and in the left middle periventricular region. **(R).** Case 16: new enhancing lesions, one of which is tumefactive, localized in the white matter of the left centrum semiovale.

February 27, 2021, 3 days after the first ChAdOx1 nCoV-19 dose, the patient developed hypoesthesia below the T6 level. She underwent a new MRI showing one enhancing lesion in the spinal cord (**Figure 1C**). She was treated with IVMP with complete recovery.

Case 4

A 66-year-old woman received the first dose of ChAdOx1 nCoV-19 on April 11, 2021 and, 1 week later, complained visual disturbance and postural instability on the right limbs. A brain MRI on May 4 showed multiple white matter lesions, four of them enhancing in the left paratrigonal and periventricular white matter (**Figure 1D**). Her CSF showed oligoclonal bands. Diagnosis of MS (7) was made, and she was treated with IVMP with partial improvement.

Case 5

In 2019 a 42-year-old woman experienced a progressive weakness on the right side of her body. After an MRI scan performed in February 2020, showing multiple lesions with dissemination in space and time, she started treatment with Ocrelizumab on May 8, 2020. She received the first dose of mRNA-1273 vaccine on March 22, 2021. Two weeks later, she experienced slight weakness of the left upper limb. On April 19, 2021, she received the booster, and after 3 days, her follow-up MRI showed an enhancing brain lesion in the right corona radiata (**Figure 1E**).

Case 6

A 57-year-old man had a diagnosis of MS in 2001. He was treated initially with injectables, then with teriflunomide, and, in 2015, with mitoxantrone. Since then, he remained clinically and radiologically stable without any treatment. On May 11, 2021, he received the booster of mRNA-1273 vaccine. Two weeks later, he experienced a severe motor deficit in both legs that made him bed bound. He was admitted to hospital where he underwent an MRI on June 7, 2021, showing an enhancing pontine lesion (**Figure 1F**). He was treated with IVMP with only partial recovery.

Case 7

A 49-year-old woman was diagnosed with MS in November 2013. She has been on treatment with dimethyl fumarate (DMF) since July 2014, with clinical and radiological stability. On April 1, 2021, she underwent a brain and spinal cord MRI scan, which was stable. On April 8, she received her first BNT162b2 dose of vaccine. Five days after, she developed numbness on the left hand and left side of her head. On April 20, she underwent a new scan, which detected a periventricular lesion and a spinal lesion at C3 level, both enhancing (**Figure 1G**). She was treated with IVMP with almost complete recovery.

Case 8

In 2014, after the onset of hypoesthesia on his left side, a 39-year-old man underwent an MRI scan, which showed multiple lesions on brain and spinal cord. He started treatment with injectables switched to DMF in 2017. After almost 3 years of clinical and radiological stability, on April 27, 2021, he received his first dose of BNT162b2 vaccine, followed, 10 days later, by the onset of paraesthesia on his left leg. He underwent an MRI scan on May 13 that showed three new lesions, two of which were enhancing in the left parietal lobe and in the periventricular white matter (**Figure 1H**). He was treated with oral steroids with partial recovery.

Case 9

A 39-year-old woman suffered from her first clinical episode in August 2019 with a complete recovery. A diagnosis of clinically isolated syndrome was made, and she was monitored by serial MRI that confirmed a radiological stability up to January 2021. On April 29, she received her first dose of BNT162b2 vaccine followed, 3 days later, by dysesthesia on her right hand and foot. A scan performed on May 11, 2021 showed a new enhancing lesion in the mesencephalon (**Figure 1I**). She was treated with IV methylprednisolone with a good recovery. A diagnosis of MS was made, and a DMT was planned.

Case 10

A 60-year-old female patient received a diagnosis of MS in 1998. In 2001, she started treatment with injectables switched to DMF in 2015. She was clinically and radiologically stable for 6 years. In April 2021, she performed the first BNT162b2 dose of vaccine presenting few days later with fatigue and numbness in both legs. A scan was performed, and one enhancing brain lesion was detected in the left periventricular white matter (**Figure 1L**).

Case 11

A 30-year-old woman was diagnosed with MS in 2018, after a clinical onset with optic neuritis and MRI suggestive of dissemination in space and time. She was treated with DMF between September 2018 and August 2020 and then she started Cladribine. A baseline MRI at the end of October 2020 was stable. She received the BNT162b2 booster on April 8, 2021. Twenty days later, she complained of a language disturbance. A brain MRI performed on June 3, 2021 revealed the presence of two enhancing brain lesions, one in the right corona radiata and one with conspicuous oedema in the left centrum semiovale (**Figure 1M**).

Case 12

A 58-year-old woman was diagnosed with MS in August 2000. She was treated with injectables and then, in 2018, with DMF that was stopped after 1 year for lymphopenia. She performed an MRI scan in February 2020 that was stable. She had her first BNT162b2 dose on March 26, 2021. Three days later, she complained headache, balance disturbances, urinary incontinence, difficulties in walking, and dysphagia. She performed an MRI on May 27, 2021 that showed a new area with ring enhancement in the white matter of the left frontal lobe (**Figure 1N**). She started IVMP with benefit.

Case 13

A 34-year-old woman developed numbness and hyposthenia on her right hand in February 2021. An MRI scan showed multiple lesions and one enhancing cord lesion at C3 level. Diagnosis of MS was made. She was treated with IVMP with almost complete recovery. A treatment with Ocrelizumab was planned. On May 18, she received the BNT162b booster. Four days later, she complained of neck pain and hypoesthesia on her right arm. She performed an MRI scan on June 7 showing three brain enhancing lesions (one right posterior paraventricular and two in the left periventricular white matter) and a new unenhanced lesion on spinal cord (**Figure 1O**).

Case 14

A 35-year-old woman received a diagnosis of MS in the 2005. She was treated with injectables, and in February 2019, she started DMF. She remained clinically and radiologically stable until May 24, 2021, when she received the BNT162b2 booster. The day after the vaccination, she developed paraesthesia on the left side of the body. She underwent a scan 13 days later, which showed three enhancing lesions in the left temporal lobe and left centrum semiovale (**Figure 1P**).

Case 15

A 54-year-old man was diagnosed with MS in 2003. He was treated with injectables and switched to teriflunomide in November 2020. He was clinically stable and without new lesions on MRI performed on February 25, 2021. On April 7, 2021, 1 week after the first dose of BNT162b2 vaccine (March 31, 2021), he developed a right hemiparesis. A brain scan showed two ring-enhancing lesions located in the left periventricular white matter (**Figure 1Q**). IVMP was administered with full recovery. He received the BNT162b2/Pfizer-BioNTech booster on May 11, 2021. without any further medical problem.

Case 16

A 37-year-old man was diagnosed with MS in 2019. In April 2020, he started DMF with clinical stability. On June 4, 2021, he had the BNT162b2 booster. On June 15, the patient presented with weakness on his right limbs. On June 24, he underwent a brain MRI that, compared with a previous routine scan of May 20, 2021, showed a new tumefactive contrast-enhancing lesion in

the left fronto-parietal white matter (**Figure 1R**). The patient was treated with IVMP with partial recovery.

DISCUSSION

There have been few cases reported of neurological complications associated with COVID-19 vaccination. These include cases of transverse myelitis (8), of Bell's palsy (9), of unusual variant of Guillain-Barre syndrome, and of cerebral venous sinus thrombosis (10, 11). In MS, there are suggestions of an unchanged rate of relapse in vaccinated, when compared to non-vaccinated, patients following the vaccination (12). However, this latter finding has not been supported by radiological evidence of disease activity and the period of observation was limited.

Only two cases of acute relapse after COVID-19 vaccination have been reported so far (13, 14), both having a good outcome.

Here, we describe a series of 16 patients with MS relapses occurring from 3 days to 3 weeks after their COVID-19 vaccination, between March and June 2021. During this period, at least 2500 patients with MS accessed the four MS Centres. During this period, a total of 69 verified (i.e., treated with high dose IV steroids) relapses were observed in the Centers, while 52 relapses were measured in the preceding 4 months. Although seasonal variation in relapse rate associated with monthly hours of sunshine should be taken into account (15), an increase in the total number of relapses was observed during the SARS-COV-2 vaccination campaign.

Out of 16 cases, 3 received a diagnosis of MS after COVID-19 vaccination; the remaining 13 had already a diagnosis of MS made from few months to several years before the vaccine administration. Nine patients were on DMTs; four patients were no longer on DMTs, although they had used them in the past, and were clinically and radiologically stable. Disease reactivation is reported after both the first vaccine administration ($n = 10$) and the booster ($n = 6$). All patients had evidence of radiological activity on MRI to support the relapse diagnosis. Age, sex, and level of disability reflect what may be expected for a relapsing MS cohort. The characteristics of the enhancing lesions varied from small to large lesions, in both the brain and the spinal cord.

The role of vaccines on the risk of developing MS and MS relapses remains to be elucidated, with no sufficient data to support or refute an association between the development of MS and the antiviral vaccinations (16, 17). Therefore, currently, there are no contraindications for vaccination in patients with MS, with the only exception regarding live-attenuated vaccines that are contraindicated for MS patients who receive immunosuppressive or immunomodulating treatments. Unless the risk of infection outweighs the risk of adverse reactions induced by the vaccine, MS relapses are not a contraindication for vaccination, but they are a reason to delay vaccination until remission (17).

Although the evidence of an association between vaccination and MS activity is still debated (18), a link between them has been suggested, within the first 30 days after immunization, given the possibility of vaccines to accelerate the transition from subclinical to clinical disease through a stimulation of the immune system (19). In a previous case series, we have looked into the safety of receiving the influenza vaccine in MS patients by clinical and MRI studies, adding a note of caution in those subjects with evidence of recent disease activity (20).

The exact mechanisms through which autoimmune reactions can be triggered by vaccination are not fully understood, although they probably vary according to the type of vaccine and individual genetic susceptibility (21, 22).

Immunological studies have shown that coordinated interactions between T and B lymphocytes of the adaptive immune system are necessary for the successful generation of immunological memory and the production of neutralizing antibodies following recognition of antigens by the innate immune cells (3). However, the T/B cell interaction may be altered in MS even in the absence of DMTs (23, 24). In addition, new technologies currently used for mounting an immune response to the COVID-19 vaccine, such as mRNA vaccines, have not been tested in populations suffering from autoimmune conditions before the vaccination campaign.

Although the clinical cases described here experienced neurological symptoms that were temporally associated with administration of the vaccine, causality cannot be assumed. Indeed, it cannot be disentangled whether radiologically confirmed relapses occurring after vaccination are triggered by the vaccination-induced inflammatory state or are relapses that would have happened anyway, independently from vaccination.

After the authorization of vaccines against SARS-CoV-2 in Italy, MS patients were prioritized for vaccination starting in March 2021. The availability of COVID-19 vaccines met the willingness of approximately 80% of European MS patients to receive vaccination (ref). The greatest interest in vaccination was observed in older patients and in those with comorbidities (25). This evidence is reflected in our case series, where mean age was 46.7 $\pm$ 10.3 and median EDSS score was 2.5. Immunosenescence increases the risk of adverse events in older adults. Beyond reduced response to vaccines, changes that take place in the immune system with aging generally result in higher susceptibility to infections and prevalence of autoimmunity (26), factors that can precipitate reactivations in MS patients. During mass immunization campaign, such as that occurred in France between 1995 and 1997, several cases of MS were reported a few weeks after HBV vaccination, suggesting that vaccine may accelerate the transition from subclinical to clinical disease (27). However, two subsequent case-control studies showed a non-significant increase in risk of developing MS following the HBV vaccine (ref). Therefore, conclusions derived from case reports and case series are not free from biases and should not influence vaccine hesitancy (28).

Adverse events of vaccination can occur in rare cases, but benefits generally outweigh adverse effects, given that acute infections may have dangerous consequences (29). Indeed, patients with MS have an increased mortality risk from COVID-19, especially if older and with significant disability and/or comorbidities (30).

CONCLUSION

The elevated number of MS patients with relapse after COVID-19 vaccine coming to our observation during a relative short period of time suggests the need for robust post-vaccination

surveillance in patients with MS. Large prospective controlled studies are required to estimate the frequency of MS relapses, both clinically and MRI proved, which might occur during the post-vaccine period when a new COVID-19 vaccination program will be planned.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CP and RN wrote the manuscript with support from EB, AI, LT, FM, LP, GD, VP, and VT. CP and VR conceived of the presented idea. All authors have collected the data.

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CASE REPORT
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Case Report: Amphiphysin Antibody-Associated Stiff-Limb Syndrome and Myelopathy: An Unusual Presentation of Breast Cancer in an Elderly Woman

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Background: Paraneoplastic stiff-limb syndrome (SLS) is a rare manifestation of underlying malignancy and could have distinctive features different from the classic stiff-person syndrome (SPS).

Case Description: We present a case of anti-amphiphysin antibody (Ab)-associated paraneoplastic SLS, in an 83-year-old woman with invasive ductal carcinoma of the breast. She presented with stiffness, painful spasms of the distal legs, and asymmetrical fixed posturing of the foot. There are coexisting long-tract disturbance and lower-extremity weakness. Treatment with diazepam provided symptomatic relief while plasma exchange (PLEX) did not lead to significant clinical improvement. The patient was bedridden within 3 months and passed away within 6 months from symptom onset.

Conclusion: This case highlights the importance of recognition of uncommon presentation of SPS and its oncological significance. This entity requires a high degree of suspicion for initiation of the proper workup. The rapid identification and treatment of the underlying tumor might offer the best chance for recovery.

Keywords: stiff person syndrome, stiff limb syndrome, amphiphysin antibody, neurologic paraneoplastic syndromes, paraneoplastic myelopathy

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INTRODUCTION

More than half a century has passed since classic stiff-person syndrome (SPS) was first described in 1956 by Moersch and Woltman in a case series of 14 patients at the Mayo Clinic (1). Classic SPS is a rare neuroimmunological disorder that is characterized by symmetrical muscle stiffness and painful spasms affecting the axial and limb muscles, without extrapyramidal or pyramidal tract signs. SPS is currently considered as a spectrum disorder including classic SPS, paraneoplastic SPS, and SPS variants. SPS variants include focal forms like stiff-limb syndrome (SLS), jerking SPS, progressive encephalomyelitis with rigidity and myoclonus (PERM), and SPS plus (ataxia, epilepsy, etc.) (2). SPS has been linked most commonly to anti-GAD 65 (glutamic acid decarboxylase, 70–80%) and less commonly to anti-GlyR (anti-glycine receptor, 10%), anti-amphiphysin (5%), anti-DPPX (anti-dipeptidyl-peptidase-like protein), anti-gephyrin, and anti-GABAaR antibodies (Abs) (3).

Paraneoplastic SPS occurs in 5–10% of all patients with SPS and is frequently associated with underlying malignancies of breast, lung, colon, thymus, and Hodgkin's lymphoma (3, 4). Anti-amphiphysin Ab is the most common marker of this variant most commonly associated with breast cancer. Paraneoplastic neurologic syndromes occur as a result of immune cross-reactivity between the tumor and host cells. In 80% of the cases, paraneoplastic neurologic syndromes can precede a tumor diagnosis and can help detect an occult malignancy (5). The diagnosis of SPS is challenging given its heterogeneity in symptomatology, clinical course, and presence of autoimmune Abs.

We hereby present a case of rapid progressive paraneoplastic SLS with the coexistence of myelopathic features. These distinctive clinical features are extremely uncommon and therefore will contribute to the pool of literature to understand this rare entity.

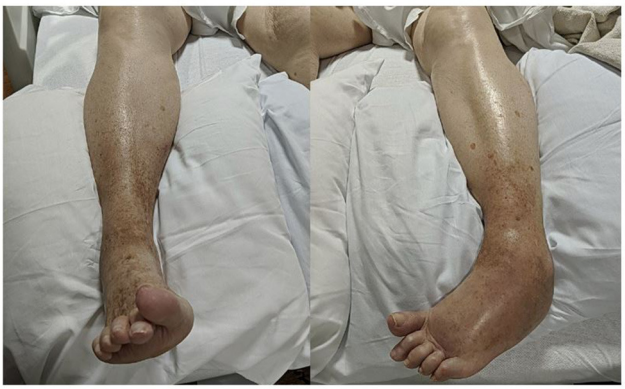

FIGURE 1 | Asymmetrical dystonic posturing on both sides (left more than right) with significant swelling and redness in the dorsum of the left foot.

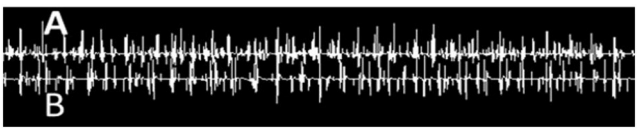

FIGURE 2 | Needle EMG recording of simultaneous co-activation of agonist–antagonist muscle pair using a concentric needle electrode and two-channel recording from **(A)** tibialis anterior and **(B)** gastrocnemius muscles.

CASE PRESENTATION

An 83-year-old white female with a medical history of hypertension, celiac disease, and gout presented with bilateral lower-extremity weakness and painful spasms for 3 months, which were worsening over 2 weeks. She had spasms in the feet, causing dystonic posturing resembling "clubfoot," and she was unable to straighten them or bend her knees. She also endorsed numbness, primarily on the left foot. She initially used a cane for ambulation when her symptoms started but later used a wheelchair. She denied any bowel or bladder incontinence, but due to restricted mobility, she was using diapers. About 6 weeks before the presentation, the patient noted swelling in the bilateral lower extremity and was prescribed steroids for a presumed gout flare. However, the spasms and pain worsened, and the swelling did not resolve. There was also reduced appetite, which caused weight loss of ∼20 lb in the month prior to presentation. She had regular mammograms in the past. She reported that her last mammogram at 70 years old was abnormal but could not provide any specifics. She noticed a painless left-breast mass, which grew progressively in size slowly. She did not pursue any further evaluation given her age. She denied use of tobacco, alcohol, or illicit drugs. Family history indicated that her two sisters were both diagnosed with breast cancer in their 60's.

During the examination, she was alert and oriented. Cranial nerves were intact. She had normal strength and reflexes in the upper extremities (UE). Strength was 3/5 in the left lower extremity and 4+/5 in the right lower extremity proximally but 3/5 in ankle dorsiflexion and plantar flexion. Patellar reflexes were normal, and ankle reflexes were absent bilaterally.

Pinprick sensation, proprioception, and vibration were diminished in the left lower extremity up to the ankle, but there was no sensory level or saddle anesthesia. She had dystonic posturing of bilateral feet (left more than right), with significant swelling and redness in the dorsum of the left foot (**Figure 1**). Babinski signs were present bilaterally. She had multiple intermittent spasms in both lower limbs distally, triggered by mild tactile stimuli and causing significant pain. The breast exam showed a 5 × 6-cm firm palpable mass in the upper outer quadrant of the left breast and a left axillary firm, non-tender, and enlarged lymph node.

Brain and whole-spine magnetic resonance imaging (MRI) were unremarkable. Cerebrospinal fluid (CSF) showed mild lymphocytic pleocytosis, elevated protein level (white blood cell [WBC] 6, red blood cell [RBC] 53, protein 66, and glucose 52), and oligoclonal bands (CSF-restricted). The CSF meningitis panel was negative. Creatinine kinase was transiently elevated (1,253 U/L on admission) with an elevated erythrocyte sedimentation rate (ESR) of 40 mm/h and C-reactive protein (CRP) of 14.6 mg/dl. The patient was started on multiple muscle relaxants including methocarbamol, cyclobenzaprine, and baclofen with minimal response. Electromyography (EMG) showed sensorimotor axonal polyneuropathy in lower extremities, as well as continuous motor unit activity and co-activation of agonists and antagonist muscles (**Figure 2**), typical for SPS.

Following the EMG, the patient was prescribed diazepam, which relieved the painful spasms. Due to the reported depression from prior steroid use and newly diagnosed diabetes (HbA1C 7.2), methylprednisolone was not initiated. She was treated with five sessions of plasma exchange (PLEX). Serum amphiphysin Ab was identified as positive in the Autoimmune Neurologic Disease Panel and Paraneoplastic Reflexive Panel (ARUP) laboratory, but the titer was not available. The GAD 65 Ab result was negative. Other relevant laboratories revealed

TABLE 1 | Summary of laboratory testing.

Laboratory work	Result	Reference interval
Amphiphysin	Positive	Negative
Glutamic acid decarboxylase antibody 65 (GAD 65)	<5.0 IU/ml	0.0–5.0
Purkinje cell/neuronal nuclear IgG	None detected	None detected
Striated muscle antibodies	<1:40	<1:40
NMDA receptor antibody	<1:10	<1:10
CV2.1 antibody	<1:10	<1:10
Acetylcholine binding antibody	0.0 nmol/L	0.0–0.4
Voltage-gated calcium channel (VGCC) antibody	0.0 nmol/L	0.0–24.5
Aquaporin-4 receptor antibody	1.0 U/ml	≤2.9
Voltage-gated potassium channel antibody	0.0 nmol/l	0–31
Titin antibody	<0.09 IV	0.00–0.45
Gastric parietal cell antibody	1.8 units	0.0–24.9
Ganglioside panel	Asialo-GM1, GM1, GM2, GD1a, GD1b, and GQ1b antibodies unremarkable	0–50
Thyroid peroxidase antibody (TPO)	<0.3 IU/ml	0.0–9.0
Thyroglobulin antibody	<0.9 IU/ml	0.0–4.0
Vitamin B12	782 pg/ml	240–930
Folic acid	8.9 ng/ml	3.0–20.0
Cancer antigen 27.29	<3.5 U/ml	0.0–40.0
CSF oligoclonal bands	Positive (4 bands)	Negative (0–1)
CSF meningitis/encephalitis panel by PCR	*Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, Cytomegalovirus, Enterovirus, Herpes simplex virus 1 and 2, Human herpesvirus 6, Human parechovirus, Varicella zoster virus, and Cryptococcus neoformans negative	Negative

normal vitamin B12 level (782 pg/ml), as well as negative thyroid peroxidase Ab (TPO), thyroglobulin Ab, gangliosides, and polymyositis panel (**Table 1**).

A computed tomography (CT) scan of the chest, abdomen, and pelvis showed a 4-cm left-breast mass with central necrosis and multiple large left axillary lymph nodes (**Figure 3**). Left-breast mass and the left infraclavicular lymph node biopsy revealed invasive ductal carcinoma with metastatic breast carcinoma cells in the lymphoid tissue (**Figure 4**), Stage IIIC. Neoplastic cells were positive for estrogen and progesterone receptor staining but negative for Her2 protein. Oncology

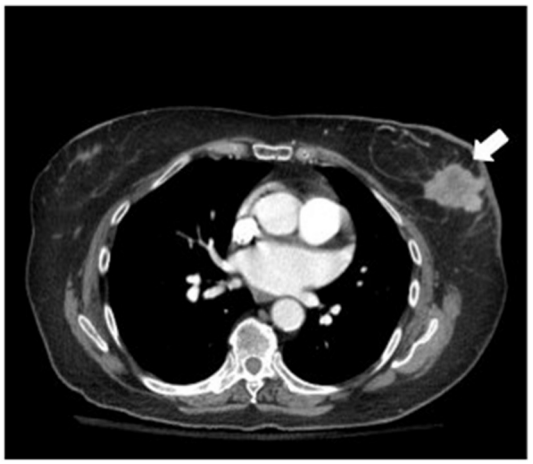

FIGURE 3 | Chest CT showed a 4-cm left-breast mass with central necrosis.

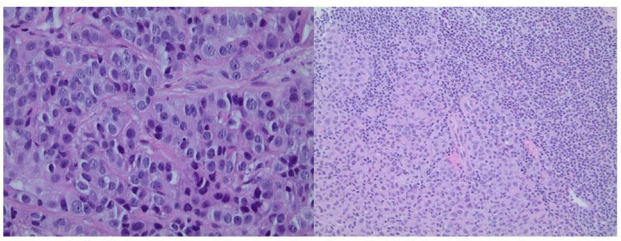

FIGURE 4 | Left panel: Core biopsy section from the left-breast mass shows invasive ductal carcinoma (×400 magnification). Right panel: Core biopsy section from the left infraclavicular lymph node shows metastatic breast carcinoma cells in the lymphoid tissue (× 200 magnification).

recommended anastrozole and outpatient follow-up visits. However, the patient and her family were hesitant with surgery, radiation, or chemotherapy given her age and comorbidities. She eventually declined the aggressive treatment of her breast cancer. She was bedridden upon discharge and passed away within 6 months after the initial presentation.

DISCUSSION

SPS is a rare neurological disorder with an estimated prevalence of one to two cases per million, affecting women two to three times more often than men. In classic SPS, rigidity and stiffness are usually symmetric and most prominent in axial and proximal limb muscles. They typically start in patients below the age of 50 and progress slowly over several years (2). However, in our patient, she developed asymmetrical stiff-leg syndrome (distal more than proximal) with coexisting myelopathy in her 80's, requiring the use of a wheelchair within 3 months from symptom onset. These unique clinical features have posed a diagnostic challenge to clinicians. The initial neurological localization is in the spinal cord, and differential diagnoses include myelopathy, atypical multiple sclerosis, motor neuron disease/primary lateral

sclerosis, and focal dystonia. The EMG finding and the detection of anti-amphiphysin Ab are key to the diagnosis of paraneoplastic SPS in this case. Based on the diagnostic criteria by Dalakas (6), which include (1) muscular rigidity in the limbs and axial muscles; (2) continuous co-contraction of agonist and antagonist muscles, confirmed clinically and electrophysiologically; (3) episodic spasms; (4) absence of any other neurological diseases that could explain the symptoms; (5) and positive serology for GAD 65 (or amphiphysin) autoantibodies in the serum; the patient presented in this report met the criteria for diagnosis of SPS.

The pathogenesis of SPS is not fully understood. There is strong evidence that the impairment of GABAergic neurotransmission medicated by pathologic autoantibodies has caused lower GABA levels in the central nervous system (CNS) and has led to a loss of neural inhibition of skeletal muscles (6). The synaptic vesicle protein amphiphysin was discovered in 1992 by Lichte et al. (7). This protein is responsible for endocytosis of the vesicle membrane after the exocytosis of GABA from the axonal terminal (2). Anti-amphiphysin Abs are strongly associated with the paraneoplastic variant of SPS. Underlying cancer can be occult at the time and be diagnosed within years from the initial neurological symptoms. Rarely, underlying cancer can be detected after 5 years from the initial manifestation (8). In our patient, although a breast mass was noted about a decade before the onset of stiffness and spasms, the patient did not seek any medical attention. A decade-long progression of breast cancer followed by manifestations of SLS is atypical for paraneoplastic neurologic syndromes. The age of disease onset and the rapidly progressive course in our patient are distinctively different from those of classic SPS.

Experts used to believe that amphiphysin Ab-associated paraneoplastic SPS cannot be distinguished from classic SPS on clinical grounds since both groups have proximal muscle involvement (9). However, in a large case series (Yale SPS project) by Murinson et al. (10), 11 out of 621 patients had amphiphysin Ab-associated SPS, and all 11 patients had arm and neck involvement. Compared with classic SPS, amphiphysin Ab-associated SPS has been described to have a different pattern of stiffness, more likely to involve the arms and neck. In contrast to what is known in the literature, our patient had asymmetrical stiffness in the legs (predominantly in the distal legs) with dystonic posturing of the feet. McKeon et al. (11) have suggested that amphiphysin Ab-associated SPS should be considered in patients with stiffness and spasms confined to the extremities.

In amphiphysin Ab-associated SPS, additional clinical features including myelopathy, neuropathy, encephalopathy, and cerebellar ataxia have been described in case series (12), indicating that its clinical phenotype could be different from that of classic SPS. Our patient has myelopathic features including lower-extremity weakness and pyramidal tract sign. Considering the clinical course, coexisting paraneoplastic myelopathy is highly suspected. Although the brain and whole-spine MRI are unremarkable and infectious myelopathy is excluded through CSF studies, B12 and folate are normal; copper and vitamin E are not checked, which could be a limitation of our study. Her nerve conduction study shows evidence of sensorimotor axonal polyneuropathy, but there is a confounding factor of newly diagnosed diabetes (HbA1C 7.2).

Based on the pathogenesis, there are two main treatment approaches for SPS: first, the use of GABA-enhancing drugs and, second, immunomodulation. In a small randomized controlled trial with 16 patients who had SPS and anti-GAD Abs, intravenous immunoglobulins (IVIGs) were effective in reducing spasms and improving functional outcomes (13). A recent study suggested the safety and efficacy of therapeutic PLEX as an adjunct to immunosuppressive therapy in GAD Ab-associated SPS (14). However, in paraneoplastic SPS, randomized controlled trials are lacking due to the rarity of the disease. Anecdotal evidence suggests that amphiphysin-associated SPS may not respond to IVIG (15), and there are case reports proposing PLEX with steroids in this condition (16). In the Yale SPS project, Murinson et al. (10) suggested that amphiphysin-associated SPS is steroid responsive and that tumor excision with chemotherapy may produce marked clinical improvement. Our patient has received oral glucocorticoids for presumed "gout flare" before hospitalization without significant response; however, the exact dose and duration are unclear. The lack of response to steroids could be due to inadequate dosing or advanced disease.

Our patient responded to symptomatic management with diazepam (GABAa agonist), but not to immunomodulatory therapy with PLEX during the hospitalization. She declined aggressive cancer treatment including surgical resection as well as chemotherapy and passed away 2 months after discharge. This is consistent with the literature that the mainstay therapy in paraneoplastic neurologic syndromes remains the treatment of the underlying malignancies.

CONCLUSION

SPS is a broad-spectrum disorder with heterogeneity in clinical phenotypes and associated Abs; it can be autoimmune or paraneoplastic. This case illustrates that the anti-amphiphysin SLS as a paraneoplastic neurologic syndrome associated with breast cancer can lead to devastating neurologic deterioration. This entity requires a high degree of suspicion for initiation of proper workup including neuroimaging, EMG/nerve conduction study (NCS), onconeural Ab testing, and cancer screening.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

BG produced the first draft of the paper and summarized the results. ES undertook the neurophysiology study and edited the paper. XF reviewed and edited the paper. JH helped with the pathology study and reviewed the paper. XL identified the case, revised, edited, and submitted the paper for publication. All authors made clinical and scientific contribution in writing the paper, read, and approved the final manuscript.

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frontiers in Neurology

CASE REPORT
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Case Report: Persisting Lymphopenia During Neuropsychiatric Tumefactive Multiple Sclerosis Rebound Upon Fingolimod Withdrawal

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Fingolimod (FTY) is a disease modifying therapy for relapsing remitting multiple sclerosis (RRMS) which can lead to severe lymphopenia requiring therapy discontinuation in order to avoid adverse events. However, this can result in severe disease reactivation occasionally presenting with tumefactive demyelinating lesions (TDLs). TDLs, which are thought to originate from a massive re-entry of activated lymphocytes into the central nervous system, are larger than 2 cm in diameter and may feature mass effect, perifocal edema, and gadolinium enhancement. In these cases, it can be challenging to exclude important differential diagnoses for TDLs such as progressive multifocal leukoencephalopathy (PML) or other opportunistic infections. Here, we present the case of a 26-year-old female patient who suffered a massive rebound with TDLs following FTY discontinuation with primarily neuropsychiatric symptoms despite persisting lymphopenia. Two cycles of seven plasmaphereses each were necessary to achieve remission and ocrelizumab was used for long-term stabilization.

Keywords: multiple sclerosis, rebound, tumefactive, lymphopenia, neuropsychiatric, fingolimod

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INTRODUCTION

Fingolimod (FTY), an effective oral disease modifying therapy (DMT) for relapsing remitting multiple sclerosis (RRMS), sequesters lymphocytes in lymphatic tissue such as the lymph nodes. Accordingly, in some cases it can lead to severe lymphopenia. This prompts many neurologists to discontinue therapy in order to avoid opportunistic infections even though clear proof of such a risk is still lacking (1). Since 2012, several cases have been reported describing severe disease reactivation following FTY withdrawal featuring tumefactive demyelinating lesions (TDLs) (2, 3). TDLs are defined as demyelinating lesions larger than 2 cm in diameter and may feature mass effect, perifocal edema and gadolinium (Gad) enhancement (4). Important differential diagnoses for TDLs are progressive multifocal leukoencephalopathy (PML) and/or opportunistic infections. In almost, all of these cases disease reactivation is accompanied by rapid lymphocyte reconstitution. Here, we present the case of a 26-year-old female patient (after obtaining written and informed consent) who suffered a massive rebound with subcortical edematous TDLs after FTY discontinuation due to lymphopenia which persisted for more than 6 weeks after therapy was halted. Her clinical

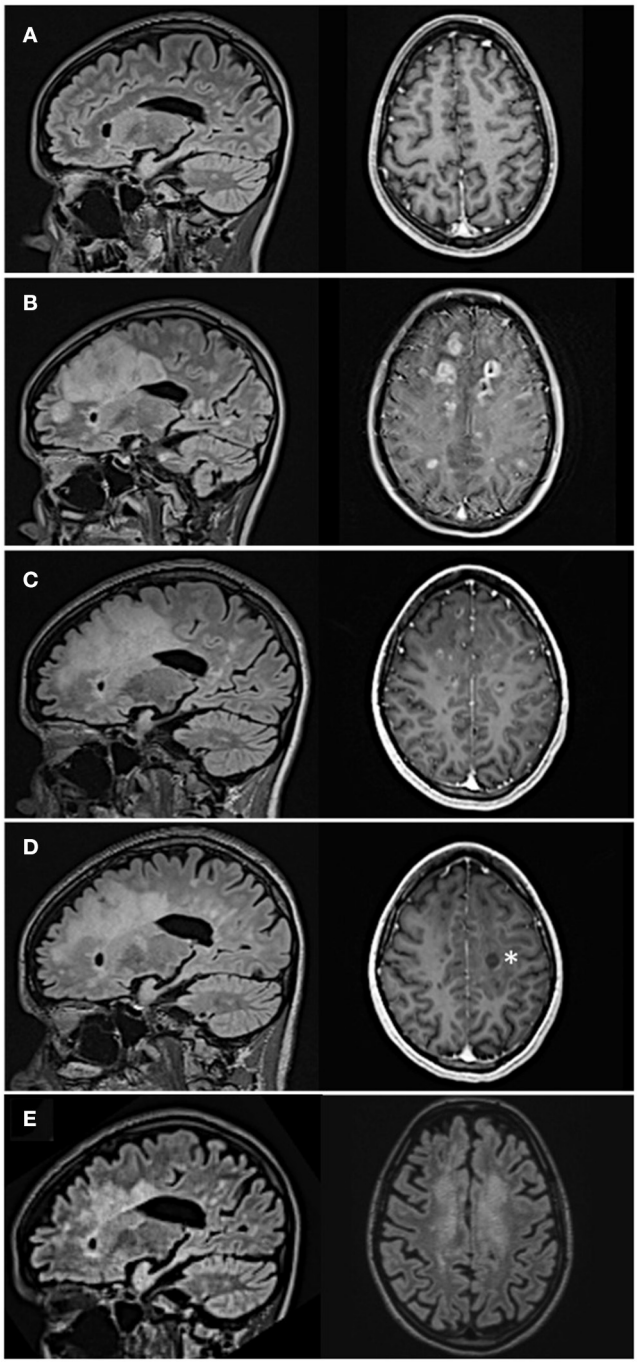

FIGURE 1 | MR-imaging during disease course. Sagittal FLAIR- and axial T1 gadolinium sequences. **(A)** Moderate lesion load under fingolimod treatment. **(B)** Frontoparietal tumefactive lesions with disseminated Gadolinium-enhancement 6 weeks after discontinuation of fingolimod. **(C)** Remittent Gadolinium-enhancement after four cycles of plasmapheresis. **(D)** Further remission at re-admission 2 weeks after the last cycle of plasmapheresis; asterisk indicates active lesion. **(E)** Lesions decreasing in size 6 months after ocrelizumab initiation (only axial FLAIR available).

symptoms were primarily neuropsychiatric including affective incontinence and motoric aphasia. To our knowledge, only one similar case was reported in the literature by Ashtari et al. (3).

CASE PRESENTATION

In a 26-year-old female patient with a 9-year history of RRMS, FTY treatment was discontinued due to lymphopenia of 225/μl and persisting disease activity in the form of optic neuritis. Prior to FTY she had been treated with interferon beta 1a and dimethylfumarate under which she had developed several relapses. Six weeks after FTY withdrawal the patient developed neuropsychiatric symptoms over the course of a few days including apathy, affective incontinence, and motoric aphasia. MRI revealed numerous tumefactive lesions with Gad enhancement and edema atypical of her prior disease course (**Figure 1A** prior MRI; **Figure 1B** MRI at admission). Under intravenous methylprednisolone therapy (1 g/d) over 5 days her neurological status deteriorated further. She could neither drink nor eat, suffered from psychomotor agitation and was unable to communicate with her caregivers, corresponding to an Expanded Disability Status Scale (EDSS) of 9.5. Her peripheral blood lymphocyte count at that time was 190/μl. After transfer to our clinic, we performed CSF analysis to rule out an infectious etiology. While we found a mild pleocytosis of 16/μl, three independent PCRs for JCV-DNA from serum and CSF were negative ruling out PML as a differential diagnosis. An extensive PCR and serological workup for borrelia, lues, and cryptococcosis was also negative, as well as anti-Aquaporin-4- and anti-MOG-antibodies. MR spectroscopy of a progressive lesion in the left frontal lobe yielded results suggestive of acute MS lesions (creatinin, cholin, and N-acetylaspartate slightly decreased, lactate slightly increased). The following day plasmapheresis was initiated, and the patient began to improve slowly. After the fourth plasmapheresis, she regained the ability to communicate and walk and was able to ingest small amounts of food. Follow-up MRI showed a decrease of the lesion size and number as well as the Gad enhancement (**Figure 1C**). After completion of seven plasmaphereses the patient could be transferred to a rehabilitation facility with an EDSS of 7.5. However, 2 weeks later she developed right sided hemiparesis. Corticosteroid therapy was started, and she was eventually readmitted to our hospital. Peripheral lymphocytes had increased to 890/μl but were still below the lower limit of normal. While MRI showed an overall decrease of Gad-enhancing lesions one subcortical lesion had remained active (**Figure 1D**, asterisk). As her symptoms had failed to improve under corticosteroids, a second cycle of seven plasmaphereses was initiated and the patient improved daily so that she was, again, released to a rehabilitation facility. The first dose of ocrelizumab (300 mg) was administered 7 weeks later. Six months after ocrelizumab initiation the patient remained relapse-free and showed clinical improvement now walking 1 km without help (EDSS 4.5). MRI showed a further remission with no remaining Gad enhancement (**Figure 1E**). **Figure 2** shows an overview of the clinical course including relapses and DMT switches as well as total lymphocyte counts.

DISCUSSION

Several case reports describe tumefactive disease rebounds associated with fingolimod treatment (5) which may be linked

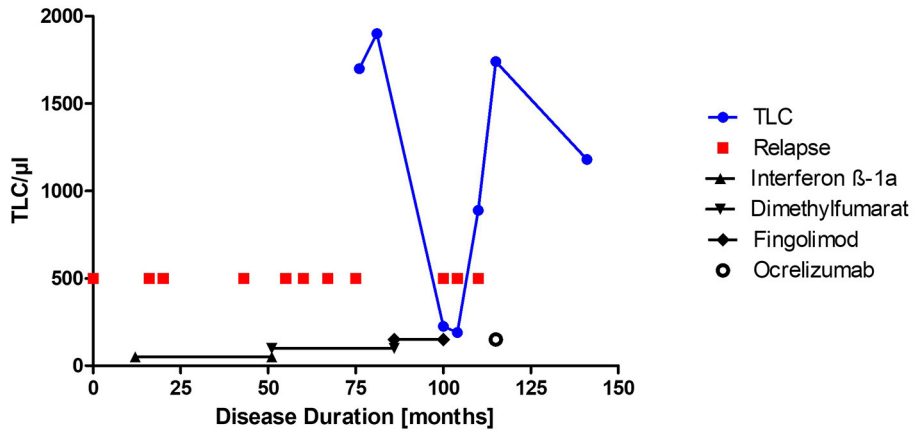

FIGURE 2 | Clinical course and total lymphocyte count. Total lymphocyte count (TLC)/µl is depicted over the disease course. Relapses are shown as red squares. Duration of disease modifying therapies is shown with the black symbols, respectively. Ocrelizumab therapy was initiated and is still ongoing.

to fingolimod-induced modulation of vascular permeability as observed in macular edema (6). However, the cases that occurred after FTY discontinuation are of particular interest as *post-hoc* analyses of the FREEDOMS and FREEDOMS II trials did not find a significantly increased risk of severe disease reactivation after FTY discontinuation (7). Sato et al. (8) presented a case series of 19 patients who were switched from fingolimod to dimethylfumarate. Ten of them experienced disease reactivation after cessation, with seven meeting the definition of rebound. Two patients suffered from persisting lymphopenia after 4 weeks but experienced no rebound. The seven rebound patients had a normal total lymphocyte count (TLC) at reactivation. However, most other case reports report either a normal lymphocyte count or provide no information on TLC. In rebound cases, it is hypothesized that rapid lymphocyte reconstitution and consecutive re-entry of lymphocytes into the CNS may cause an immune reconstitution inflammatory syndrome (IRIS)-like condition (9). This concept is corroborated by the fact that severe rebound events typically occur 2–4 months after therapy discontinuation at which time lymphocyte counts usually reach normal levels again. Furthermore, in mice FTY discontinuation can induce sphingosine-1-phosphate 1 (S1P1) overexpression in lymph-node entrapped lymphocytes leading to a massive sequential egress of lymphocytes (10). The resulting inflammatory spinal cord infiltrates are significantly higher than in vehicle-treated mice. However, in our patient disease reactivation occurred during persisting lymphopenia, which has been shown to be associated with low TCL before and under FTY treatment (11). In this context, the activity of brain-resident astrocytes may play a pivotal role. Giordana et al. (12) reported a fatal case of disease reactivation initially presenting with TDLs and symptoms similar to our patient. Autopsy revealed a strong S1P1 immunoreactivity on hypertrophic reactive astrocytes in active demyelinating lesions and in the periplaque normal appearing white matter (NAWM). The authors propose that upon FTY withdrawal, overexpression of S1P receptors on hyperactive astrocytes may lead to an activation of the pro-inflammatory transcription factor NFκB. A subsequent massive release of inflammatory cytokines and nitric oxide (NO) may explain the remarkable radiological characteristics and velocity of clinical deterioration. Due to an impaired blood brain barrier (BBB), these brain-derived inflammatory cytokines might diffuse into the peripheral blood where they would be cleared by plasmapheresis. This could explain the clinical improvement observed in our case. However, *in vitro* or *in vivo* data describing the precise mechanism of astrocyte cytokine release after FTY withdrawal is currently lacking. The main aspect to be learned from this case is that lymphocyte counts following FTY cessation are not a reliable tool to predict the probability of rebound. One of the most important risk factors is, however, persisting disease activity under FTY treatment flaring up after cessation (13). Moreover, with regard to impending disease reactivation a 6-week drug-free period before starting a new DMT could be too long even with persistent lymphopenia as stated by Bigaut et al. (14) in the Guidelines of the French Multiple Sclerosis Society. The authors recommend starting a new first-line therapy without a washout period and starting therapy with ocrelizumab and natalizumab after a washout period of 1 month. In both cases, TLC should not be taken into account concerning pre-therapeutic assessments. Thirdly, as suggested by Sato et al. (8), it is worthwhile to measure the ratio of TLCs even if that was not applicable in our case. This could help to decide when to start a new DMT after FTY cessation despite persisting lymphopenia. However, further studies are needed to define a cut-off value. Regarding differential diagnoses for tumefactive lesions the clinician should always rule out opportunistic infections such as herpes simplex virus (HSV), varicella zoster virus (VZV), cerebral cryptococcosis and PML. As of February 2020, 37 MS patients had contracted PML in the context of FTY therapy. Even though several studies could not confirm an increased infection rate due to lymphopenia (1) the European Medicines Agency (EMA) recommends discontinuation of FTY treatment

when lymphocyte counts drop below 200/μl. Irrespective of these considerations, in the case presented here FTY discontinuation was indicated due to persisting disease activity.

CONCLUSION

In summary, we conclude that more detailed and standardized guidelines are needed for either continuation or termination of therapy in persistent lymphopenia. However, a definitive potential risk factor for rebound to be considered is persistent disease activity under prior treatment (13). Secondly, the washout period after FTY cessation before starting a new DMT should not exceed 1 month and should not be dependent on TLC at the time of cessation (14). Finally, for the clinician it is important to bear in mind that neuropsychiatric symptoms in young MS patients might indicate disease rebound.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

VK, SM, and DK gave the idea of case reporting. VK and DK analyzed the case and prepared the MRI scans as well as the figure and the table. VK drafted the manuscript for intellectual content. MF, KB, EA, PA, OA, PK, SM, and DK critically reviewed the manuscript and were involved inpatients' healthcare. All the authors contributed to the article and approved the submitted version.

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CASE REPORT
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A New Report of Combined Central and Peripheral Demyelination: A Case Report

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Combined central and peripheral demyelination (CCPD) is not encountered frequently in the clinical practice, and it requires a high level of suspicion for diagnosis. We describe a case of a young man who was diagnosed with radiologically isolated syndrome (RIS) after presenting initially with symptoms suggestive of central nervous system (CNS) insult in the form of double vision, slurred speech, left-sided numbness, and unsteadiness. However, on the next day of admission, his neurological examination was remarkable for ataxia, areflexia, and ophthalmoplegia, the typical triad of Miller Fisher syndrome (MFS). After confirming both diagnoses, the final diagnosis of CCPD was made. The challenges one may face to diagnose and treat CCPD urge sharing of similar cases to open the door for further extensive and thorough investigations and to encourage further studies and analysis of available data to come up with consolidated management guidelines for rare disorders.

Keywords: radiologically isolated syndrome, multiple sclerosis, miller-fisher syndrome, combined central and peripheral demyelinating disease, MRI, GQ1b

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INTRODUCTION

Demyelinating disorders are usually divided into the central nervous system (CNS) and peripheral nervous system (PNS) demyelination. The presence of both—CNS and PNS-demyelinating disease—in a patient is relatively rare (1). In this case report, our patient was diagnosed with Miller Fisher syndrome (MFS), which is a syndrome characterized by ataxia, ophthalmoplegia, and areflexia (2). Moreover, the patient was diagnosed with radiologically isolated syndrome (RIS) based on the MRI findings that are highly suggestive of multiple sclerosis (MS). MS is a chronic inflammatory demyelinating disease of the CNS characterized by multiple lesions disseminated in time and space (3). Our case is notable for the presence of characteristic MS-demyelinating lesions in a patient newly diagnosed with MFS.

CASE PRESENTATION

A 31-year-old left-handed Saudi man, a heavy smoker, who does not consume substance or alcohol, and has no remarkable medical or family history, was admitted with double vision, slurred speech, left-sided numbness, unsteadiness, and constipation. He had no fever on admission, was fully conscious, and had no symptoms of meningeal

irritation, history of contact with sick individuals or antecedent vaccination or infection. Before his presentation, the patient had a 2-week history of left upper limb paroxysmal numbness lasting for only a few seconds and was labeled as a possible case of MS at an outside medical facility after brain and spinal magnetic resonance imaging (MRI). There was a history of unintentional 20-kg weight loss in the past 6 months; however, there were no other constitutional symptoms.

Initial examination findings and vital signs were within normal limits, and gastrointestinal, respiratory, and cardiovascular examinations were normal. On neurological examination, the patient was conscious, alert, and oriented. Visual acuity was 20/16 bilaterally, pupillary reflex was 7 mm and non-reactive bilaterally, and bilateral internuclear ophthalmoplegia with left-sided non-fatigable ptosis were observed. The patient had normal tone and muscle bulk. Power was 5 of 5 in all limbs, and all tendon reflexes were +1, with a normal plantar reflex. There was a decrease in vibration sensation up to the head of the fibula on the left side. Dysmetria was noted bilaterally on the finger-to-nose and heel-to-shin tests and was more profound on the left side. Truncal ataxia was noted, and the patient could only walk with assistance and was unable to perform tandem gait.

Biochemical, hematological, liver, and renal functions, virological (HIV, hepatitis B, hepatitis C, herpes simplex Types 1 and 2, rubella, COVID-19), brucellosis, and toxoplasmosis test results were all negative or within normal ranges. Toxicological screening results were negative. Cerebrospinal fluid (CSF) examination showed the following: white blood cells, 2 cu mm; red blood cells, 70%; albumin, 20 mg/dl; protein, 33 mg/dl, glucose, 83 mg/dl; and serum glucose was 128 mg/dl. Oligoclonal bands (OCB) were detected in the CSF and absent in the serum. CSF culture and encephalitis or meningitis panel were negative. Immunological studies were performed; antinuclear antibody, antiphospholipid IgM and IgG, anti-dsDNA, anticardiolipin IgM and IgG, anti-Sjogren antibody SSA and SSB, and extractable nuclear antigen were all negative.

In the imaging, brain MRI with contrast was performed on the day of admission and showed multiple abnormal high signal intensities involving cortical, juxtacortical, subcortical, and periventricular with one lesion at the left anterior aspect of the pons. Additionally, some lesions were perpendicularly oriented to the corpus callosum representing Dawson's fingers (**Figure 1**). Spinal cord MRI showed multiple abnormal high signal intramedullary lesions at the central, posterior, and lateral aspects of the cervical and thoracic spinal cord (**Figure 2**). Pan computed tomography (CT) scan and bronchoscopy were also performed and were unremarkable for malignancies.

On the second day of admission, the patient received 1 g of intravenous methylprednisolone with a presumptive diagnosis of MS relapse. Unexpectedly, the patient deteriorated 5 h after receiving the dose. He initially complained of nausea, which was followed by choking on liquids, worsening numbness on the left side, and followed by inability to swallow his saliva. The pupils were 7 mm and non-reactive bilaterally, and there was decreased facial sensation on the left side associated with a head drop. The power was normal in all limbs except for the left upper limb, which was 3 of 5. Reflexes were absent, and the plantar response was equivocal. Then, the patient was intubated and transferred to the intensive care unit (ICU) on the third day of admission. In the ICU, a central line was placed in the internal jugular vein, and plasma exchange was started. Replacement fluid consisted of fresh frozen plasma and normal saline in equal volumes. Plasma exchange sessions were done on a daily basis; after 8 days, improvement in the pupil size and eye movement has been noticed, and we have decided to add two more sessions. During the treatment period, the patient did not experience any complications related to the replacement fluid or vascular access, and the total volume of plasma exchanged was 3,600 cc.

Following the deterioration of the patient, MRI with contrast of the brain and whole spine was performed and showed no new changes compared with the MRI findings performed on admission. A follow-up MRI was done 10 days on the 13th day of admission and revealed no changes compared with the previous one.

On the third day, visual evoked potential was performed and revealed a left P100 wave latency prolongation: left, 170 ms; right, 191 ms. Nerve conduction study (NCS) was performed and showed normal findings. However, the NCS's interpretation was limited by ICU artifacts. Additionally, lumbar puncture was repeated on the fourth day of admission and showed 0 white blood cells, and the protein level of 71 mg/dL, which showed typical albuminocytologic dissociation.

Further diagnostic tests were ordered and showed the following: Testing for anti-ganglioside antibodies revealed positivity for anti-GQ1b with titers of 324. Anti-NMO antibodies, anti-MOG antibodies, anti-VGKC, GlyR, anti-neurofacin antibodies, botulism toxin, and paraneoplastic panel were all negative. Antibodies against *Campylobacter jejuni* were negative.

The patient was in the ICU for 18 days; during which, he developed ventilator-associated pneumonia and was managed with antibiotics. Tracheostomy was performed 10 days after ICU admission due to failure of weaning off intubation.

Electromyography and NCS were repeated on the 25th day of admission. The NCS of the left and right median, ulnar, peroneal, and tibial nerves revealed normal distal latencies, compound muscle action potentials (CMAPs), and conduction velocities. Electromyography detected changes in enervation in the form of fibrillation and positive sharp waves in the right frontalis and orbicularis oris muscles with rapidly firing motor unit action potentials (MUAPs), which showed reduced recruitment.

The tracheostomy weaning-off protocol was started soon after transfer to the ward. The nasogastric tube was removed with closure of the tracheostomy, and the patient tolerated a regular diet. On the 40th day, the patient was cleared for discharge as

Abbreviations: CCPD, Combined central and peripheral demyelination; RIS, radiologically isolated syndrome; CNS, central nervous system; MFS, miller-fisher syndrome; PNS, peripheral nervous system; MS, multiple sclerosis; CSF, cerebrospinal fluid; OCB, oligoclonal bands; MRI, magnetic resonance imaging; CT, computed tomography; ICU, intensive care unit; NCS, nerve conduction study; CMAPs, compound muscle action potential; MUAPs, motor unit action potentials; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy.

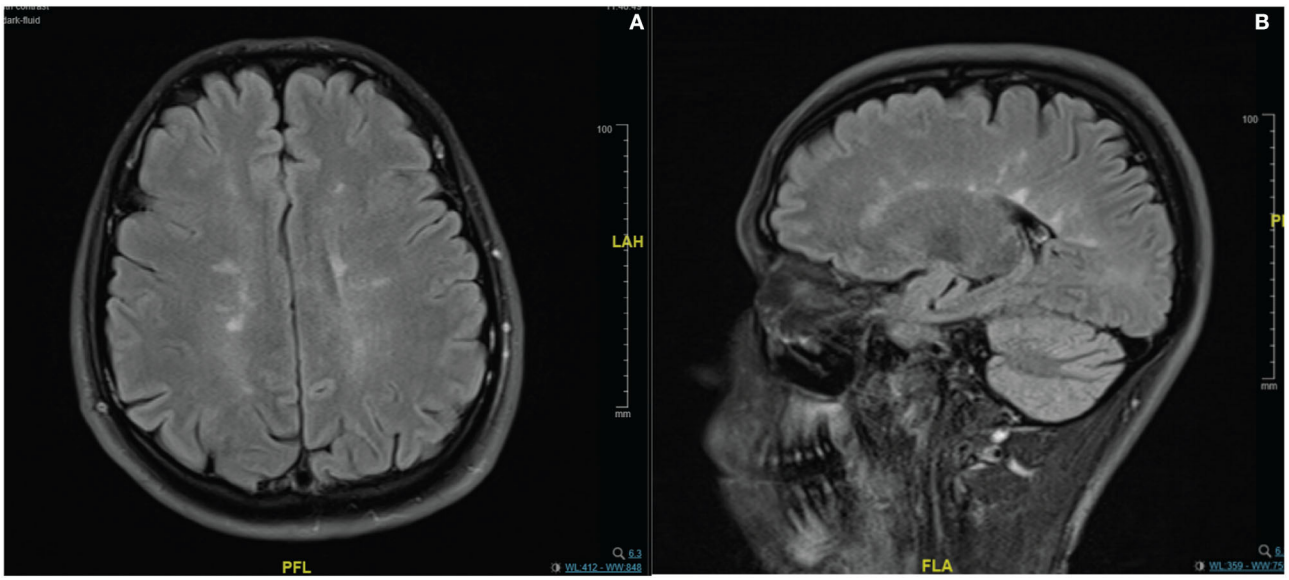

FIGURE 1 | Contrast enhanced MRI brain imaging on the day of admission. Fluid attenuated inversion recovery (FLAIR) sequence **(A,B)**. Showing multiple abnormal high signal intensities involving cortical, juxtacortical, subcortical, and periventricular regions. Some lesions were perpendicularly oriented to the corpus callosum representing Dawson's fingers.

he was able to feed himself independently and ambulate by using a walker.

On the 66th day, the patient visited the clinic, was able to walk without any assistance, and has reported significant improvement in ataxia and diplopia. On examination, the right pupil was 4 mm reactive, and the left pupil was 5 mm with a sluggish reaction to light. Additionally, there was a mild limitation in the vertical gaze and adduction movement of both eyes. Muscle tone was normal, and power was 5/5 in the right upper and lower limbs, and 4/5 in the left upper limb. Deep tendon reflexes were +1 in the right and left upper limbs and absent in the lower limbs. The neck flexors and extensors had a power of 5/5. There was a noticeable improvement in the finger-to-nose test; however, dysmetria was noted more on the left side. The patient can walk unassisted with mild ataxia and can perform tandem gait with moderate difficulty. After almost 7 months from discharge, the brain MRI with contrast was repeated and showed a stable demyelinating process with no new T2 hyperintense lesions or enhancement.

DISCUSSION AND CONCLUSIONS

Our patient fulfills the MRI McDonald criteria for dissemination in space along with the presence of OCBs; however, the diagnosis of MS could not be made as the patient did not exhibit a clear clinical demyelinating attack as the numbness was intermittent, lasting only for a few seconds. Additionally, the numbness could be explained as a part of Miller Fisher's initial symptoms. Furthermore, the INO is most likely a pseudo-INO rather than a true one, as the site and the size of the lesion seen in the pons do not explain the occurrence of a true INO.

During the course of his hospital stay, the patient exhibited the typical triad of MFS, consisting of ataxia, areflexia, and ophthalmoplegia. Another finding supporting the diagnosis of MFS was the presence of albuminocytologic dissociation in the second CSF sample of the patient. GQ1b antiganglioside antibody, which is associated with MFS, was also positive, with a titer of 324 (4).

Our differentials steered away from MS relapse and toward other PNS disorders, following rapid deterioration after methylprednisolone administration. Guillain-Barre syndrome was considered as one of the differential diagnoses; however, the clinical picture of the patient in the form of ophthalmoplegia and ataxia did not support the diagnosis. Furthermore, the absence of deep tendon reflexes and the lack of alteration in the mental status of the patient during the course of the disease argued against Bickerstaff encephalitis. Another differential was botulism; however, it was relatively unlikely because of its rarity and unremarkable history of recent ingestion, which was objectively ruled out by the negative result of the botulism toxin test.

Currently, there is no established diagnostic criteria for combined central and peripheral demyelination (CCPD) (5). The patient was labeled as a case of CCPD due to the involvement of both CNS and PNS. A study performed by Pender et al. in 2003 showed that patients with primary progressive MS have a significant increase in peripheral T-cell reactivity to GM3 and GQ1b gangliosides compared with healthy subjects and patients with other CNS diseases, which might explain the co-occurrence of MFS and the characteristic MS lesions in our patient (6). The absence of enhancing lesions and the possibility of having transient OCBs in the CSF makes it unlikely that

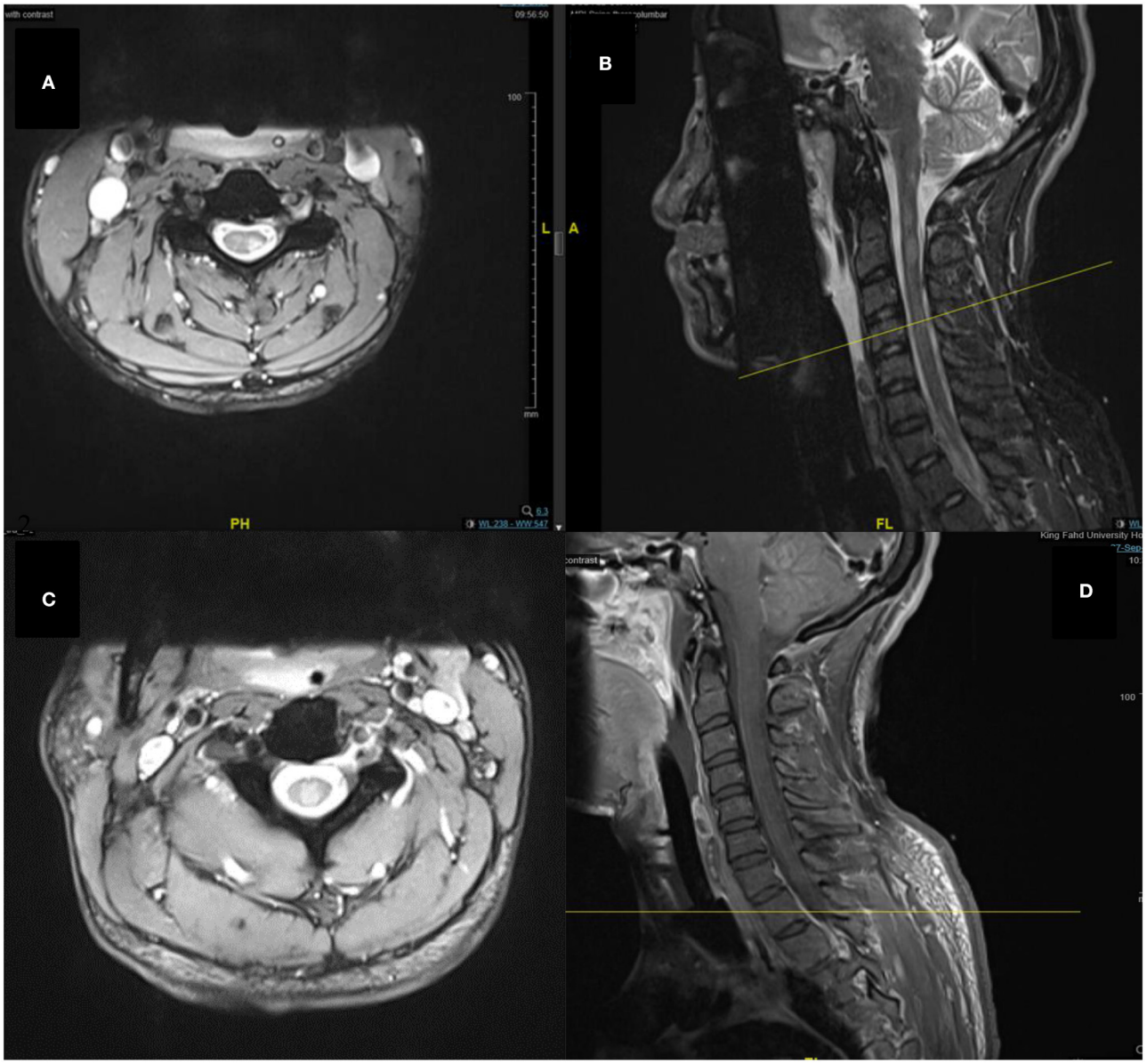

FIGURE 2 | Spine MRI images of T2-weighted **(A)**, sagittal short tau inversion recovery (STIR) **(B)**, T2-weighted **(C)**, and sagittal T1-weighted with contrast **(D)** sequences. Showing multiple abnormal high signal intramedullary lesions at the central, posterior, and lateral aspects of the cervical and thoracic spinal cord.

the patient is having the two conditions simultaneously. For that, further follow-up is needed for possible future relapses and recurrences to confirm the diagnosis of MS. Managing this patient was challenging since there was no previous treatment guide for a similar course of illness to predict the outcomes.

We searched PubMed and other databases with the following search words: "miller fisher," "central nervous system," and "magnetic resonance imaging." Multiple studies describing patients diagnosed with MFS with a concurrent CNS lesion have been found (7–10); however, the clinical course, CSF results, and MRI features in these patients were not typical for MS (**Table 1**). In a case reported by Xu and Liu a 37-year-old man presented with diplopia, dizziness, ptosis, and bilateral upper limb numbness (7). Through investigation of the patient, MRI revealed multiple lesions at the juxtacortex, subcortex, and deep white matter in the left frontal and occipital lobe, the signals were hypointense in T1-weighted images and isointense in diffusion-weighted images, and there was no enhancement after contrast administration. CSF analysis was significant for pleocytosis alone. The NCS was normal, apart from the absent tibial H reflexes. During the stay of the patient, no antibodies were detected. The patient was managed with IVIG (0.4 g/kg per day for 5 days) and recovered fully

TABLE 1 | Reported cases of Miller-Fisher syndrome with concurrent central nervous system lesions.

References	Present case	Xu and Liu (7)	Tezer et al. (8)	Echaniz-Laguna et al. (9)	Urushitani et al. (10)
Age	31	37	54	42	50
Sex	M	M	M	F	M
Initial symptoms	Diplopia, dysarthria, left sided numbness, unsteadiness, and constipation	Diplopia, unsteady gait dizziness, left eyelid ptosis and distal numbness on both upper limbs	Vertigo, diplopia, difficulty in swallowing, and unsteadiness	Diplopia, unsteadiness, and lower limb weakness	Diplopia, bilateral eyelid ptosis, ataxic gait, nausea, and vomiting
Albuminocytological dissociation	Yes	No	No	Yes	Yes
CSF OCB	Detected	Not reported	Negative	Negative	Not reported
NCS	Abnormal	Abnormal	Abnormal	Abnormal	Normal
Antibodies profile	GQ1b	Negative	Not tested	Negative	Not tested
MRI findings	Brain: multiple lesions in cortical, juxtacortical, subcortical, periventricular, and pons Spine: multiple cervical and thoracic intramedullary lesions	Brain: multiple lesions in the juxtacortex, subcortex and deep white matter	Lesions in the pons, medulla oblongata and cerebellar peduncle	Lesions in cerebral white matter, brainstem, and cerebellum	Enhancing lesions in the spinocerebellar tracts at the level of the lower medulla
Treatment	Plasma exchange (10 sessions)	IVIG (1 course)	IVIG (1 course) Acyclovir	IV methylprednisolone	IV methylprednisolone plasma exchange
Outcome	Partial recovery after 66 days	Complete recovery after 60 days	Complete recovery after 6 months	Complete recovery after 40 days	Complete recovery after 3 months

CSF, cerebrospinal fluid; OCB, oligoclonal bands; NCS, nerve conduction study; IVIG, IV immunoglobulin.

after 60 days. The mentioned case had an almost identical initial clinical presentation to our patient, in addition to being male in the same age group. However, there was no diagnosis of CNS lesions, and findings of our patient did not return to the baseline after 66 days and 10 sessions of plasma exchange.

In a case report published in 1995, a 50-year-old man presented with diplopia, bilateral ptosis, and ataxic gait (10). MRI revealed bilaterally enhancing lesions in the lateral lower medulla, consistent with the anterior and posterior spinocerebellar tracts. The patient was diagnosed with MFS, managed with methylprednisolone and plasma exchange, and had full recovery within 3 months. As shown in **Table 1**, all cases reported to have MFS with CNS lesions achieved full recovery; moreover, their recovery period was variable and ranged from 40 days to 6 months.

Compared with studies reporting on CCPD cases, a case reported by Katchanov et al. where they describe a patient diagnosed with acute disseminated encephalomyelitis and acute inflammatory demyelinating polyradiculoneuropathy, the laboratory workup was significant for a positive GQ1b and GM1; he was managed with methylprednisolone, and the condition worsened; following which, he received one course of IVIG, followed by six sessions of plasma exchange and had partial recovery within 1 year (11). Another patient diagnosed with clinically isolated syndrome and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) simultaneously was managed with prednisone 100 mg one time daily and azathioprine 100 mg two times daily and achieved partial recovery within 6 months (12). Moreover, a case reported in 2019 with an unspecified disease of the CNS accompanied with CIDP had a positive anti-neurofacin, which is associated with CCPD, and it has been recently found that patients with positive anti-neurofacin respond well to IVIG or plasma exchange (5, 13). Although our patient had a negative anti-neurofacin during the investigation, he responded well to plasma exchange, which may indicate that plasma can be still beneficial in cases with CCPD and negative anti-neurofacin. As for the case mentioned earlier, he was managed with IVIG and motor rehabilitation, and there was a good response to treatment for

3 months; after which, the condition of the patient worsened; after which, he received methylprednisolone. Then, he had relapsed and was prescribed azathioprine and steroids, and partial recovery was achieved after 3 years. In a case reported by Nouha et al., the patient was diagnosed with MS and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (14). They managed him with methylprednisolone and interferon β-1a; however, the treatment resulted in only mild initial improvement and was ineffective. Regarding the management of CCPD cases, plasma exchange was found to be effective in 87.5% of the cases, and it was, indeed, effective in this case (15). Although recovery periods varied between patients diagnosed with CCPD, none of the reported cases we accessed gained full recovery.

This case sheds light on a different combination of CNS and PNS involvement consisting of RIS and MFS, which warrants extensive investigation in CCPD cases, which is now generally viewed as a combination of MS and CIDP alone. Further studies and analysis of available data are needed with respect to this topic since the resources and cases shared are insufficient to have a clear guideline for their management or follow-up to determine the possible prognosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

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CASE REPORT
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Recurrent Anti-AMPA Receptor Limbic Encephalitis: A Case Report and Literature Review

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Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor encephalitis is a relatively rare anti-neuronal surface antigen autoimmune encephalitis (LE). We described a case of a 47-year-old Chinese man having anti-AMPA receptor limbic encephalitis initially presented with cognitive decline, undetectable antibodies, and normal imaging findings in magnetic resonance image (MRI) and then developed into typical autoimmune limbic encephalitis a few months later with a course of multiple relapses. In addition, we found progressive brain atrophy in our case, which was a rare presentation of LE. This report also summarized the characteristics of nine reported cases of anti-AMPA receptor limbic encephalitis with relapse up to date. This case highlighted that autoimmune limbic encephalitis is an important differential diagnosis for patients with typical symptoms even when the MRI and antibodies are normal, and more attention should be paid to the relapse of anti-AMPA receptor encephalitis.

Keywords: autoimmune encephalitis, anti-AMPA receptor, relapse, brain atrophy, case report

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INTRODUCTION

Autoimmune limbic encephalitis is a neurological disorder characterized by a sub-acute onset of clinical manifestations including mood change, cognition impairment, confusion and seizures, and brain abnormality in the medial temporal lobe on MRI (1). Autoimmune limbic encephalitis is usually accompanied with antibodies, consisting of antibodies against intracellular antigens including Hu, Ma2, and glutamic acid decarboxylase (GAD), and antibodies against cell-surface antigens including synaptic receptors including gamma-aminobutyric acid type B ($GABA_B$) receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and leucine-rich glioma inactivated 1 (LGI 1) (1). The encephalitis associated with antibodies against neuronal cell-surface antigens is more responsive to immunotherapy than those with antibodies against intracellular antigens. The anti-AMPA receptor encephalitis is relatively rare, compared to other autoimmune encephalitides (2). This report describes an anti-AMPA receptor limbic encephalitis case, in which the patient was presented with cognitive decline and without detectable antibodies at first, and developed into typical limbic encephalitis a few months later. The case is unique for its insidious onset with undetectable antibodies at first and the relapses of encephalitis. In addition, this report also summarized the cases of anti-AMPA receptor limbic encephalitis with relapse from January 1, 2000, to December 31, 2020.

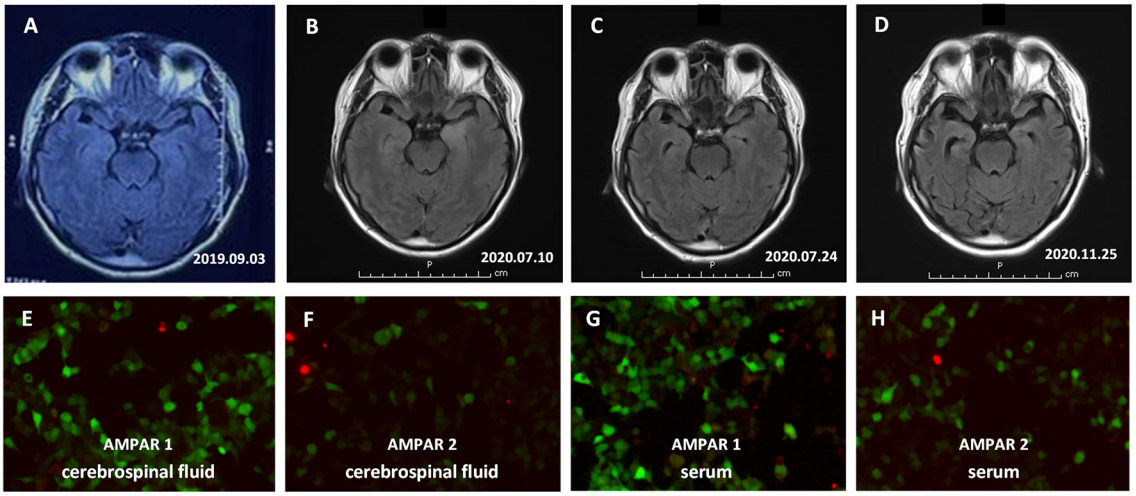

FIGURE 1 | The result of Brain MRI and Anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR) antibodies in the serum and cerebrospinal fluid (CSF). **(A–D)** Brain MRI showed high signal changes on fluid-attenuated inversion recovery sequences predominantly affecting the bilateral medial temporal lobe combined with some parts of the temporal cortex and progressive brain atrophy. **(A)** At the onset of the disease; **(B)** Onset for more than 10 months; **(C)** After 2 weeks of hormone shock therapy; **(D)** Follow-up for 4 months after discharge. **(E–H)** Anti-AMPAR1 and Anti-AMPAR2 antibodies in the serum and CSF of the patient were positive, as tested by the CBA method. **(E)** Anti-AMPAR1 antibodies in CSF; **(F)** Anti-AMPAR2 antibodies in CSF; **(G)** Anti-AMPAR1 antibodies in serum; **(H)** Anti-AMPAR2 antibodies in serum.

CASE PRESENTATION

A 47-year-old man was admitted to our hospital for progressive cognitive decline and apathy for 10 months. History taking revealed no infection, vaccination, or significant weight loss within 6 weeks and no other medical history. His family had no history of auto-immune and hereditary diseases. Further general and neurological examination of the body revealed no abnormalities except for cognitive decline and active tendon reflexes in limbs. The long-term and short-term memory, the ability of calculation, as well as temporal and spatial perception were found to be impaired.

In further elaboration, 10 months ago (September 3, 2019), the patient was admitted to the first hospital for memory loss in 4 days. The symptoms of the patient started with the inability to remember what happened just now, unresponsive, and apathy. But the ability of daily living was not significantly impaired. Intracranial infection and acute cerebrovascular disease were suspected, but initial brain MRI (**Figure 1A**) and lumbar puncture were normal. The autoantibodies and paraneoplastic antibodies in serum and CSF were not performed in the hospital. The scores of the Geriatric Depression Scale were 12, accordingly, the patient was treated with flupenthixol/melitracen and escitalopram.

About 2 months later (October 28, 2019), he was admitted to the second hospital because of his worsened short-term memory, temporal, and spatial perception. The examination of Mini-Mental State Examination (MMSE) scores was 22/30. Normal findings of routine blood tests included neutrophil/hemoglobin/platelet counts, liver and renal function tests. Other investigations included thyroid function, erythrocyte sedimentation rate, antinuclear antibody, anti-neutrophil cytoplasmic antibody, anti-β2 glycoprotein antibody, anti-cardiolipin antibody, extractable nuclear antigen, complement levels, serum protein electrophoresis, porphyria screen, tumor biomarkers, organic acid, poison screening were within normal limits. Hepatitis B virus serology, HIV serology, treponema pallidum serology, tuberculosis, and CD4 T cell count were negative. CSF analysis was normal, including cells, protein, glucose, oligoclonal bands, herpes simplex virus 1 and 2, varicella-zoster virus, enterovirus, meningococcus, parasites, treponema pallidum. The metagenomic next-generation sequencing (mNGS) was also conducted in the CSF sample but no pathogen (detection ranging from viruses to bacteria, fungi, and parasites) was identified. A repeat MRI brain was normal. Video electroencephalogram (EEG) showed low-amplitude fast waves. Even though the MRI brain and CSF of the patient were normal, autoimmune or paraneoplastic encephalitis was suspected based on the clinical presentation. Further ultrasonography examination of the abdominal organs, thyroid gland, and CT scan of the thorax showed no evidence of malignancy. Screening tests were also negative for autoimmune encephalitis antibody (NMDA-R, CASPR2, AMPA1-R, AMPA2-R, and LGI1), paraneoplastic antibody (Hu, Yo, Ri, PNMA2, CRMP5, and amphiphysin), and myelin-related antibodies (MBP-Ab, MOG-Ab, AQP4-Ab). No special treatment was given due to an unclear diagnosis. While in hospital, he developed rapidly progressive memory deficits, abnormal behavior like

Abbreviations: AMPA, Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; LE, autoimmune encephalitis; MRI, magnetic resonance image; GAD, glutamic acid decarboxylase; GABAB, gamma-aminobutyric acid type B; LGI 1, leucine-rich glioma inactivated 1; MMSE, Mini-Mental State Examination; EEG, electroencephalogram; CSF, Cerebrospinal fluid; IVIG, Immunoglobulin; OCB, oligoclonal bands.

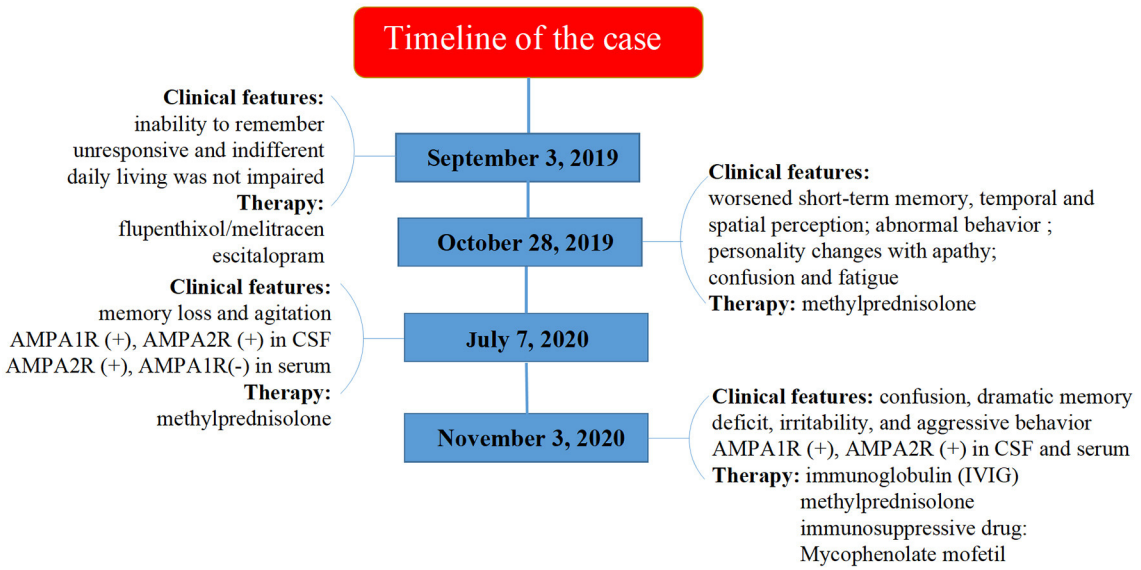

FIGURE 2 | Timeline of the case.

teasing children and making funny faces, and personality changes with apathy. He was easy to get lost, in addition to confusion and fatigue. Based on the results of the preliminary physical examination and progression of the disease, autoimmune/viral encephalitis was suspected. Accordingly, the patient was treated with intravenous injection of methylprednisolone 1 g daily, halved every 3 days, and tapered over 12 days and at the same time with antiviral drug acyclovir. Oral prednisolone (70 mg/day) was initiated on day 13, and then gradually tapered to a maintaining dose (10 mg/day). The condition of the patient gradually improved, and he could come back to normal life and work.

In July 2020, the patient was admitted to our hospital for a relapse characterized by memory loss and agitation. Repeat brain MRI showed high signal changes on T2 and fluid-attenuated inversion recovery sequences predominantly affecting the bilateral medial temporal lobe combined with some parts of the temporal cortex (**Figure 1B**). CSF neural-specific antibodies detection *via* cell-based assay (further details around the laboratory were provided in **Supplementary Materials**) found antibodies against AMPA1R (titer, 1:1) and AMPA2R (titer, 1:10); serum also showed the presence of anti-AMPA2R (1:32), but anti-AMPA1R was undetected. EEG showed diffuse slow waves. CT scan of thorax/abdomen/pelvis was negative for neoplasia. The diagnosis of autoimmune encephalitis prompted immediate treatment with a second course of methylprednisolone for 12 days (methylprednisolone 1 g daily, halved every 3 days, and tapered over 12 days). A repeat brain MRI showed the increased signal in temporal lobes had improved and there was atrophy of the medial temporal lobe (**Figure 1C**). The memory of the patient improved, and he could take care of himself with the assistance of family members when discharged.

After 4 months (November 3, 2020), the patient was admitted to our hospital again for a relapse characterized by confusion, dramatic memory deficit, personality changes with irritability, and episodes of aggressive behavior. Antibodies against AMPAR1 and AMPAR2 were detected both in the serum and CSF of the patient. The titer of AMPAR1 is 1:10 in CSF (**Figure 1E**) and serum (**Figure 1G**), and the titer of AMPAR2 is 1:100 in CSF (**Figure 1F**), 1:1000 in serum (**Figure 1H**). Owing to the recurrence, the patient was treated with intravenous injection of immunoglobulin (IVIG) combined with a repeat course of methylprednisolone and oral immunosuppressive drug (mycophenolate mofetil). He responded well to the treatment with the improvement of abnormal and aggressive behavior. Repeat MRI brain 3 weeks after admission showed significant atrophy of bilateral medial temporal lobe and temporal cortex (**Figure 1D**). Mycophenolate mofetil (3 g/day) was maintained when discharged. During the follow-up of a half year, he has had no further relapses and returned to work (MMSE 27 and mRS 1).

The timeline of the case was summarized in **Figure 2**.

DISCUSSION

Anti-AMPA receptor encephalitis can present with partial or total manifestations of typical limbic encephalitis syndromes (including memory loss, confusion, abnormal behavior), diffuse encephalopathy, and other symptoms like seizures and motor deficits (3). It usually affects middle-aged women, has an abnormality in the medial temporal lobes or hippocampus on T2 or FLAIR MRI, and accompanies by tumors involving the lung, thymus, breast, and ovary according to previous reports (3–5). The response to immunotherapy is variable with outcomes ranging from

TABLE 1 | Summary of nine cases with relapse of AMPA-R antibodies encephalitis.

Sex/Age	Symptoms					Tumor	Antibody	MRI*	EEG	CSF	Treatment		Outcome
	M	A	C	S	other						At presentation	At relapse	
F/65(4)	1	1	1		nystagmus	None	AMPA 1	Bilateral medial temporal lobe	normal	cell↑ protein↑ OB +	Steroids PLEX	Steroids IVIg AZA	3 relapses 7 months between presentation and last relapse First episode: returned to baseline; After relapse: residual behavioral problem and memory deficit
F/44(4)	1		1	1	combativeness nystagmus	thymoma	AMPA 2 ANA dsDNA ACA	medial temporal lobe (Right; Left)	diffuse theta activity; episodes of epileptic activity in left temporal lobe	cell↑ protein↑ OB -	Tumor removal Steroids IVIg AZA	Steroids IVIg AZA	3 relapses 101 months between presentation and last relapse First episode: returned to baseline; After relapse: residua memory deficit
M/38(4)	1		1	1	agitation	thymoma	AMPA 2 GAD	right medial and lateral temporal lobe, right frontal, left insular and occipital regions	NA	cell↑ protein↑ OB +	Tumor removal Radiation PLEX Steroids IVIg		1 relapse 60 months between presentation and last relapse First episode: returned to baseline; After relapse: residual memory deficit; steroid dependent muscle spasms and rigidity
F/87(4)	1			1	disorientation	None	AMPA 1 ANA	Bilateral medial temporal lobe	Diffuse slow activity, delta activity in anterior frontotemporal area	protein↑	Steroids		1 relapse 16 months between presentation and last relapse First episode: partial improvement; After relapse: death
F/61(4)	1			1	decreased level of consciousness	breast cancer	AMPA 2	Normal	Theta activity in posterior temporal regions	cell↑ protein↑	Steroids	Tumor removal PLEX Steroids	1 relapse 9 months between presentation and last relapse First episode: response to treatment; After relapse: residual behavioral problem and memory deficit
M/44(6)	1				dystonia	thymoma	AMPA CRMP-5	Bilateral hippocampal	general slowing	Normal	Steroids IVIg rituximab	Steroids IVIg rituximab	1 relapse 3.5 weeks between presentation and last relapse First episode: response to treatment and discharge After relapse: mRS 0 and return to work
M/30(9)			1	1	difficulty walking	thymoma	AMPA VGKC NMDA	left caudate nucleus	NA	cell↑	Tumor removal Steroids IVIg PLEX CTX	Tumor removal Rituximab CTX	1 relapse 1 month between presentation and last relapse First episode: response to treatment and discharge After relapse: significant improvement
F/34(10)	1		1		agitation gait disturbance	thymoma	AMPA	left caudate nucleus; right insula and right temporal lobe	focal epileptic discharges at the left temporal-parietal region	Normal	Tumor removal Steroids	Steroids	1 relapse 47 months between presentation and last relapse First episode: residual depressive symptom; After relapse: MMSE 29
F/72(3)	1	1	1	1		None	AMPA	Bilateral medial temporal lobe	general slowing	cell↑ protein↑	Steroids IVIg		1 relapse 2 months between presentation and last relapse First episode: partial response to treatment; After relapse: lost to follow-up

M, memory deficits; A, abnormal behavior; C, confusion; S, seizure; MRI, magnetic resonance image; EEG, electroencephalogram; CSF, Cerebrospinal fluid; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANA, antinuclear antibody; dsDNA, double stranded DNA; ACA, anti-cardiolipin antibodies; GAD, glutamic acid decarboxylase; CRMP-5, collapsing response mediator protein-5; VGKC, voltage-gated potassium channel; NMDA, N-methyl-D-aspartate; OB, oligoclonal bands; NA, not applicable; PLEX, plasma exchange; IVIg, intravenous immunoglobulin; AZA, azathioprine; CTX, cyclophosphamide; mRS, modified Rankin Scale; MMSE, Mini-Mental State Examination.

**Brain regions with increased signal on FLAIR MRI are listed.*

complete neurological recovery, partial recovery, or even death (6).

According to the current criteria (1), the diagnosis items of definite autoimmune limbic encephalitis include four parts: (1) subacute onset of symptoms of memory loss, seizures or psychiatric symptoms, (2) bilateral abnormalities of medial temporal lobes on FLAIR MRI, (3) CSF pleocytosis or EEG abnormity with epileptic or slow-wave activity involving the temporal lobes, (4) exclusion of other possible causes. Although antibodies are not needed in the proposed criteria, the measurement is still very important. When the items of criteria are not fully met, the detection of antibodies can help to establish the diagnosis.

Therefore, the diagnosis of definite autoimmune limbic encephalitis could not be made for the patient at the first attack, because of the normal manifestation of brain MRI and CSF. Through complete testing, alternative causes, such as cerebrovascular disease, intracerebral tumor, and a primary psychiatric disorder, were excluded. Although the antibodies were also not detected, the patient was diagnosed with possible autoimmune limbic encephalitis. Owing to the detection of AMPA receptor antibodies at the second attack and findings on MRI, we made a final diagnosis of autoimmune limbic encephalitis with anti-AMPA receptor antibodies. For patients with CNS syndromes including autoimmune encephalitis and without evidence of MRI and CSF abnormalities, one study showed that the antibodies testing was important for the diagnosis (7). Furthermore, one study also suggested that autoimmune limbic encephalitis can happen without detectable autoantibodies like the situation in our case (8). When the diagnosis is not defined, it is a matter of debate whether the patient should receive immunotherapy. In our case, after discussion with his family, the patient received immunotherapies after 2nd presentation and there was some improvement with the treatment. We didn't find a similar case in anti-AMPA receptor encephalitis in previous reports. Our case suggested the autoimmune limbic encephalitis is an important differential diagnosis for patients with typical symptoms, even when the MRI, CSF, and antibodies are normal.

Another important feature in our case was the relapse of encephalitis. We found 63 cases of anti-AMPA receptor encephalitis with sufficient clinical data and identified 9 cases with relapse of encephalitis (3, 4, 6, 9, 10) (**Table 1**). The patient median age was 44 years (range 30–87 years); six were female and three were male. The patients presented with typical symptoms of limbic encephalitis, including memory deficit ($n = 8$), abnormal behavior ($n = 2$), confusion ($n = 6$), and many patients presented with seizure ($n = 6$). Six patients had a neoplasm, including thymoma ($n = 5$) and breast cancer ($n = 1$). Five patients had additional antibodies except for the anti-AMPA receptor antibody. The most common abnormality on FLAIR MRI was the increased signal in the medial temporal lobe ($n = 7$) and more than half of patients showed an abnormal EEG. The CSF testing demonstrated an increased cell number or protein level in most patients ($n = 7$). For the treatment of encephalitis, immunotherapies were applied in all cases, including steroids ($n = 9$), intravenous immunoglobulin ($n = 6$), plasma exchange ($n = 4$), azathioprine ($n = 2$), rituximab ($n = 2$), cyclophosphamide ($n = 1$). All the patients responded to the treatment at the first episode with only 3 patients returning to the baseline and having one or more relapses in a median period of 9 months (range 1–101 months). The outcome of these patients varied: one patient was lost to follow-up, one patient died, four patients had residual symptoms, and three patients with almost a full recovery. It was noted that these patients all received immunotherapies but still experienced the relapse of encephalitis a few months later. Complete recovery could occur in some cases, but most patients had residual symptoms or even death. The patient in our case also had a residual memory deficit. Therefore, the relapse of anti-AMPA receptor encephalitis is an important item in the follow-up and should attract the attention of the doctor.

Furthermore, serial brain MRI of the patient clearly revealed progressive brain atrophy, which was predominantly in the medial temporal lobes and temporal cortex. Brain atrophy is a rare presentation of LE and only reported in one case up to date (11). In our case, the patient had no hypoxic event and status epilepticus. Two possible mechanisms of brain atrophy may be considered: one is the use of steroid treatment and the other is the internalization of AMPA receptors. It had been reported that brain atrophy is associated with the use of corticosteroids in the previous study (12). High-dose corticosteroids may contribute to reversible short-term loss of volume, while chronic low doses of corticosteroids may induce irreversible loss of tissue through steroid-induced protein catabolism (12). Our patients received high-dose intravenous methylprednisolone during the acute and relapsed stage of the disease and low-dose oral prednisone/methylprednisolone after discharge. Therefore, we cannot exclude a potential effect of corticosteroids treatment. Moreover, receptor internalization may be another possible mechanism (4, 13). It is supposed that the internalization of AMPA receptors might cause synaptic silencing, dendrite degeneration, or neuronal loss (14). It was suspected that the progressive brain atrophy of our patients may be related to a potential effect of AMPAR immune response. Despite the presence of progressive brain atrophy, the gradual function recovery of our patient does not necessarily indicate a poor clinical outcome, which needs a long-term follow-up to confirm.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the participant for the publication of this case report. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YF and HH designed the study, drafted, and revised the manuscript. YF mainly drafted the part of abstract and case presentation. HH performed the part of introduction and discussion. DP provided input and suggestions into the study. HH had full access to the data in the study and takes responsibility for the integrity of the data and accuracy of the case. All authors reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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CASE REPORT
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Case Report: HSV-2 Encephalitis Presenting With Chorea; Effects of Infection Alone or Combination of Infection and Autoimmunity?

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Background: Chorea as a symptom of late-onset post-infectious autoimmune encephalitis has been reported with HSV-1 but not HSV-2 encephalitis. Extrapyramidal symptoms are typically associated with the presence of anti-NMDA receptor antibodies but may also exist in antibody-negative individuals.

Case: This case highlights a patient who presented with mental status changes and chorea as the initial manifestation of HSV-2 encephalitis. The choreiform movements failed to respond to antiviral medications but were rapidly responsive to plasmapheresis, which, together with abnormal intrathecal immunoglobulin synthesis, suggests a potential contribution of parainfectious immune-mediated process. The patient made a full recovery and a complete resolution of the chorea.

Discussion: This is the first case associating HSV-2 encephalitis presentation with chorea. The neurological complications, including chorea, are largely related to active CNS HSV-2 infection, possibly together with triggered CNS autoimmunity despite undetectable CSF neuronal autoantibodies and normal neuroimaging. Early diagnosis and treatment with antiviral agent and immune therapies might be pivotal to optimize the clinical outcome.

Keywords: herpes simplex 2 encephalitis, chorea, CSF negative, MRI negative, antibody negative

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INTRODUCTION

Herpes Simplex Virus (HSV) is the most common viral cause of encephalitis (1). Given the limbic system predilection, it often manifests clinically with behavior changes, memory impairment, and language dysfunction. Extrapyramidal symptoms are less common. While this is most frequently caused by HSV-1, it can rarely be due to HSV-2 invasion in up to 2–10% of HSV encephalitis cases (2, 3).

HSV-2 may present as a primary infection or latent reactivation. Neurological complications related to primary infection are most commonly observed in neonates, such as the neonatal herpes simplex encephalitis (4). In contrast, primary HSV-2 infections in immunocompetent adults are often asymptomatic as the virus lays dormant in the sacral and trigeminal ganglia, which are sites for potential reactivation. Thus, neurological complications of HSV-2 infections in adults are often due to latent viral reactivation and include adult aseptic meningitis, recurrent aseptic meningitis, adult encephalitis and meningoencephalitis, rhombencephalitis, myelitis, radiculopathy, and cranial neuropathy (4, 5).

Autoimmune encephalitis is an immune mediated central nervous system (CNS) inflammatory process that is largely related to neuronal autoantibodies (6). Viruses, including HSV-1, can serve as immunological triggers, causing post-infectious autoimmune encephalitis in addition to meningoencephalitis (6–8). Early recognition and treatment of HSV meningoencephalitis and its post-infectious sequelae are important as it has been shown to reduce mortality from 70 to 16% (9, 10).

Chorea, among other movement disorders, as a sequela or relapse of HSV-1 encephalitis, is well documented (9–11). It is mechanistically linked to secondary post-infectious autoimmunity against neuronal surface proteins or receptors, such as N-methyl-D-aspartate receptor (NMDAR) and dopamine-2 receptor (12), although in some cases neuronal autoantibodies are not detected (6–11). Further, relapses associated with chorea are shown to be associated with a worse prognosis and a greater risk of long-term neurological deficits (12).

We report the first case of HSV-2 encephalitis presenting with chorea, in addition to acute mental status changes, presumably due to infection with, potentially, concurrent central nervous system (CNS) autoimmunity despite undetectable neuronal autoantibodies.

CASE PRESENTATION

A 72-year-old woman with a history of gastritis and urinary incontinence presented with depressed level of consciousness after being found at her home. This is preceded by one day of confusion and lethargy as noted by her family. General examination and vitals revealed a fever of 38.6°C without meningismus. Neurological examination demonstrated a patient who was awake and oriented to self and location with noted psychomotor slowing in response to questioning and commands with noted impaired attention and distractibility during history taking. Cranial nerve testing was intact. The patient had full strength throughout her body and had clearly visible choreiform movements involving her neck and left upper extremity which were predominantly in the proximal part of the extremity. She was unable to suppress movements and was unaware of them when asked to control them. Reflexes were normal. Gait was not tested as it was unsafe to do so. Serologies demonstrated a normal white blood cell count and erythrocyte sedimentation rate with mildly elevated C-reactive protein of 6.8 mg/L (reference < 4.9). The patient was found to have a urinalysis that was positive for leukocyte esterase, bacteria, and white blood cells. She was empirically treated with ceftriaxone 1 g daily. However, despite several days of antibiotic coverage and urine cultures growing ceftriaxone-sensitive E. coli, the patient continued to have fevers, impaired attention and awareness, and chorea. It was decided to continue to search for a source of infection and hence, a lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis revealed a pleocytosis of 234 cells/ul (reference 0–5 cells/ul) with 95% lymphocytic predominance, elevated protein of 72 mg/dl (reference 15–45 mg/dl), normal glucose of 49 mg/dl (reference 40–70 mg/dl), 15 present oligoclonal bands with CSF restriction, and increased IgG index of 2.2 (reference < 0.7) with increased IgG synthesis of 32.3 mg/day (reference ≤ 8.0). CSF PCR was positive for herpes simplex virus 2. The remaining CSF infectious workup was negative, including HSV-1, VDRL, Lyme, cryptococcal antigen, bacterial and fungal cultures, and acid-fast stain. Urinalysis did not reveal any signs of infection. Blood cultures, HIV, Treponema antibody, and COVID-19 PCR were negative. A Mayo Clinic CSF autoimmune encephalitis panel was negative (Mayo Laboratories ID:ENC2). Serum autoimmune encephalitis panel was inadvertently omitted. MR brain with Gadolinium was unremarkable. The patient was started on acyclovir given the positive HSV-2 PCR without notable improvement in mental status or choreiform movements. On hospital day six, a parainfectious CNS autoimmunity was suspected for which the patient was started on intravenous immunoglobulin (IVIG), which was discontinued after two sessions due to severe hypotension. Alternatively, plasmapharesis was initiated on hospital day 9. It resulted in significant improvement of chorea which was noted after only one session and its complete resolution after the fourth session. Overall, she received a total of five plasmapharesis sessions and three weeks of acyclovir treatment. The patient's mental status, however, improved only minimally at the time of discharge to acute rehabilitation on hospital day 27.

Outcome and Follow up

The patient successfully completed rehabilitation and returned to the neurology clinic three months following discharge. She achieved complete recovery without any neurological sequelae.

DISCUSSION

To the best of our knowledge, this is first case that associates HSV-2 encephalitis with chorea. Although this patient is immunocompetent, the neurological complications of HSV-2 infection are likely related to a latent reactivation of a previous clinically silent infection, as opposed to one following a primary infection that typically occur in neonates (4). While the fever and urinary tract infection are possibly implicated in the latent viral reactivation in an immune competent state, the precise involved pathways in our patient remain uncertain (13). This case is unique as it underscores the following: (1) Chorea can be among the neurological complications of HSV-2 infection despite normal neuroimaging (14); (2) Although chorea appears to be likely related to active CNS viral infection, the contribution of concurrent CNS autoimmunity affecting basal ganglia cannot be excluded. The rapid resolution of chorea, temporally associated with plasmapheresis rather than an antiviral agent, together with abnormal intrathecal immunoglobulin synthesis and evidenced by elevation of CSF IgG index and detection of oligoclonal bands with CSF restriction in, suggest a potential contributory role of CNS autoimmunity, despite the lack of detectable neuronal autoantibodies in CSF. However, given that serum testing for the neuronal autoantibodies was inadvertently omitted, and that serum testing, compared with CSF testing, can, at times, offer greater sensitivity for detecting certain neuronal autoantibodies, such as Leucine-rich glioma inactivated 1 (LGI-1) autoantibody,

one cannot completely exclude the potential contributory role of those neuronal autoantibodies. Further, given the known high and low sensitivity of brain MRI in diagnosing CNS involvement with infection-related encephalitis and inflammation-related autoimmune encephalitis (15–18), respectively, it is conceivable that concurrent CNS autoimmunity, and not active viral infection alone, contributed to CSF lymphocytic pleocytosis. With the lack of detectable neuronal autoantibodies, abnormal MRI findings, and absence of any EEG data or brain biopsy, we may only, at best, fulfill a diagnosis of a possible autoimmune cause of chorea (6). (3) These findings suggest that concurrent autoimmunity might occur in HSV-2 encephalitis. This is in contrast to the commonly observed later-onset immune response associated with sequelae or relapse of CNS HSV-1 infections, which is often associated with neuronal autoantibodies; (4) Recognizing that chorea, among other movement disorders, can be among early presenting symptoms of HSV-2 encephalitis may permit early diagnosis, and adding immune therapies to antiviral agents have the possibility to improve clinical outcomes. However, the optimal time to start immunotherapy has not yet been established. Although, both early and delayed glucocorticoid administration has been shown to equally improve outcomes, it is typically withheld early in the course of active infections in order to presumably limit viral replication (9). In addition, randomized trials examining concurrent administration of glucocorticoid and acyclovir are also inconclusive (19). In this case, early initiation of plasmapheresis clearly yielded full and rapid resolution of chorea. Our case suggests that concurrent immune therapies and antiviral agents might be beneficial in expediting the recovery and limit long-term neurological sequelae.

Finally, a diagnostic challenge lies in that there have been rapidly emerging cases of encephalitis with preceding viral-like illness of suspected immune origin but with undetectable neuronal autoantibodies in serum and CSF and normal neuroimaging as in this case (15–18). This is confounded with an overdependence on antibody status to diagnose encephalitis of suspected immune origin, which may delay diagnosis and treatment (19). Therefore, a high index of clinical suspicion is pivotal to timely diagnose and treat such patients.

CONCLUSION

This is the first case associating HSV-2 encephalitis with chorea. The neurological complications, including chorea, are largely related to active CNS HSV-2 infection, possibly together with triggered CNS autoimmunity despite undetectable CSF neuronal autoantibodies and normal neuroimaging. Early diagnosis and treatment with antiviral agents and immune therapies might be pivotal to optimize the clinical outcome.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MK, AB, NH, and SN contributed to the writing and critical revision of the manuscript. All authors gave important contributions to the final form of the manuscript.

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CASE REPORT
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Case Report: Takotsubo Cardiomyopathy in Bickerstaff Brainstem Encephalitis Triggered by COVID-19

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Takotsubo cardiomyopathy (TCM) is a stress-induced cardiomyopathy triggered by critical illness including severe neurological disorders. However, an association between TCM and Bickerstaff brainstem encephalitis (BBE) has rarely been described. During the current coronavirus disease 2019 (COVID-19) pandemic, growing evidence indicates that COVID-19 often leads to various neurological disorders, but there are few reports of an association between COVID-19 and BBE. Here we report a case of TCM associated with BBE triggered by COVID-19, which subsided with immunotherapy for BBE. Both transthoracic echocardiography and electrocardiography led to early and accurate diagnosis of TCM. Sustained hemodynamic instability due to TCM was immediately lessened with immunotherapy whereas additional plasmapheresis and immunotherapy were required to treat BBE. This case indicates that BBE might follow COVID-19 and TCM should be considered when hemodynamic status remains unstable in a patient with BBE.

Keywords: Bickerstaff brainstem encephalitis, anti-GQ1b ganglioside antibody, Takotsubo cardiomyopathy, intravenous immunoglobulin therapy, coronavirus disease 2019, transthoracic echocardiogram, hemodynamic instability

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), often leads to various neurological disorders such as ischemic stroke, encephalomyelitis, necrotizing myositis, and Guillain-Barré syndrome (GBS) (1–3). A proposed mechanism for the neurological complications of COVID-19 is direct SARS-CoV-2 invasion of neural cells such as neurons, glial cells, and vascular endothelial cells through angiotensin converting enzyme 2 receptor (4). The mechanism of neurological autoimmunity associated with COVID-19 remains uncertain.

Bickerstaff brainstem encephalitis (BBE) is a rare autoimmune encephalitis caused by autoantibodies against gangliosides such as GQ1b, present in ∼75% of patients with BBE (5, 6). BBE involves acute onset of bilateral ophthalmoparesis, ataxia, impaired consciousness, and pyramidal

signs. The prognosis is usually good (7). Although GBS often follows COVID-19 (1–3), there are few reports of BBE triggered by COVID-19 (8).

Takotsubo cardiomyopathy (TCM) is a stress-induced cardiomyopathy that presents with malignant arrhythmias and hemodynamic instability. There are specific myocardial wall motion abnormalities and elevated levels of myocardial enzymes. It is occasionally fatal (9). TCM is triggered by critical physiological and psychological events that are hypothesized to be associated with excessive catecholamine release (10), such as intense fear, pain, anxiety; surgery; natural disasters; and infectious diseases including COVID-19 (11). Moreover, severe neurological disorders such as subarachnoid hemorrhage, intracerebral hemorrhage, stroke, epilepsy, migraine, encephalitis, traumatic brain injury, and amyotrophic lateral sclerosis are also associated with TCM (12). To date, an association between TCM and BBE has rarely been described, although GBS is often accompanied by TCM (13).

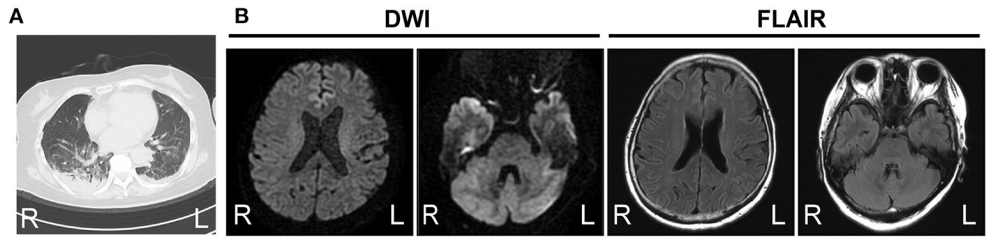
Here we report a rare case of TCM associated with BBE triggered by COVID-19, which subsided with immunotherapy for BBE. Like GBS, BBE might follow COVID-19 and an association with TCM should be considered when there is sustained hemodynamic instability with BBE.

CASE REPORT

A 68-year-old Japanese woman was admitted to another hospital due to acute onset of dysarthria and gait disturbance (day 1), after antecedent symptoms of upper respiratory tract infection such as fever and cough lasting 2 weeks. She had not received any COVID-19 vaccination before onset. She developed altered mental status and rapidly deteriorated within 2 days. She was transferred to our hospital on day 5. She had a history of hypertension, but family history was unremarkable. On admission, she was bed-ridden and unconscious [modified Rankin Scale (mRS), grade 5; Glasgow Coma Scale (GCS), E1V1M1] with blood pressure of 152/114 mmHg, heart rate of 120 beats per minute, and body temperature of 33.2°C. Chest computed tomography (CT) detected bilateral pneumonia, presumably caused by COVID-19 (**Figure 1A**). Although her polymerase chain reaction results for SARS-CoV-2 in sputum and cerebrospinal fluid were negative, she was seropositive for anti–SARS-CoV-2 antibodies (Elecsys Anti–SARS-CoV-2, Roche Diagnostics), which was evidence of SARS-CoV-2 infection. Because of airway obstruction secondary to glossoptosis, she was intubated and supported by mechanical ventilation. Her eyes were fixed in position and she had complete flaccid paralysis with diminished tendon reflexes in all extremities. No pathological reflex was observed in all extremities. There was mydriasis (pupils were 6 mm in diameter bilaterally) and no pupillary light responses accompanied by lack of oculocephalic reflex, gag reflex, corneal reflex, and jaw jerk. Cerebrospinal fluid analysis revealed normal cell count (2 cells/μL) and protein level (20 mg/dL) with high glucose level (164 mg/dL) and the presence of oligoclonal bands. Brain magnetic resonance imaging (MRI) detected no significant abnormalities (**Figure 1B**). Electroencephalography demonstrated no neither evidence of seizure activity nor response to photic and sound stimuli. A nerve conduction study revealed a slight reduction in both compound muscle action potentials and sensory nerve action potentials. F-wave examination showed no responses in the upper and lower extremities (**Figure 1C**). Auditory brainstem responses were completely normal, although there was bilateral loss of both R1 and R2 in the blink reflex. During median nerve somatosensory evoked potential testing, normal P13/14 and N18 were detected, whereas N20 was lost (**Figures 1D,E**). The results of these neurophysiological studies suggest the presence of mild motor and sensory axonal neuropathy and brainstem dysfunction. Autoantibodies against gangliosides such as GQ1b, GT1a, and GM1/GT1a complex were positive in the serum. There was no serological evidence of recent infection with *Campylobacter jejuni, Haemophilus influenzae, Mycoplasma pneumoniae,* cytomegalovirus, or Epstein-Barr virus. Accordingly, she was diagnosed as having probable BBE (5) triggered by COVID-19. On the other hand, electrocardiography showed deep T-wave inversions in multiple leads (**Figure 1F**). Laboratory testing detected elevated levels of troponin I (967.1 pg/mL), creatine kinase (CK) (287 mg/mL), and B-type natriuretic peptide (BNP) (1,110.2 pg/mL). CT angiography revealed no significant coronary stenosis. Transthoracic echocardiography showed apical akinesis with preserved basal function and a depressed ejection fraction of ∼50%, consistent with the diagnosis of TCM (**Figure 1G**). Both inotropic support and heparinization were introduced promptly for the management of TCM. For BBE, two cycles of intravenous methylprednisolone pulse therapy (IVMP, 1 g/day for 3 consecutive days) and intravenous immunoglobulin therapy (IVIG, 400 mg/kg/day for 5 consecutive days) were simultaneously started on day 6 (i.e., hospital day 2) because sustained hemodynamic instability did not allow for plasmapheresis (**Figure 2**). Following the first immunotherapies, her hemodynamic status stabilized and levels of CK, troponin I, and BNP decreased, but neurological status did not improve. Next, plasma exchange (PE) was performed 7 times, starting on day 14. PE immediately enabled extubation. She became able to obey some commands although it was hard to open her eyes actively because of external ophthalmoplegia (GCS, E1VTM6) on day 24 (**Figure 2**). Therefore, additional IVIG was required to achieve a gradual but substantial neurological recovery. Follow-up echocardiography on day 66 showed a marked decrease in apical ballooning of the left ventricle, indicating good recovery from TCM. Finally, she became able to walk without assistance (mRS, grade 2) on day 87 (i.e., hospital day 83). At discharge, she had residual double vision and bilateral disturbance in abduction.

DISCUSSION

BBE is an autoimmune neurological disorder affecting both the central and peripheral nervous systems that is usually associated with antibodies against gangliosides such as GQ1b. It is clinically characterized by acute onset of external ophthalmoplegia, ataxia, and altered consciousness, but may also present with limb



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Nerve conduction study		Median	Ulnar	Tibial	Sural
Motor nerve	Distal latency (ms)	3.3	2.5	3.4	
	Conduction velocity (m/s)	52.6	63.0	47.1	
	Distal CMAP amplitude (mV)	6.15	5.75	11.89	
Sensory nerve	Conduction velocity (m/s)	51.7	55.6		54.0
	SNAP amplitude (μV)	2.0	3.5		1.6
F-wave	Minimum latency (ms)	Not evoked	Not evoked	41.4	
	Conduction velocity (m/s)			48.65	

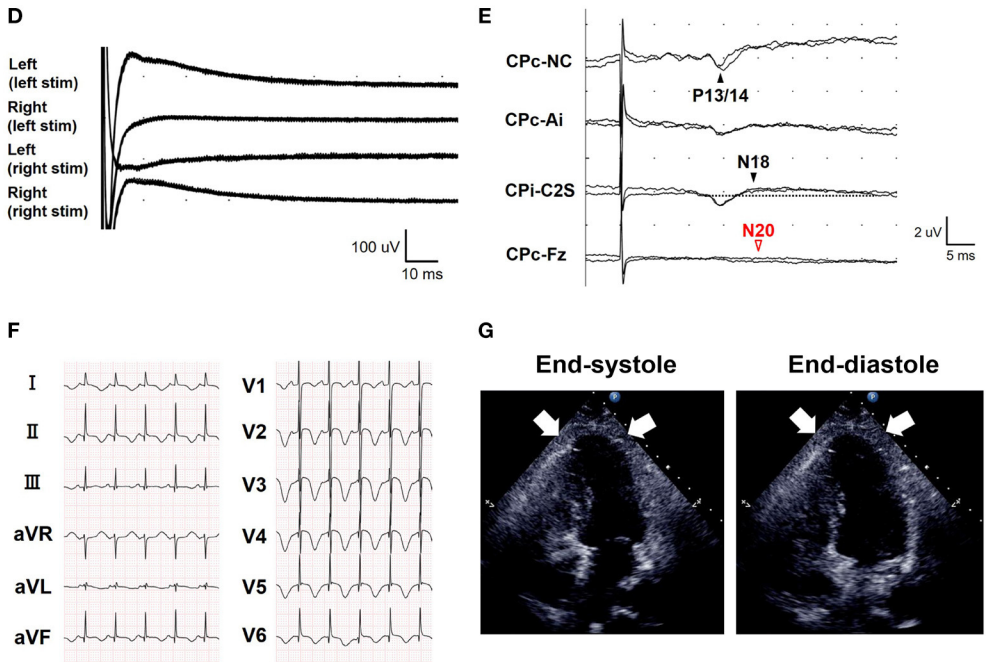

FIGURE 1 | Brain magnetic resonance imaging (MRI) and electrophysiological tests. **(A)** Chest computed tomography detected possible COVID-19 pneumonia on admission. **(B)** Axial brain MRI diffusion weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) images on admission. No abnormalities were detected. **(C)** Nerve conduction study on the 6th day from onset (i.e., hospital day 2). The motor nerve conduction study revealed a slight reduction in compound muscle action potential amplitudes and no conduction block with an apparent increase of stimulation threshold. The orthodromic sensory nerve conduction study showed a reduction in sensory nerve action potentials. F-wave examination exhibited no responses in the upper and lower extremities. CMAP, compound muscle action potential; SNAP, sensory nerve action potential. **(D)** Blink reflex test on day 7 (i.e., hospital day 3) showed bilateral loss of both R1 and R2 with bilateral trigeminal nerve stimulation. **(E)** Median nerve somatosensory evoked potential testing on day 6 (i.e., hospital day 2). P13/14 and N18 were normally evoked, whereas N20 was lost. These results suggested interruption of the somatosensory pathway in the brainstem. Ai, the ipsilateral earlobe. CPc and CPi, the centroparietal electrode contralateral and ipsilateral to the stimulation, respectively. C2S, the spinous process over the second cervical spine. Fz, the midline frontal electrode. NC, non-cephalic reference on the contralateral shoulder. **(F)** Standard 12-lead electrocardiography on admission (day 5) demonstrated inverted T-waves in leads I, II, aVF, and V1–V6. **(G)** Transthoracic echocardiography on admission (day 5). Images in end-diastole (left) and end-systole (right) revealed segmental wall motion abnormalities with apical akinesis (arrows) and hyperkinesis in the basal segments, which was compatible with Takotsubo cardiomyopathy.

weakness, pyramidal tract signs, long-tract sensory impairment, and autonomic dysfunction (5, 14). Autonomic dysfunction includes malignant arrhythmia and hemodynamic instability, which resemble the symptoms of TCM.

Recent evidence has shown that COVID-19 leads to anti-ganglioside antibody–mediated disorders such as GBS and Miller Fisher syndrome (2, 3). Regarding BBE, only one case report mentioned anti-GD1a antibody–positive atypical BBE occurring

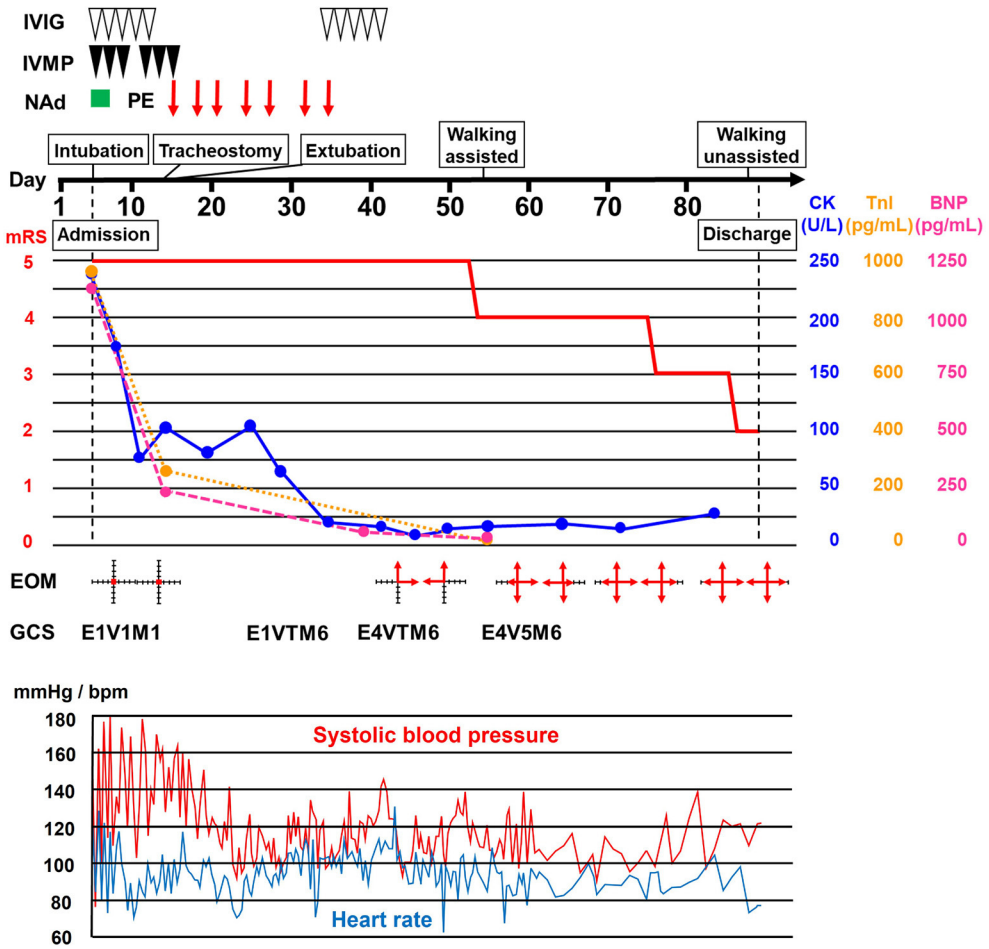

FIGURE 2 | Clinical course. Clinical and treatment course. The horizontal axis represents the day from onset. BNP, B-type natriuretic peptide; CK, creatine kinase; EOM, extraocular movement; GCS, Glasgow Coma Scale; IVIG, intravenous immunoglobulin therapy (400 mg/kg/day for 5 consecutive days); IVMP, intravenous methylprednisolone pulse therapy (1 g/day for 3 consecutive days); mRS, modified Rankin scale (0, no symptoms; 1, no significant disability; 2, slight disability, able to look after own affairs without assistance, but unable to carry out all previous activities; 3, moderate disability, require some help, but able to walk unassisted; 4, moderately severe disability, unable to attend to own bodily needs without assistance, and unable to walk unassisted; 5, severe disability, require constant nursing care and attention, bedridden, incontinent); NAd, noradrenaline administration; PE, plasma exchange; TnI, troponin I.

1 month after SARS-CoV-2 infection, in which acute brainstem and cerebellar dysfunction developed without ophthalmoplegia (8). A 1-month interval seems too long to conclude that it was COVID-19–associated BBE because the mean latency between SARS-CoV-2 infection and presentation of anti-ganglioside antibody–mediated disorders has been reported to be 11 to 13 days (15). In contrast, our patient developed probable BBE according to the diagnostic criteria (5) at 2 weeks after SARS-CoV-2 infection and typically had autoantibodies against GQ1b and GT1a, plausibly suggesting that BBE was triggered by COVID-19.

The precise mechanism underlying the association between COVID-19 and anti-ganglioside antibody–mediated disorders is still unclear. One proposed mechanism is cross-reactivity between viral protein–associated gangliosides and peripheral nerve gangliosides as the result of molecular mimicry (4). However, Keddie et al. recently reported that SARS-CoV-2 proteins, including the spike protein, have no significant similarity to any known human proteins (16), which accounts for a strikingly lower rate of seropositivity for anti-ganglioside antibodies in COVID-19–associated GBS (7%) (15) than in conventional GBS (60%). Since our patient presented with BBE with anti-ganglioside autoantibodies 2 weeks after SARS-CoV-2 infection, the molecular mimicry theory seemed more plausible than the secondary epitope spreading theory for SARS-CoV-2 infection. Further studies are needed to clarify this issue.

Among autoimmune neurological disorders, GBS is well known to cause TCM. However, reports of TCM associated with BBE are rare. Only one previous report described a 62-year-old woman who developed TCM during the acute stage of BBE and required intubation and inotropic support due to decreased consciousness and severe hypotension (17).

The precise pathophysiology of TCM is still controversial, but the most likely cause is catecholamine stress induced by a variety of physical and emotional stressors in patients with underlying disease or even in healthy individuals (18). Among the multiple etiologies for these stressors, direct involvement of the cardiovascular autonomic center in the medulla oblongata has been reported in central nervous system diseases such as multiple sclerosis (19). Thus, BBE might be associated with TCM via brainstem involvement, which influences excessive and sustained activation of the sympathetic nervous system. Nevertheless, it is possible that TCM has so far been underdiagnosed in patients with BBE due to masking of chest symptoms by altered consciousness or misdiagnosis as BBE-related cardiovascular autonomic dysfunction *per se* (20). Another important possibility is that COVID-19 is a trigger of TCM. Giustino et al. documented TCM in 4.2% of 118 consecutive patients with laboratory-confirmed COVID-19 (21). TCM occurs mostly during the acute phase of COVID-19 (11). In our patient, the presence of TCM was confirmed 2 weeks after the onset of COVID-19 and the timing of TCM improvement coincided with IVIG treatment for BBE (**Figure 2**), favoring BBE over COVID-19 as the cause of TCM. IVIG therapy might have exerted a marked favorable impact on TCM, presumably through anti-inflammatory actions on the cardiovascular autonomic center in the brainstem. However, simultaneous conventional TCM treatment might also have been effective.

In conclusion, in the setting of the COVID-19 pandemic, BBE might be triggered by COVID-19 as well as GBS. The possibility of TCM should be always considered because both BBE and COVID-19 are important risk factors for TCM.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

MKi, SH, KTan, MH, KTak, YM, HJ, and HD examined and treated the patient. MKo assessed serum anti-ganglioside antibodies. HT and FT designed and supervised this study. MKi, SH, HT, and FT wrote the manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Neurology

CASE REPORT
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Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy Associated With Area Postrema Syndrome: A Case Report

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Glial fibrillary acidic protein astrocytopathy is an immunotherapy-responsive autoimmune disease of the central nervous system with various clinical manifestations; among these, there are few reports about area postrema syndrome (APS). The authors present the case of a female patient admitted to the hospital with intractable nausea and vomiting as the predominant symptom. The patient's cerebrospinal fluid was tested by cell-based assays (CBA) and found positive for the presence of anti-glial fibrillary acidic protein (GFAP) antibody, in addition, serological testing showed elevated levels of thyroglobulin and thyroperoxidase-specific antibodies. Brain and cervical MRI showed abnormally high signal on the T2 sequence in the dorsal medulla oblongata and right pontine arm. Therefore, the patient was diagnosed with autoimmune GFAP astrocytopathy. The symptoms improved rapidly after treatment with corticosteroids, and no recurrence has been observed thus far. APS may be a relatively rare clinical manifestation of GFAP astrocytopathy. Importantly, such presentation is challenging to correctly diagnose without typical MRI imaging findings. However, the detection of antibodies in the cerebrospinal fluid or serum may be valuable. Systemic and neurological autoimmunity often coexist, comprehensive antibody screening should be conducted.

Keywords: glial fibrillary acidic protein astrocytopathy, area postrema syndrome, case report, autoimmune disease, immunotherapy-responsive

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INTRODUCTION

Several recent reports have outlined the clinical and pathophysiological characteristics of autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy (1–3). Specifically, GFAP-immunoglobulin G (IgG) has been highlighted as fundamental in the diagnosis of the disease, as its presence in the cerebrospinal fluid (CSF) is considered to be a highly specific biomarker. Regardless, the pathogenesis and pathophysiological mechanisms underlying GFAP astrocytopathy have yet to be elucidated. An association to tumors, viral infection, and autoimmune disease have been proposed as possible pathogenic mechanisms (4).

The predominant clinical presentations of the disease are meningoencephalomyelitis and its different forms. Common clinical symptoms include fever, headaches, epilepsy, blurred vision, and ataxia (3), but intractable nausea and vomiting are rarely reported as the predominant symptoms. Here we report the case of a patient with prolonged vomiting and nausea associated with GFAP astrocytopathy.

CASE DESCRIPTION

A 21-year-old female patient was admitted to our hospital with complaints of intractable nausea and vomiting, which had been present for the previous 25 days. Medical history was unremarkable. On the 3rd day after onset, she visited a neurologist, who confirmed that CT imaging of the brain showed no abnormalities. During the disease course, the patient also developed dizziness, right facial numbness, and right ear distension with hearing loss, but no improvement was observed after symptomatic treatment. Neurologic examination revealed ataxia, right horizontal gaze-evoked nystagmus, hearing loss in the right ear, and decreasing superficial sensation on the right side of the face. Intracranial pressure measured through lumbar puncture fell within the reference range (135 mmH_2O; reference range 80–180 mmH_2O). However, CSF analysis revealed an elevated total white blood cell count of 50 cells/μl (reference range < 10 cells/μl) while protein levels were normal (0.42 g/L; reference range < 0.45 g/L). The bacterial culture, acid-fast staining, and India Ink Preparation tests were negative. Blood analysis showed high levels of thyroglobulin antibody (947.40 IU/ml; reference range < 115 IU/ml) and thyroid peroxidase antibody (93.4 IU/ml; reference range < 34 IU/ml). The levels of parathyroid hormone, glycosylated hemoglobin, ceruloplasmin, vitamin B12, thyroid-stimulating hormone (TSH), free T4, T3, rapid plasma reagin (RPR), HIV antibody, and rheumatoid factor were normal. The absence of HIV and hepatitis C virus (HCV) was also confirmed. In addition, the levels of the following autoimmune antibodies were normal: antinuclear, anti-double-stranded DNA, anti-cardiolipin, anti-Smith, anti-Scleroderma-70, Sjögren's syndrome-A, and Sjögren's syndrome-B. Similarly, the levels of antibodies against myelin oligodendrocyte glycoprotein, aquaporin-4 (AQP4), and N-Methyl-D-aspartate (NMDA) receptors antibodies in the serum and CSF were normal. However, a cell-based assay revealed abnormal levels of GFAP antibodies (1:32). Further, imaging revealed an abnormally high signal on T2 sequences in the dorsal medulla oblongata and right middle cerebellar peduncle (**Figure 1**). The abdominal ultrasound was normal. Therefore, autoimmune GFAP astrocytopathy was diagnosed, and methylprednisolone was administered intravenously (1,000 mg/day for 5 days). Somatosensory, auditory, and visual evoked potentials were normal (evaluated after 3 days of treatment). After 5 days of high-dose corticosteroids, the clinical symptoms significantly improved. Prednisone (60 mg/day) was continued orally and the dosage was decreased within 6 months. No recurrence has been observed thus far.

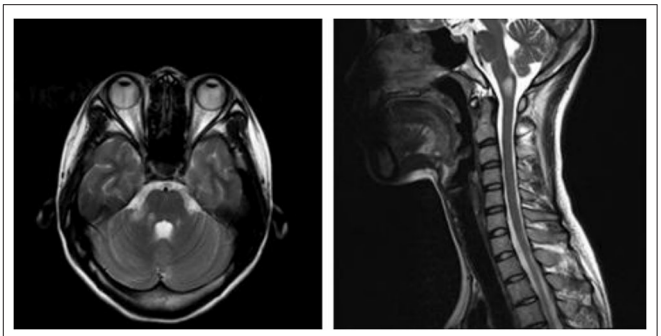

FIGURE 1 | T2-hyperintense lesions in the dorsal medulla oblongata and right middle cerebellar peduncle.

DISCUSSION

Autoimmune GFAP astrocytopathy is a recently discovered disease that was first identified in 2016 by Fang and colleagues (Mayo Clinic). Lesions are mainly present in the meninges, brain, spinal cord, and optic nerve, but other areas such as the thalamus, cerebellum, basal ganglia, midbrain, pons, and medulla oblongata are also affected (5). Common clinical symptoms include headaches, seizures, delirium, psychiatric disturbance, and blurred vision. Typically, in patients with autoimmune GFAP astrocytopathy, cranial MRI shows striking radial linear perivascular enhancement in the T2 phase that is perpendicular to the ventricles. In addition, spinal cord MRI shows extensive T2 hyperintensity in the longitudinal direction (often ≥ 3 vertebral segments), and abnormal enhancement on T1 weighted images is observed in two-thirds of patients (2). In addition, neoplasms, which usually develop within 2 years after disease onset, can be found in about 22% of patients, with ovarian teratoma being the most common type (2).

The etiology and pathogenesis of autoimmune GFAP astrocytopathy are still poorly understood. GFAP-IgG, although important for disease diagnosis, is unlikely to be directly pathogenic, as GFAP is intracellularly located in astrocytes (2, 6). In general, coexisting neurological or systemic autoimmunity are relatively common, as shown by the fact that non-neural autoantibodies have been detected in 76% of autoimmune GFAP astrocytopathy patients in a Chinese cohort (5). Our patient specifically presented with higher levels of thyroglobulin and thyroperoxidase-specific antibodies. Consequently, considering the prevalence and adverse effects of autoimmune conditions in the disease (7), comprehensive antibody screening should be conducted. In addition, the symptom improvement observed in our patient after high-dose corticosteroids further solidify the mainstream hypothesis that sensitivity to corticosteroids is a hallmark of the disease (2).

Area postrema syndrome is defined as intractable nausea, vomiting, or hiccups that cannot be explained by other conditions. The diagnosis of this syndrome is performed according to clinical rather than MRI features, as clinical symptoms may not match with imaging findings (8–10). Due to the absence of the blood-brain barrier in this region, the area postrema is particularly susceptible to the infiltration of many proteins and peptides that are usually excluded from other brain tissues. The area postrema is one of the most easily attacked areas by AQP4 antibodies due to the increased presence of astrocytes, which are rich in APQ4 antigens. In recent years, APS has been recognized as one of the core symptoms of neuromyelitis optica spectrum disorder (NMOSD) (11), the involvement of the area postrema, and the presence of clinical APS symptoms

are the major features in this disorder (12). A multicenter study showed that, in patients with NMOSD, isolated APS was the first symptom in 7.1–10.3% of cases, while it accompanied other symptoms in up to 60% of individuals. In addition, about 20% of patients presenting with APS had been misdiagnosed as having digestive system diseases (2).

Thus far, only one patient with autoimmune GFAP astrocytopathy has been reported to present with APS as the first symptom (13), suggesting that APS may be a relatively rare clinical manifestation. Specifically, the absence of typical MRI features in our patient, where lesions were mostly confined to the dorsal medulla oblongata, prompted a preliminary diagnosis of NMOSD. Moreover, non-specific viral-like prodromal symptoms, such as chronic diarrhea, nausea, and vomiting, have been shown to be common in patients with autoimmune GFAP astrocytopathy and can mimic APS (14, 15). However, the unresponsiveness to symptomatic therapies in our patient favored an APS over viral-like gastrointestinal prodromes (8).

It is worth noting that both our patient and the individual reported by Ciron et al. were admitted to the neurology department nearly 1 month after symptom onset. In this regard, Kimura et al. suggest that early immunotherapy prior to irreversible injury may reduce the probability of recurrence (3). Accordingly, a follow-up study showed that patients who were diagnosed with autoimmune GFAP astrocytopathy more than 1 year after symptom onset and were treated with corticosteroids and immunoglobulin had a poor prognosis (16). Although this was a small sample study, it suggested that the long timespans that in some cases are necessary to obtain a correct diagnosis result in the poor recovery of daily functions. Therefore, we recommend that GFAP-IgG detection in the CSF be considered for patients who present with intractable nausea and vomiting, especially in those cases where extensive gastroenterological evaluation is negative and MRI findings suggest neurological autoimmune diseases.

There are several limitations in this report. Firstly, a variety of conditions can cause intractable nausea and vomiting, including food poisoning, gastroesophageal reflux disease, and gastroparesis. However, in this case, we did not perform an extensive gastroenterological evaluation to identify any potential digestive system diseases or associated malignancies. Secondly, imaging and serological follow-up tests were not performed due to the rapid improvement of symptoms, thus, it is unknown that whether radiographic changes match with the improvement of clinical symptoms. In conclusion, atypical autoimmune GFAP astrocytopathy with APS could be easily missed or misdiagnosed even by experienced neurologists. Therefore, we recommend that in case disease etiology remains unclear even after detailed examinations and symptomatic treatment is ineffective, autoimmune GFAP astrocytopathy should be considered for patients with intractable nausea and vomiting.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

XG performed case information collection, literature review, and drafted the manuscript. YT, G-DY, and WW contributed to the collection of case information. All authors contributed to the manuscript and approved the submitted version.

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CASE REPORT
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Case Report: Need for Caution in the Diagnosis of GFAP Astrocytopathy—A Case of GFAP Astrocytopathy Coexistent With Primary Central Nervous System Lymphoma

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Fang J, Tong Z and Lu W (2022) Case Report: Need for Caution in the Diagnosis of GFAP Astrocytopathy—A Case of GFAP Astrocytopathy Coexistent With Primary Central Nervous System Lymphoma. Front. Neurol. 13:806224. doi: 10.3389/fneur.2022.806224

We reported a case of primary central nervous system lymphoma (PCNSL) coexistent with glial fibrillary acidic protein (GFAP) astrocytopathy, and discussed the problems needing attention in the diagnosis and differential diagnosis of GFAP astrocytopathy. Our patient was a 51-year-old female who presented with somnolence for a month, and memory declination for 10 days. Brain magnetic resonance imaging (MRI) demonstrated multiple abnormal enhancement lesions in bilateral basal ganglia and around the third ventricle, as well as transient T2-weighted hyper-intensity lesions at the splenium of the corpus callosum during the course of the disease. The cerebrospinal fluid (CSF) was positive for anti-GFAP antibodies by antigen-transfected HEK293 cell-based assay (indirect immunofluorescence assay). She was initially diagnosed with autoimmune GFAP astrocytopathy. After treatment with corticosteroids for about 2 months, she displayed poor response and even worsened clinical manifestations when the dose of prednisone reduced to 45 mg. Stereotactic brain biopsy was adopted and the diagnosis of large B-cell lymphoma, non-germinal center type was established on pathological examination. The results of brain biopsy also showed perivascular inflammation and CD8+ T cell infiltration, which also accorded with GFAP astrocytopathy. After chemotherapy with rituximab and methotrexate, the patient showed clinical and radiological improvement significantly. Our findings suggest that positivity of GFAP antibody calls for cautious interpretation. Cancer screening appropriate for age, sex, and risk factors is recommended for GFAP antibody-positive patients, especially for patients with atypical clinical and radiologic manifestations.

Keywords: case report, autoimmune GFAP astrocytopathy, lymphoma, brain biopsy, glial fibrillary acidic protein, steroid

INTRODUCTION

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a newly described entity of immunotherapy-responsive autoimmune inflammatory central nervous system diseases which is confirmed by specific GFAP-immunoglobulin G (IgG) in the cerebrospinal fluid (CSF) (1). Its clinical presentations include encephalopathy, headache, myelopathic symptoms, abnormal vision/optic neurities, postural tremor, and cerebellar ataxia (1). Brain magnetic resonance imaging (MRI) abnormalities are common. Lesions involved the subcortical white matter, basal ganglia, hypothalamus, brainstem, cerebellum, meninges, ventricle, and skull, often accompanied by a hallmark brain linear perivascular radial gadolinium enhancement on MRI (2).

However, whether GFAP antibody is a bystander or directly involved in pathogenesis still remains controversial (3). One-third of cases with positive GFAP-antibody have serologic evidence of autoimmune endocrinopathy; more than one-third are paraneoplastic (4). Therefore, it is recommended to screen for underlying neoplasms within 2 years of GFAP disease onset (5).

Herein, we described a case of autoimmune GFAP astrocytopathy coexistent with primary central nervous system lymphoma (PCNSL), and investigated common problems in diagnosis and differential diagnosis of autoimmune GFAP astrocytopathy.

CASE PRESENTATION

On December 25, 2020, a 51-year-old Chinese female went to our hospital with chief complaints of somnolence for a month, and memory declination for 10 days. No previous history of infection or vaccination before disease onset was found. Her medical and family history was unremarkable. A weight loss of more than 10 kg was reported in the last month. Pertinent positive finding on physical examination at hospital admission included somnolence. Her cranial nerves, strength, and sensory examinations were normal. Antinuclear and antineutrophil cytoplasmic antibodies, human immunodeficiency virus, hepatitis B virus, hepatitis C virus, JC virus, and syphilis were negative. Chest X-ray, abdominal ultrasonography, and gynecological ultrasonography were normal. Lumbar puncture revealed a slightly elevated white blood cell count (12/mm^3) with 83% monocytes and a nearly normal protein level of 0.455 g/l (normal range: 0.15–0.45 g/l). High titers of anti-GFAP IgG antibodies (1:32) were found in CSF but not in serum (**Figure 1**). No malignant cells were found in the CSF. Tests of other autoantibodies in CSF and serum, including MOG-IgG, MBP-IgG, AQP4-IgG, NMDAR-IgG, AMPA-IgG, LGI1-IgG, CASPR2-IgG, and GABABR-IgG were negative. Blood neoplastic and paraneoplastic markers were negative. Electroencephalogram indicated mild abnormality. FDG-PET scan suggested autoimmune or infectious lesions, however neoplasia cannot be excluded. There were patchy and nodular areas with increased glucose metabolism in bilateral basal ganglia and periventricular area. Magnetic resonant imaging (MRI) of brain (**Figure 2A**) showed multiple abnormal enhancement lesions in bilateral basal ganglia and around the third ventricle. Based on clinical data and CSF analysis, a diagnosis of GFAP astrocytopathy was established. The patient was treated with intravenous methylprednisone (1,000 mg for 3 days) followed by a 50% reduction of the dose after 3–5 days, and subsequently oral prednisone tablets (60 mg/day), which was then tapered (reduced 5 mg/day every 2 weeks). A repeated brain MRI (**Figure 2B**) scan showed a significant reduction in the former lesion size and a new T2 signal in the splenium of the corpus callosum without contrast enhancement. After discharge, the patient took prednisone to inhibit immunity. Her drowsiness and short-term memory has significantly improved. One month after discharge, the patient went to the outpatient clinic of our hospital for follow-up. A repeat CSF analysis was unremarkable. The GFAP antibody in CSF and serum was negative. She was admitted again for cognitive impairment and slow response when the dose of prednisone reduced to 45 mg. Positive physical examinations included somnolence, near memory loss and decreased computational ability. A rechecked lumbar puncture revealed 0 WBC/μl, glucose of 4.42 mmol/L, and normal protein level (451 mg/l). Serological tests for infectious, autoimmune, and neoplastic parameters were all normal. The GFAP antibody in CSF and serum was negative either. The brain MRI scan (**Figure 2C**) showed attenuated T2 signal abnormality in the splenium of the corpus callosum, but lesions in bilateral basal

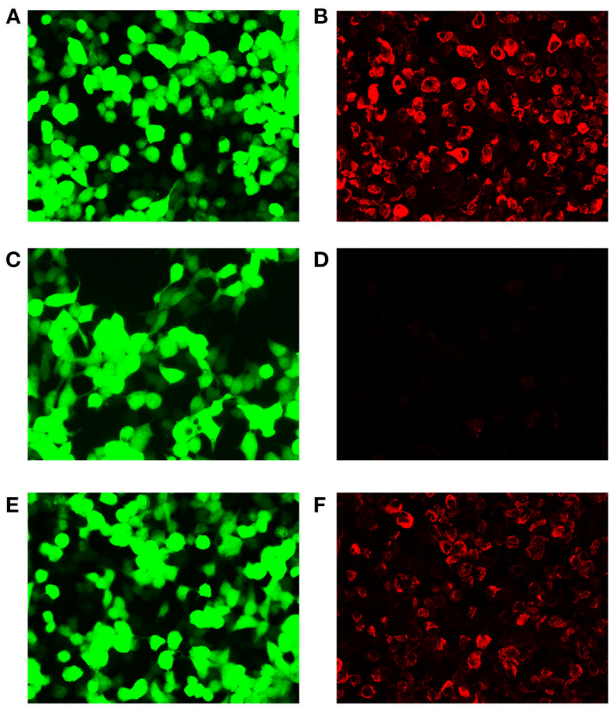

FIGURE 1 | Demonstration of GFAP-IgG by GFAP-transfected HEK293 cell-based immunofluorescence assay. **(A,C,E)** HEK293 cells expressing green fluorescent protein (GFP)-tagged GFAP (green). **(B,D,F)** HEK293 cells immunostained (red if positive); **(B)** Positive control with human anti-GFAPα IgG. **(D)** Negative with healthy control. **(F)** Positive result of cerebrospinal fluid (CSF) (titer at 1:32). Scale bar = 50 μm.

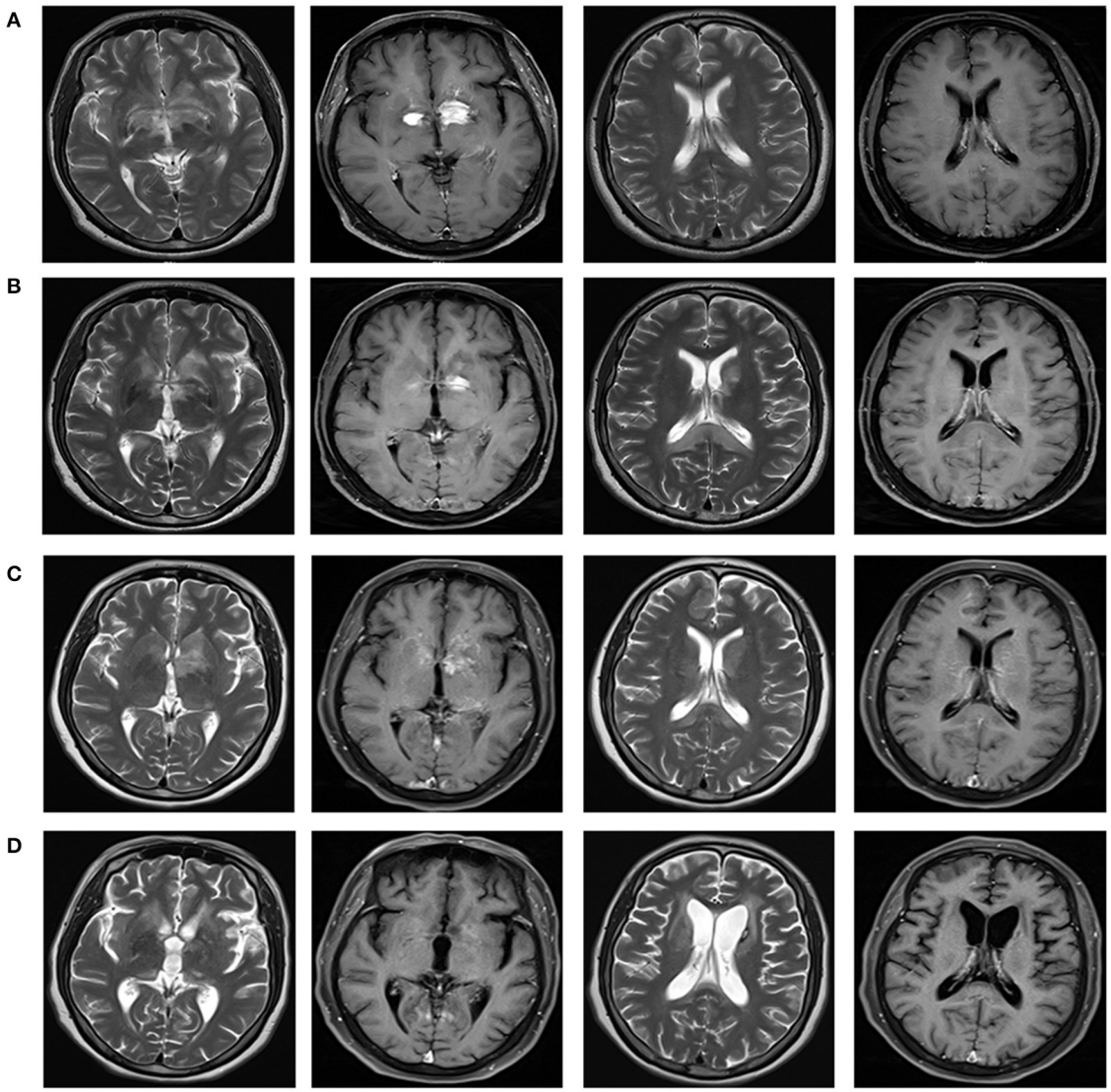

FIGURE 2 | Brain magnetic resonance imaging reflecting the imaging changes of lesions in bilateral basal ganglia and around the third ventricle, and the changes of splenial corpus callosum lesions during the course of disease. Brain MRI with T2-weighted and T1 contrast-enhanced were shown in different columns. **(A)** In December 2020, multiple abnormal enhancement lesions in bilateral basal ganglia and around the third ventricle were demonstrated. **(B)** In January 2021, lesions in bilateral basal ganglia and around the third ventricle reduced significantly with less enhancement. A new T2 signal in the splenium of the corpus callosum without enhancement was shown. **(C)** In March 2021, lesions in bilateral basal ganglia and around the third ventricle were the same as before, with increased enhancement. Attenuated T2 signal abnormality in the splenium of the corpus callosum was observed. **(D)** In August 2021, lesions in the bilateral basal ganglia and around the third ventricle significantly reduced, with complete resolution of the enhanced lesions. Abnormal signal foci in the splenium of the corpus callosum disappeared.

ganglia and around the third ventricle were the same as before, with increased enhancement, and new lesions in the right frontal lobe. PET-CT demonstrated enhanced glucose metabolism in the bilateral basal ganglia and periventricular area, with lesion size larger than before and there was new nodular increase of glucose metabolism under the right frontal cortex. Considering the poor response to steroid therapy, coexistence of malignancy was suspected and a stereotactic brain biopsy was adopted.

Histopathology was confirmatory for diffuse large B-cell lymphoma, non-germinal center B-cell type. Pathological examinations revealed cellular infiltrates of large cells with prominent nucleoli. The tumor was immunopositive for CD20, BCL-2, and MUM-1, with Ki-67 being approximately 80% (**Figure 3**). CD10 was expressed in only a minority (<10%) of cases. BCL6 protein was expressed in 30% of cases. PCR analysis of B-cell immunoglobulin gene rearrangement detected monoclonal rearrangement of IGH FR2-JH and IGK Vk-Jk (**Figure 3**). Pathological examination also revealed extensive infiltrating CD3+ T-cells and CD8+ T-cells rather than CD4+ T-cells in the brain parenchyma. The infiltrations of CD68+

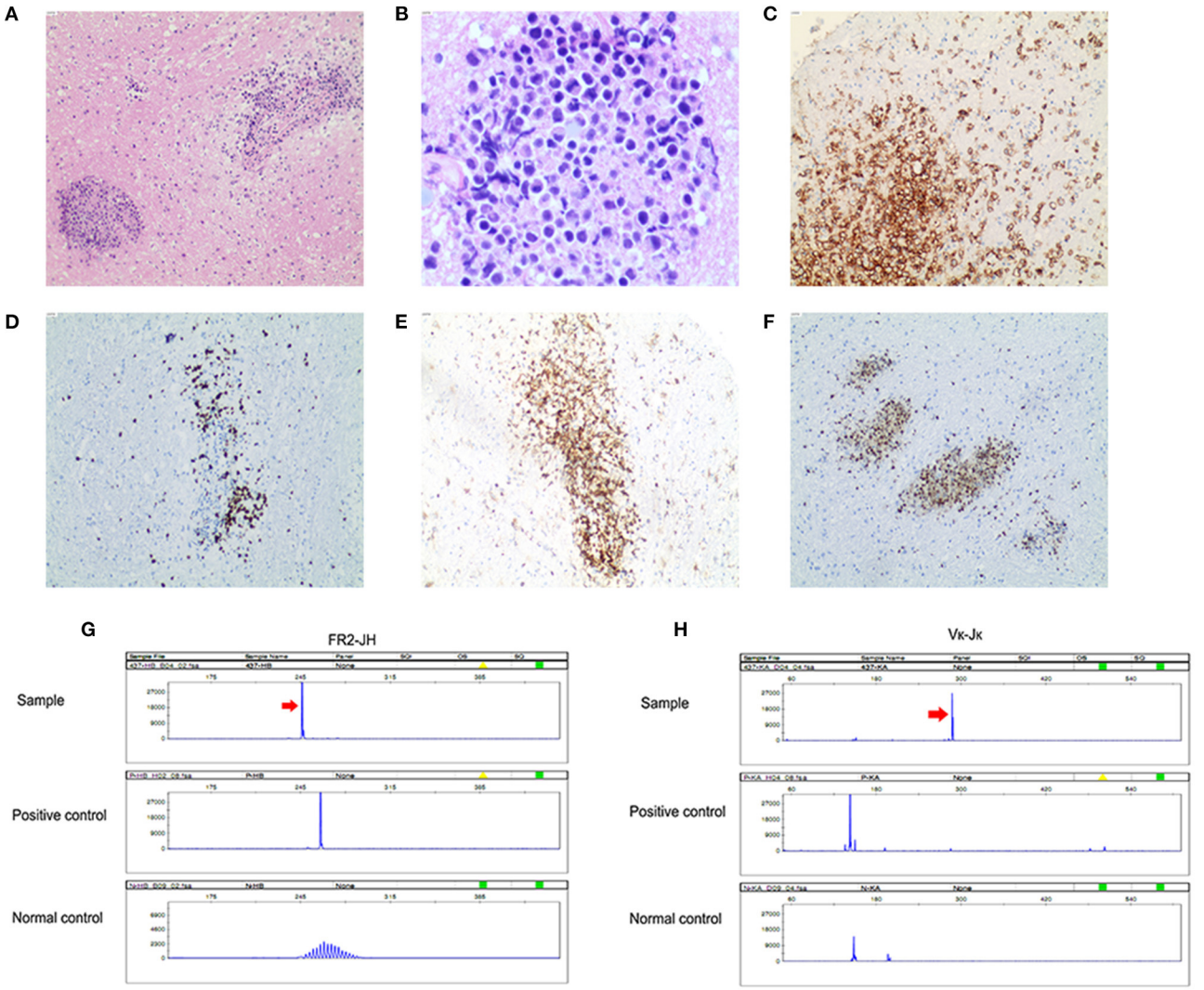

FIGURE 3 | Primary central nervous system lymphoma (diffuse large B-cell lymphoma). **(A)** Angiocentric pattern of distribution of atypical lymphoid cells (original magnification ×100); **(B)** Atypical lymphoid cells are large with irregular nuclei and scant cytoplasm (original magnification ×400); **(C)** Tumor cells are diffusely positive for CD20 (original magnification ×100) and **(D)** usually show a high Ki-67 proliferation index (original magnification ×100); **(E)** Tumor cells are positive for BCL 2 (original magnification ×100); **(F)** Tumor cells are positive for MUM-1 (original magnification ×100). PCR analysis of B-cell monoclonal immunoglobulin heavy chain gene rearrangement detected monoclonal rearrangement of IGH FR2-JH **(G)** and IGK Vκ-Jκ **(H)**.

and CD163+ macrophages were also observed in the brain parenchyma, which was consistent with GFAP astrocytopathy reported previously (6, 7) (**Figure 4**).

The patient was transferred to the department of oncology for further treatment. She received a chemotherapy regimen of rituximab plus methotrexate every 21 days. After three courses of chemotherapy, her drowsiness and cognitive impairment significantly improved. Follow-up brain MRI showed resolution of abnormal signal foci in the splenium of the corpus callosum, and lesions in the bilateral basal ganglia and around the third ventricle significantly reduced with complete resolution of the enhancing lesions (**Figure 2D**). At present, she can complete simple daily activities, such as eating, combing her hair, and dressing.

DISCUSSION

Glial fibrillary acidic protein is an intracellular protein of the astrocytic cytoskeleton. So far, GFAP antibody detected in serum or CSF has been reported in various disorders such as traumatic brain injury, some neoplasms, autism, Tourette syndrome, multiple sclerosis, diabetes, inflammatory brain disorders following daclizumab treatment, and idiopathic

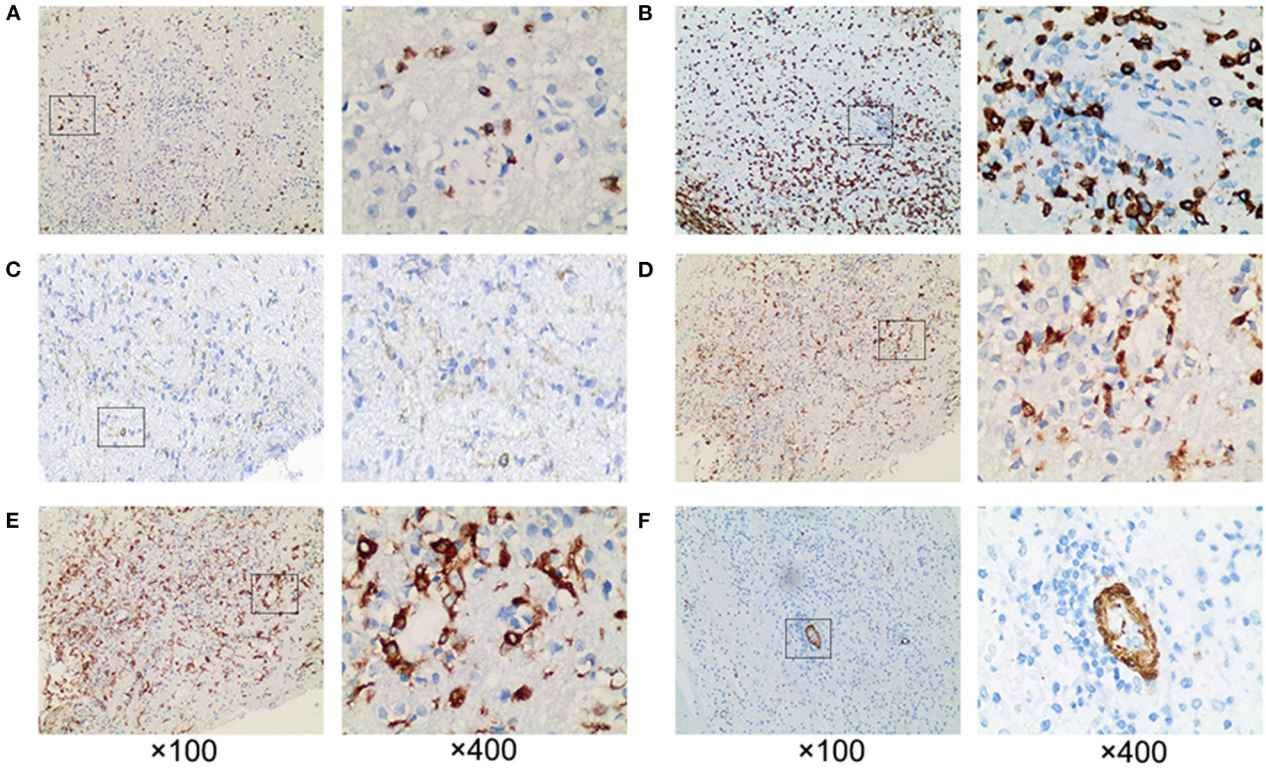

FIGURE 4 | Pathological examination revealed extensive perivascular inflammation. **(A)** CD8+ T cells and **(B)** CD3+ T cells were infiltrated throughout the brain parenchyma, rather than **(C)** CD4+ T cells. Prominent perivascular cuffing of **(D)** CD68+ and **(E)** CD163+ macrophages were seen scattered around small vessels and in the parenchyma. **(F)** The vessel wall indicated by SMA was intact. ×100 and ×400.

intracranial hypertension, etc. (4, 8–14). As GFAP is a cytoplasmic protein, the pathogenicity of GFAP antibody remains controversial. Perhaps it is only a biomarker for the process of immune inflammation caused by GFAP peptide-specific CD8+ T lymphocytes (2, 15). Some researchers bring forward the question whether GFAP antibody is a secondary phenomenon of reactive gliosis (13). An alternative explanation is that GFAP antibody may be accompanied by an as yet unidentified pathogenic autoantibody targeting the astrocytic plasma membrane (15).

Glial fibrillary acidic protein astrocytopathy is a recently defined autoimmune disease of the central nervous system associated with GFAP-IgG antibody (15). Approximately one-third of patients with GFAP astrocytopathy is accompanied with systemic neoplasia (15). Currently, there are no uniform diagnostic criteria or consensus for GFAP astrocytopathy. Based on relevant literature reports, the key points of diagnosis mainly include the followings (2, 16, 17): (1) Typical clinical presentations include acute or subacute meningitis, encephalitis or myelitis, or any combination of these. (2) Radiological hallmark is a radial periventricular enhancement or T2-hyperintensity, while spinal imaging demonstrates longitudinally extensive lesions with central cord enhancement on MRI. (3) Positive GFAP antibody in CSF (cell-based assay or tissue-based assay). (4) Brain biopsy reveals inflammation around small vessels with vascular wall unaffected. (5) The responsiveness to corticosteroids. (6) Other possible diseases are excluded.

The diagnosis of GFAP astrocytopathy should not be based solely on the positivity of GFAP antibody, especially when the imaging is not typical and the effect of corticosteroid treatment is not satisfactory. Other mimic disorders should be excluded when diagnosing GFAP astrocytopathy. For our patient, the positive presence of GFAP-IgG in CSF suggested GFAP astrocytopathy, but the imaging and treatment response were not typical. Herein, instead of the characteristic MRI feature of brain linear perivascular radial gadolinium enhancement in the white matter perpendicular to the ventricle, our patient had MRI features suggestive of reversible splenial lesion syndrome and multiple abnormal enhancement lesions in bilateral basal ganglia and around the third ventricle. It's suggested that reversible splenial lesions could be considered as a radiological feature in patients with autoimmune GFAP astrocytopathy (18). However, reversible splenial lesions have been reported in patients with heterogeneous pathogenesis triggered by viral infection, hypoglycemia, seizure, lymphoma, and other causes (19–21). Supposedly, a subsided splenial lesion could form either by direct lymphoma involvement or secondarily through

the influx of infammatory T-cells (21). As corticosteroids may induce a rapid improvement in clinical symptoms and radiographic features in PCNSL (22), the reversible splenial lesion could also be the MRI presentation of PCNSL in our case. The outcome of our patient suggested that if there was no typical change of radial periventricular enhancement, other diagnoses should be considered even if there is reversible splenial lesion syndrome. Corticosteroid-responsiveness is a hallmark of autoimmune GFAP astrocytopathy (14). Most of the patients had favorable corticosteroid response without relapse (5). This patient demonstrated worsening of clinical conditions despite treatment with corticosteroids during the disease course, which suggested that there may be coexistent malignancy. Finally PCNSL was diagnosed after stereotactic biopsy of a brain lesion. After receiving chemotherapy with rituximab and methotrexate, the clinical symptoms and imaging features of the patient significantly improved.

In addition to the pathological manifestations of lymphoma, the pathology of this patient also conformed to the manifestations of GFAP astrocytopathy. There were perivascular inflammation, T and B cell infiltration, with vascular wall unaffected. CD8+ T cells were frequently found adjacent to neurons and astrocytes, indicating a pathogenic role of CD8+ T lymphocytes in GFAP astrocytopathy, consistent with the pathological features of GFAP astrocytopathy reported previously (23, 24). It is currently not clear whether such inflammatory pathological characteristics reflected a coexistence of lymphoma with GFAP astrocytopathy, or was a genuine feature of PCNSL which can be induced as a consequence of immunosupressive treatment (22)? However, GFAP antibody in CSF of this patient turned negative after steroid treatment, suggesting that the two diseases may coexist, that was, this patient's GFAP astrocytopathy could be the result of a paraneoplastic syndrome. Interestingly, it's reported recently that GFAP astrocytopathy could resemble isolated central nervous system lymphomatoid granulomatosis, which is classified as a subclass of mature B-cell neoplasms (7, 25). Speculatively, there may be a link between lymphomatoid granulomatosis and GFAP astrocytopathy, as well as between PCNSL and GFAP astrocytopathy.

To the best of our knowledge, this is the first case of overlapping syndrome of GFAP astrocytopathy and PCNSL. Primary central nervous system lymphoma is an uncommon and aggressive subtype of extra-nodal non-Hodgkin lymphoma. Most common intracranial lesions on MRI include periventricular white matter, basal ganglia, and corpus callosum. Primary central nervous system lymphoma lesions are often isointense to hyperintense on T2-weighted MRI images and enhanced homogeneously. Corticosteroids cause transient regression of PCNSL at the radiological and histological level. The differential diagnosis includes high grade gliomas, tumefactive demyelinating lesions, metastases, and infectious and granulomatous diseases (22). Confirmation of PCNSL requires a histological or cytological diagnosis (26). For this patient, a diagnosis of PCNSL was supported by histological examination and polymerase chain reaction for B-cell immunoglobulin gene rearrangements.

In conclusion, we should treat the positivity of GFAP antibody rationally, especially seropositive cases. When diagnosing GFAP astrocytopathy, patients need to be investigated for the possibility of other autoimmune conditions and malignancies, which can coexist (16). Cancer screening appropriate for age, sex, and risk factors is recommended for GFAP-specific IgG-positive patients, especially for patients with atypical symptoms. When a PCNSL is considered to be differentiated, early biopsy should be performed before administering a steroid. Prompt diagnosis and initiation of treatment are vital for improving clinical outcomes of patients with PCNSL (27).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of Second Xiangya Hospital. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in the article.

AUTHOR CONTRIBUTIONS

WL designed the study, edited, and revised manuscript. JF and ZT collected data and performed analyses. JF drafted the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Overlap Between Long COVID and Functional Neurological Disorders

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Long lasting symptoms have been reported in a considerable proportion of patients after a severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection. This condition, defined as either "post-acute coronavirus disease (COVID)," "long COVID," or "long-haul COVID," has also been described in outpatients and in individuals who are asymptomatic during the acute infection. A possible overlap exists between this condition and the functional neurological disorders (FNDs). We report a 23-year-old man who developed, after asymptomatic COVID-19, a complex symptomatology characterized by fatigue, episodic shortness of breath, nocturnal tachycardia, and chest pain. He also complained of attention and memory difficulties, fluctuating limb dysesthesia, and weakness of his left arm. After neurological examination, a diagnosis of FND was made. Notably, the patient was also evaluated at a post-COVID center and received a diagnosis of long COVID-19 syndrome. After 4 months of psychoanalytic psychotherapy and targeted physical therapy in our center for FNDs, dysesthesia and motor symptoms had resolved, and the subjective cognitive complaints had improved significantly. However, the patient had not fully recovered as mild symptoms persisted limiting physical activities. Long-term post COVID symptoms and FNDs may share underlying biological mechanisms, such as stress and inflammation. Our case suggests that functional symptoms may coexist with the long COVID symptoms and may improve with targeted interventions. In patients presenting with new fluctuating symptoms after SARS-CoV-2 infection, the diagnosis of FNDs should be considered, and the positive clinical signs should be carefully investigated.

Keywords: COVID-19, functional neurological disorders, post-acute COVID, long COVID, case report

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INTRODUCTION

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) has been associated with a broad range of clinical manifestations including fever, respiratory, cardiovascular, gastrointestinal, and neurological symptoms during the acute phase of the disease (1). Long lasting symptoms, such as fatigue, dyspnea, cognitive dysfunction, and sleep disorders have been described in a considerable proportion of patients who suffered from Coronavirus disease 2019 (COVID-19) (2). This condition, defined as "post-acute COVID," "long COVID," or "long-haul COVID," negatively affects the quality of life and often requires additional clinical assistance. Notably, long term sequelae have been reported not only in patients who are previously hospitalized in intensive care units, but also in non-hospitalized patients with mild symptoms during the acute infection, as

well as in asymptomatic patients (3). Considerable effort is being made to better understand the pathogenesis of post-COVID symptoms. While it is important to monitor the long-term effects of SARS-CoV-2, alternative factors should be considered, among them is the functional neurological disorders (FNDs).

CASE PRESENTATION

Herewith, we report a 23-year-old man who contracted COVID-19 in February 2021. The diagnosis was made by rRT-PCR on a nasopharyngeal swab performed after contact with an infected individual. The patient was asymptomatic at the time of test positivity and started a period of quarantine. He was alone, abroad for study reasons, and the notification of the infection, together with self-isolation, caused an intense stress. In the following days he began to complain of fatigue, episodic shortness of breath, nocturnal tachycardia, and chest pain; an electrocardiogram and chest x-ray were negative. After his return to Italy, the symptoms persisted. In addition, he developed attention and memory difficulties, and a fluctuating limb dysesthesia. Physical examination and an extensive diagnostic work-up including Holter ECG, echocardiogram, and chest CT were within normal limits. In April 2021, the patient underwent his first neurological examination, reporting weakness and clumsiness of his left arm. He was diagnosed with a functional movement disorder as his complaints were variable and distractible and not compatible with an organic neurological disorder (brain MRI, nerve conduction studies, electromyography, and evoked potentials were negative). Arm weakness was characterized by extreme slowness and drift without pronation, and deep tendon reflexes were normal. Importantly, weakness has been reported as one of the most common functional motor symptoms, being frequently associated with non-motor disturbances such as anxiety and fatigue (4). The patient was then referred to our center for FNDs. The patient had no history of psychiatric disturbances or mood disorders, and no pathological personality traits were identified. Stress related to social expectations and isolation, along with health concerns related to SARS-CoV-2 infection may be considered as precipitating factors. Neuropsychological evaluation showed a normal cognitive profile, presence of depression, and elevated anxiety levels. After carefully discussing the diagnosis of FND with the neurologist, a course of psychoanalytic psychotherapy and targeted physical therapy was planned (5). Notably, a few weeks later, the patient was evaluated at a post-COVID center of another hospital. After an additional diagnostic assessment with negative results, he received a diagnosis of a post-COVID-19 syndrome.

After 4 months, dysesthesia and motor symptoms had resolved, and the subjective cognitive complaints had improved significantly. The patient returned to his studies and social activities but had not fully resumed the physical activity, as post-exertional malaise and chest pain, and a fluctuating muscle tension in his back and left arm persisted.

DISCUSSION

Patients presenting with new symptoms after COVID-19, whether asymptomatic during the acute infection, are currently referred to post-COVID centers. New signs and symptoms that appear during or after SARS-CoV-2 infection, that persist for at least 2 months even if fluctuating or relapsing, and were not explained by an alternative diagnosis, meet the criteria for post-COVID-19 syndrome (2). A broad spectrum of symptoms has been reported including shortness of breath, palpitations, chronic fatigue, pain, motor, and sensory deficits. It is worth noticing that this new clinical entity may have some overlap with the FNDs.

According to the DSM-5, FNDs are characterized by one or more neurologic symptoms that show incompatibility with established neurological or medical disorders (6). Therefore, the diagnosis of FNDs is based on positive clinical signs suggestive of a functional basis and on the exclusion of organic disease (6). The presence of psychiatric or mood disorders is not required, although it is generally accepted that both play a role as predisposing factors.

The COVID-19 pandemic profoundly influenced the lifestyle in both healthy subjects and patients with neurological conditions, and has been associated with psychiatric features, sleep disorders, and worsening of neuromuscular symptoms (7–9). The COVID-19 pandemic produced a significant increase in psychiatric symptoms, including anxiety, depression, and post-traumatic stress disorder (10). In addition to health concerns, difficulties in social, family, and work relationships represented a source of stress, made even worse by periods of self-isolation and lockdown.

As expected, the emergence of functional neurological symptoms, such as tremor and tic-like behaviors were evident, after COVID-19 has been described (11, 12). Similarly, in patients with psychogenic non-epileptic seizures (PNESs), COVID-19 pandemic influenced the characteristics of functional seizures (13). In these patients, often affected by mild symptoms in the acute phase, distinctive clinical features (i.e., positive clinical signs), along with an association with mood disorders and psychosocial stressors, have been reported (12, 13). These findings suggest that COVID-19 pandemic may favor the emergence of FNDs, in line with the hypothesis that stress represents a crucial precipitating factor. Furthermore, these studies confirm that FNDs can be effectively diagnosed using DSM-5 criteria, particularly in the presence of positive clinical signs, although diagnosis may be difficult in patients with pain or sensory deficits (6). In addition, it has been reported that traumatic injuries often precede the onset of FNDs (4); thus, symptomatic COVID-19 infection may act as a trigger in some patients, while also increasing the attention to physical sensations.

The pathogenesis of neurologic symptoms related to SARS-CoV-2 infection is complex, and multiple mechanisms have been hypothesized, including direct toxic effects, autoimmune activation, and inflammation (14). While some symptoms may be ascribed to a local effect of the virus (i.e., anosmia due to damage

of the olfactory nerve), others, as myoclonus, opsoclonus, and ataxia, could have an autoimmune etiology (14). Notably, cases of Guillan-Barré syndrome have also been reported after COVID-19 (15). Other long-term neurological symptoms including non-specific attention and memory complaints, fatigue, headache, and dizziness may arise from the inflammatory response to the virus, characterized by the release of proinflammatory molecules (16). In several clinical conditions, peripheral and central inflammations have been associated with behavioral alterations and mood disorders. Therefore, in the acute and subacute phases of COVID-19, inflammation may contribute to mood disorders, and indirectly promote the occurrence of FNDs.

CONCLUSION

Coronavirus disease 2019 (COVID-19), even the asymptomatic type, represents a stressor that may act in some individuals as a precipitating factor for FNDs. Functional symptoms may coexist with long COVID symptoms and can improve with targeted interventions. In patients presenting with new fluctuating symptoms after SARS-CoV-2 infection, the diagnosis of FNDs should be considered, and positive clinical signs should be carefully investigated. Long-term post-COVID symptoms and FNDs may share underlying biological mechanisms, such as stress and inflammation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors were involved in the analysis and interpretation of findings, they proved the manuscript, contributed for important intellectual content, and contributed to writing and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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CASE REPORT
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Case Series: Acute Hemorrhagic Encephalomyelitis After SARS-CoV-2 Vaccination

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We present three cases fulfilling diagnostic criteria of hemorrhagic variants of acute disseminated encephalomyelitis (acute hemorrhagic encephalomyelitis, AHEM) occurring within 9 days after the first shot of ChAdOx1 nCoV-19. AHEM was diagnosed using magnetic resonance imaging, cerebrospinal fluid analysis and brain biopsy in one case. The close temporal association with the vaccination, the immune-related nature of the disease as well as the lack of other canonical precipitating factors suggested that AHEM was a vaccine-related adverse effect. We believe that AHEM might reflect a novel COVID-19 vaccine-related adverse event for which physicians should be vigilant and sensitized.

Keywords: acute hemorrhagic encephalomyelitis, acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, Weston-Hurst syndrome, vaccination, ChAdOx1 nCoV-19, COVID-19

INTRODUCTION

In the context of the current coronavirus disease 2019 pandemic (COVID-19), the non-replicating vector vaccine ChAdOx1 nCoV-19 (AstraZeneca, UK) is one of the most frequently employed vaccines worldwide. The mass public immunization program against COVID-19 in Germany ensued in December 2020. Several side effects including demyelinating disorders of the central nervous system (1–3), Guillain-Barré syndrome (GBS) (4, 5) and vaccine-induced immune thrombotic thrombocytopenia (VITT) (6) have been reported. On the one hand, isolated cases of potential acute disseminated encephalomyelitis, ADEM, which is a rare autoimmune event potentially occurring after an immunological challenge, such as a vaccination, have been linked to COVID-19 vaccines (7–11). On the other hand, COVID-19 itself has been associated with cases of hyperacute hemorrhagic variants of ADEM (acute hemorrhagic encephalomyelitis, AHEM, Weston-Hurst syndrome or acute hemorrhagic leukoencephalitis, AHLE) (12–16). We now report three cases of AHEM occurring in the context of COVID-19 vaccination, namely within 9 days after the first shot of ChAdOx1 nCoV-19. None of the cases exhibited a cerebral venous thrombosis. Written informed consent was obtained from all patients or their legal representatives.

CASE 1

A 61-year-old male with a history of hypothyroidism and polymyalgia rheumatica developed fever, headache and apathy 2 days after the first shot of the ChAdOx1 nCoV-19 vaccine. Two days later, he was discovered by his wife unconscious in his bed foaming around the mouth. Upon arrival of the emergency doctor, he exhibited a generalized seizure, was subsequently comatose and underwent endotracheal intubation. A head CT scan including CT-angiography revealed diffuse hypodense areas in the right subcortical frontotemporal and the right thalamic region. There were no signs of vessel occlusions, especially no sinus vein thrombosis. Magnetic resonance imaging (MRI) revealed bilateral confluent cortical and subcortical FLAIR hyperintense lesions with hemorrhagic involvement of the basal ganglia (**Figure 1B**). Cerebrospinal fluid (CSF) examination revealed normal cell counts (1 leukocyte per µl) and moderate disturbance of the blood-brain-barrier [CSF/serum quotient for albumin of 22.8×10^{-3}, age-adjusted upper reference limit 10.2×10^{-3} (17)]. No CSF-specific oligoclonal bands or intrathecal IgG/-A/-M-synthesis were detected, while flow cytometry analysis revealed normal CSF cell subsets (64% $CD4^+$ T cells, 19% $CD8^+$ T cells, 7% $CD14^+$ monocytes, 0.7% $CD19^+$ B cells, and 4% $CD56^+$ NK cells as portions of $CD45^+$ cells in the CSF). Laboratory testing for bacterial and viral infectious agents of the central nervous system *via* serology (in serum) and polymerase chain reaction (CSF and/or serum) remained negative, including testing for Human immunodeficiency virus, Borrelia burgdorferi, Treponema pallidum, Herpes simplex virus, John Cunningham virus, tick-borne encephalitis virus, Epstein-Barr virus, measles, mumps, rubella West Nile/lymphocytic choriomeningitis-/varicella-zoster virus and SARS-CoV-2 repeatedly *via* RT-PCR from nasopharyngeal swabs. We did not find abnormal antibody titers against aquaporin-4 (AQP4) or myelin oligodendroyte glycoprotein (MOG) in cell-based assays (CBA). Screening for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid antibodies, neuronal and paraneoplastic antibodies were negative.

We assumed an episode of AHEM and administered high dose steroid treatment (1 g methylprednisolone intravenously per day) over 5 days, followed by seven plasma exchange sessions (**Figure 1A**) with concomitant methylprednisolone administration (250 mg per day *via* nasogastric tube on days of plasma exchange, 100 mg per day *via* nasogastric tube on days between plasma exchanges, followed by tapering beginning with 100 mg orally per day and subtraction of 20 mg every 2 days), upon which there was slight improvement of alertness and reduction in size of the brain lesions in follow-up MRI already after 5 days. On clinical follow-up after 14 weeks of rehabilitation, the patient presented with a vegetative state.

CASE 2

A 25-year-old woman without medical record developed severe cephalgia, thoracic back pain, mild weakness and ascending numbness in her legs 9 days after the first shot of the ChAdOx1 nCoV-19 vaccine. The symptoms evolved over the course of one

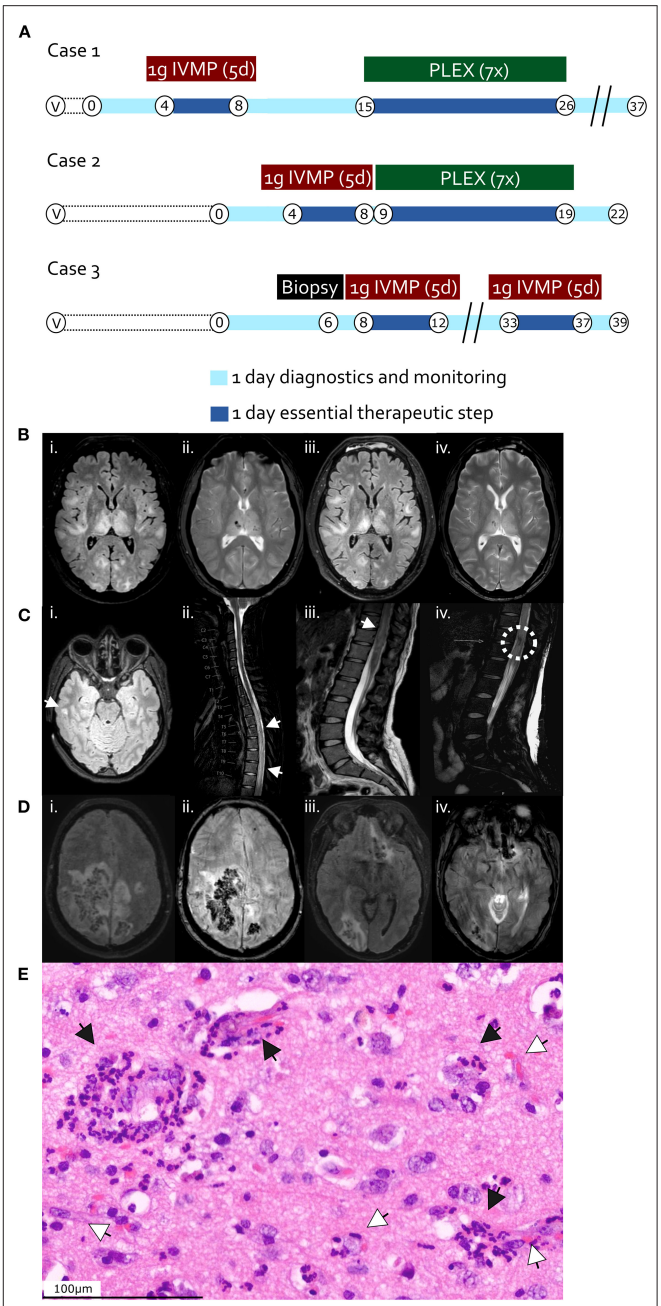

FIGURE 1 | (A) Time course and therapy in case 1 (first row), case 2 (second row), and case 3 (third row). "V", vaccination timepoint; "B", Biopsy and hemicraniectomy timepoint in case 3; "IVMP", intravenous methylprednisolone; "PLEX", Plasma exchange. Encircled numbers indicate days after admission. **(B–D)** Magnetic resonance imaging (MRI) findings. **(B)** Case 1, day 2 after admission; brain axial T2 FLAIR (i) and T2 haem-sensitive sequence (ii); follow-up brain MRI at day 7 after admission, after methylprednisolone pulse regimen; brain axial T2 FLAIR (iii) and T2 haem-sensitive sequence (iv). **(C)** Case 2, day 1 after admission; brain axial T2-FLAIR (i); sagittal cervico-thoracic spinal T2 (ii); sagittal thoraco-lumbar spinal T2 (iii, iv). White arrowheads indicate FLAIR-hyperintense lesions (i–iii), the dashed white circle in iv highlights a region of spinal hemorrhage. **(D)** Case 3, day 2 after admission; brain axial T2 FLAIR (i, iii) and SWI (ii, iv) sequences. **(E)** Hematoxylin and eosin-stained section from right temporal cortical biopsy of case 3 (day 6), displaying perivascular immune cell infiltrates including neutrophilic granulocytes (black arrow heads), tissue edema, and perivascular hemorrhage (white arrow heads). Scale bar 100 µm.

and a half days to a complete paraplegic syndrome including anesthesia below dermatome T6, absent tendon reflexes of the lower extremities and detrusor areflexia with urinary retention. Spinal MRI revealed a longitudinal edema throughout the thoracic spinal cord exhibiting mild contrast enhancement as well as focal central hemorrhages (**Figure 1C**). Cranial MRI showed bi-hemispheric white matter lesions with focal contrast enhancement. CSF examination showed granulocytic pleocytosis (initially on automatic counting, including erythrocytes, 5,284 cells/μl, on repeated tap and manual counting 241 leukocytes/μl, predominantly granulocytes) and a highly elevated CSF/serum quotient for albumin of 164.7×10^{-3} [age-adjusted upper reference limit 6.8×10^{-3} (17)]. No CSF-specific oligoclonal bands were detected. Intrathecal IgM synthesis, but not IgG or IgA synthesis was detected, while flow cytometry analysis revealed a mildly increased B cell proportion among lymphocytic populations in pink-tinged CSF (62% CD4+ T cells, 12% CD8+ T cells, 6% CD14+ monocytes, 1.7% CD19+ B cells, and 2% CD56+ NK cells). Laboratory testing for bacterial and viral infectious agents *via* serology (in serum) and PCR (in CSF and/or serum), including neurotropic viruses, meningitis bacteria, Mycobacterium tuberculosis, toxoplasmosis, bartonellosis, brucellosis, Treponema pallidum, Borrelia burgdorferi, leptospirosis, Human immunodeficiency virus and tick-borne encephalitis virus serology were negative. Moreover, glial-, neuronal-targeting, and paraneoplastic autoantibodies (CBA for AQP4- and MOG-, immunofluorescence assays in the serum for ANA, ANCA, anti-double stranded DNA antibodies) proved negative. SARS-CoV-2-RT-PCRs from nasopharyngeal swabs were also repeatedly negative.

Considering an autoimmune acute longitudinal extensive transverse and hemorrhagic myelitis (spinal variant of AHEM), the patient was put on a high dose steroid treatment (1 g methylprednisolone intravenously per day over 5 days), upon which the cephalgia improved drastically and the sensory components slightly. The therapy was followed by seven plasma exchange sessions (**Figure 1A**) with concomitant methylprednisolone administration (250 mg per day orally on days of plasma exchange, 100 mg per day orally on days between plasma exchanges) and subsequent methylprednisolone tapering over 10 days beginning with 100 mg orally per day after the last plasma exchange and subtraction of 20 mg every 2 days, leading to clinical improvement of only sensory symptoms but persistent paraplegia on 6-week follow-up.

CASE 3

A 55-year-old woman developed progressive nausea, dizziness and meningism 9 days after the first shot of the ChAdOx1 nCoV-19 vaccine. Symptoms worsened rapidly to severe spastic tetraparesis and coma. Brain MRI revealed multiple FLAIR-hyperintense and hemorrhagic lesions in the right parietal and temporal lobes, bilaterally in fronto-temporal distribution as well as in the right occipital lobe and left fronto-basal region (**Figure 1D**). There were no signs of cerebral sinus vein thrombosis. CSF showed mixed granulocytic and lymphocytic pleocytosis (10/μl) and a normal CSF/serum quotient for albumin of 7.4×10^{-3} [age-adjusted upper reference limit 10.2×10^{-3} (17)]. No CSF-specific oligoclonal bands were detected. Intrathecal IgM, IgA and IgG synthesis was detected, while flow cytometry analysis revealed an increased B cell proportion among lymphocytic populations (56% CD4+ T cells, 27% CD8+ T cells, 5% CD14+ monocytes, 6% CD19+ B cells, and 1% CD56+ NK cells). Laboratory testing for infectious agents *via* serology (in serum) and PCR (in CSF and/or serum), including cytomegalovirus, herpes simplex virus, varicella-zoster virus, tick-borne encephalitis virus, enteroviruses, Borna disease virus, West Nile Virus, Sandfly Fever Naples-Virus, human immunodeficiency virus, Treponema pallidum, Bartonella henselae, Brucella melitensis, Coxiella burnetii, Acanthamoeba, Toscana virus, Leptospirosis, Borrelia burgdorderi, Ehrlichia, Rickettsia, Babesia, Naegleria fowleri proved negative. Both autoimmune (AQP4-, MOG-autoantibodies as measured by CBA), and paraneoplastic antibodies (immunofluorescence assays in the serum) were negative. SARS-CoV-2-RT-PCRs from nasopharyngeal swabs were repeatedly negative as well. She developed increased intracerebral pressures and became comatose while developing anisocoria with right non-reactive mydriasis. Subsequent imaging a revealed 11 mm midline shift to the left, manifest trans-tentorial herniation and hydrocephalus occlusus. She underwent emergency right-sided decompressive hemicraniectomy. A brain cortex biopsy from the affected right temporal lobe revealed perivascular predominantly granulocytic infiltrates and hemorrhages (**Figure 1E**). Conventional as well as computed tomography angiography were unremarkable without signs of vasculitis.

The patient was put on a high dose steroid treatment (1 g methylprednisolone intravenously per day over 5 days) with subsequent tapering over 10 days (beginning with 100 mg *via* nasogastric tube per day and subtracting 20 mg every 2 days), which led to significant improvement of vigilance and motor function (**Figure 1A**). Two weeks after steroid therapy, her state worsened again due to new brainstem and occipital FLAIR-hyperintense and hemorrhagic lesions. A repeat high dose steroid treatment remained without positive effects and the patient died due to progressive intracerebral hemorrhage of the brain stem. An autopsy was declined by members of the family of the patient.

DISCUSSION

In this report, we describe three patients who developed acute demyelinating and hemorrhagic lesions of the central nervous system consistent with AHEM within 9 days of the first dose of the ChAdOx1 nCoV-19 vaccine during a 7-week period between May and June 2021. ADEM constitutes a rare demyelinating disease of the brain and spinal cord of mostly monophasic nature, first described toward the end of the eighteenth century following measles infection and smallpox vaccinations (18). It is a relatively seldom neurological illness, which can occur at any age, but

TABLE 1 | Reported number of potential vaccine-related adverse effects in European Economic Area (EEA) countries associated with the terms "acute disseminated encephalomyelitis" or "acute haemorrhagic leukoencephalitis" in the European Medicines Agency's (EMA) *EudraVigilance* database by 20th November 2021.

Vaccine name	ChAdOx1 nCoV-19 (AstraZeneca–University of Oxford)	BNT162b2 (Pfizer–BioNTech)	mRNA-1273 (Moderna)	Ad26.COV2.S (Johnson & Johnson)
No. of ADEM cases	46	91	27	8
No. of AHEM cases	1 (+3)	0	0	0
No. of vaccine doses administered	68,835,033	453,805,251	63,971,912	17,477,802
Derived incidence of potential vaccine associated ADEM	0.067	0.020	0.042	0.046
Derived incidence of potential vaccine associated AHEM	0.0015 (0.006)	-	-	-

Total number of vaccine doses administered as of 19th November 2021 according to the European Center for Disease Prevention and Control (ECDC). Incidence values quantified per 100,000 people per year. In case of AHEM, results without and with the current cases (numbers in brackets) presented. EEA population: 519,832,354.

predominates in children and young adults, amounting to an incidence of around 0.4 cases per 100,000 people per year.

Hyperacute hemorrhagic variants of ADEM, also known as AHEM, have firstly been described by Hurst in 1941 (19). Deducing from the very limited number of AHEM cases reported worldwide, they represent up to about 2% of ADEM cases (therefore around 0.008 cases per 100,000 people per year) (20), and exhibit a fulminant clinical presentation, comprising fever, meningoencephalopathic features, seizures and a rapid progression to coma in addition to the hallmarks of ADEM (18). Imaging reveals large white matter lesions with parenchymal edema accompanied by punctual or confluent hemorrhages (21). In contrast to ADEM, prognosis is mostly poor despite timely steroid treatment or plasma exchange (18, 21, 22). Histopathological examination reveals perivascular immune cell infiltrates including neutrophilic granulocytes, pronounced tissue edema and perivascular hemorrhage, as shown in case 3 (21–24).

The considerable variation in CSF cell numbers (case 1 – normal cell count; case 2 – >5,000/μl including blood cells, 241/μl leukocytes; case 3 – 10/μl) was not incompatible with previous reports of AHEM/AHLE in the literature, one recent review indicating CSF cell number ranges of up to 2,100/μl, but mostly up to 360/μl (mixed mono- and polymorphonuclear) (21).

The patients in the presented cases developed neurological symptoms between 2 and 9 days after the first vaccination and fulfilled the diagnostic criteria set by the International Pediatric MS Study Group (25) and the Brighton Collaboration Encephalitis Working Group (26) for ADEM. Evidence-based diagnostic criteria for AHEM have due to the rarity of the disease not yet been defined, but consensus definitions exist (18, 21). In accordance with the latter, additional clinical features like meningitic syndromes, radiological findings with multifocal hemorrhages (including the spinal cord), histopathological findings and the fulminant progression to encephalopathy suggested the rare variant AHEM in all three cases.

Reports of potential vaccine-related adverse effects from the European Medicines Agency's (EMA) *EudraVigilance* database (27) revealed slightly higher, but altogether comparable incidences of 0.07 (ChAdOx1 nCoV-19) and 0.05 (Ad26.COV2.S) per 100,000 people per year for potential vector-based vaccine associated ADEM, compared to 0.02 (BNT162b2) and 0.04 (mRNA-1273) for mRNA-vaccines (**Table 1**). Concerning AHEM, only one other report after COVID-19 vaccination was found in the *EudraVigilance* database, after inoculation with ChAdOx1 nCoV-19. Studies using the *Vaccine Safety Datalink* have reported a possible association between ADEM and vaccination (especially influenza vaccines) (20) with an incidence of 0.1–0.2 per 100,000 (28). However, even considering the present cases in addition to the single report from *EudraVigilance,* the incidence of potentially ChAdOx1 nCoV-19 associated AHEM (0.006 per 100,000 per year) would not exceed the vaccine-independent incidence (see above, 0.008 per 100,000 per year) (**Table 1**).

The cumulative occurrence of a series of rare variants of an uncommon disease in the space of a couple of months was remarkable and achieved a score of 6 ("probable") for the association with the vaccination on the Naranjo Adverse Drug Reaction Probability Scale (29). This score on the scale suggested that there was indeed a true association, possibly even a causal link between the ChAdOx1 nCoV-19 vaccine and AHEM, and that the occurrences were not purely coincidental. In this context, however, given the high numbers of people already vaccinated against COVID-19, a fortuitous link between the inoculation event and a neurological disorder occurring by chance in the post-vaccination window is also probable. The short time span from inoculation to the onset of neurological

symptoms is common for vaccine associated ADEM/AHEM, which may occur between 1 and 30 days after inoculation with non-neurotropic vaccines (30, 31). The accumulation of these 3 AHEM cases between the beginning of May to end of June 2021 coincided with a near doubling in the number of vaccinations with ChAdOx1 nCoV-19 during the months April to May 2021 in the Federal Republic of Germany (32). Also, by the beginning of June the first reports of VITT and of GBS as potential vaccine-triggered adverse reactions after vaccination with ChAdOx1 nCoV-19 had emerged, so that in light of increased general awareness the detection of other potential neurological complications in the post-vaccination window also became more probable. Considering the current population of Munich and its area of influence as well as presuming that AHEM events follow a Poisson distribution with an average rate of occurrence equal to the incidence of vaccine-associated AHEM (independent of vaccine type, see above), the observed regional accumulation of three cases in the given time span would have a not inconsiderable probability of occurrence between 0.3 and 7%.

A pathophysiologic link between vaccination and AHEM may be given by molecular mimicry (shared pathogenic epitopes between infectious agent/vaccine and molecular central nervous structures) or a re-infectious etiology (opening of the blood-brain-barrier and breakdown of immune tolerance by a preceding CNS infection) (31). ChAdOx vaccines have been proven to elicit particularly strong T cell responses (33), biased toward IFNγ secretion and a Th1-phenotype. Even though both the mRNA and vector-based vaccines encode production of the spike (S) protein of SARS-CoV-2, they differ with respect to the adjuvant required to stimulate the innate immune system: for mRNA vaccines, the mRNA itself acts as both immunogen and adjuvant, due to its recognition by endosomal and cytosolic innate sensors (i.e., TLR3, TLR7), whereas in the case of vector-based vaccines it is elements of the virus particle that are recognized by pattern recognition receptors (i.e., TLR9) (34).

In any case, we cautiously surmise that these cases demonstrate severe and fulminant AHEM and suggest physicians should be vigilant in recognizing such cases in patients who have received the ChAdOx1 nCoV-19, while vaccine surveillance programs could be sensitized to capture data on this potentially devastating outcome. The temporal relationship, however, between vaccination and AHEM alone is not sufficient to prove causality. Millions of people have received COVID-19 vaccines by now, and therefore the chance of neurological conditions occurring within the post-vaccination window by chance alone is also considerable. Even if the reported cases are indeed vaccine-associated, the benefits of vaccination in reducing morbidity and mortality still by far outweigh the risks of ongoing vaccination programs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MA, MM, and BK contributed to the study concept and design. MA, FL-S, JN, SK, CZ, CL, DK, BI, MP, BH, SW, MM, and BK participated in the data acquisition and analysis. MA and BK wrote the manuscript with contributions from all co-authors. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Autoimmune Encephalitis in Long-Standing Schizophrenia: A Case Report

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Anti-N-methyl-D-aspartate (NMDA) receptor antibody (anti-NMDAR Ab)-mediated encephalitis is an autoimmune disorder involving the production of antibodies against NMDARs in the central nervous system that leads to neurological or psychiatric dysfunction. Initially described as a paraneoplastic syndrome in young women with teratomas, increased testing has found it to be a heterogeneous condition that affects both the sexes with varying clinical manifestations, severity, and aetiology. This case report describes a 67-year-old man with a 40-year history of relapsing, severe, treatment-refractory schizophrenia. Due to the worsening of his condition during a prolonged inpatient admission for presumed relapse of psychosis, a revisit of the original diagnosis was considered with extensive investigations performed including an autoimmune panel. This revealed anti-NMDAR Abs in both the serum and cerebrospinal fluid on two occasions. Following treatment with intravenous immunoglobulin and methylprednisolone, he demonstrated rapid symptom improvement. This is a rare case of a long-standing psychiatric presentation with a preexisting diagnosis of schizophrenia subsequently found to have anti-NMDAR Ab-mediated encephalitis. Whether the case is one of initial NMDAR encephalitis vs. overlap syndrome is unknown. Most importantly, this case highlights the need for vigilance and balanced consideration for treatment in cases of long-standing psychiatric presentation where the case remains treatment refractory to antipsychotics or when atypical features including seizures and autonomic dysfunction or focal neurology are observed.

Keywords: autoimmune encephalitis, NMDA encephalitis, chronic schizophrenia, diagnostic dilemma, neuropsychiatric disorders, case report, NMDA antibody

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INTRODUCTION

Anti-N-methyl-D-aspartate (NMDA) receptor (NMDAR) antibody (Ab)-mediated encephalitis was first described in 2005 as a neurological paraneoplastic syndrome occurring in women presenting with psychiatric disturbance and teratomas (1). This led to the identification of a range of anti-NMDAR Abs with varying immunoglobulin (Ig) subclasses against NR1 and NR2

subunits of the NMDAR, in patients with numerous clinical syndromes as well as in asymptomatic healthy controls (2–5). However, it is the immunoglobulin G (IgG) anti-NR1 antibodies in the cerebrospinal fluid (CSF), with a predefined set of symptoms that are diagnostic for the syndrome (6). In the CNS, IgG NR1 antigen-antibody binding results in reversible titratable internalisation of the NMDAR that reduces NMDA signalling and results in the symptom development. Antibody presence in the serum alone is not sufficient to cause symptoms (3, 4, 7). However, processes disrupting the blood–brain barrier can allow antibody circulation within the CSF, leading to antigen–antibody binding (4).

The aetiology is attributed to tumours in 38% of cases of which teratoma is the most common type (8). Anti-NMDAR Ab-mediated encephalitis has also been associated with infective encephalitides, including herpes simplex virus (HSV) encephalitis and cryptococcal meningitis, with neuroinflammation possibly acting as a mechanism triggering anti-NMDAR Ab production (9–15).

Anti-NMDAR Ab-mediated encephalitis typically follows a multiphasic course presenting with a flu-like prodrome prodromal illness followed by psychiatric symptoms of delusions, hallucinations, agitation, thought disorder, catatonia and sometimes even coma (16, 17). Later, neurological symptoms such as seizures (70% of cases) or autonomic dysfunction (hyperthermia, hypertension, and hypersalivation) may also occur (16–21). Common investigations in addition to antibody testing include electroencephalograms (EEGs) with abnormalities in 80% of patients and the pathognomonic "extreme delta brush" pattern in 30–58% of cases, MRI that is transiently abnormal in 33–50% of patients, and ^{18}F-Fluorodeoxyglucose-PET (FDG-PET), which show focal or multifocal abnormalities in ∼70% of cases (8, 16, 18, 20, 22–28).

Relapse has been shown to occur in 12–24% of patients with anti-NMDAR Ab-mediated encephalitis, with a relapse up to 13 years postfirst episode of encephalitis reported (8, 29, 30). Relapse risk is increased in patients with non-tumor and those who do not receive immunotherapy (8, 29, 30). The majority of literature discussing cases of anti-NMDAR Ab positivity has focused on either acute encephalitis or primary psychiatric presentations (8, 31). There are limited examples of cases reported of chronic presentations or those with prolonged latency between symptom onset to diagnosis, though anecdotally we are aware of cases with intervals of up to 10 years. Those with chronic psychiatric diagnoses form a separate category where it can be difficult to ascertain if the psychiatric diagnosis still stands or if the underlying aetiology is that of an autoimmune condition.

We present a case of a man with a long-standing psychiatric diagnosis where anti-NMDAR Abs were subsequently found in the CSF and serum. This case highlights the need for clinical vigilance in not only first-presentation psychosis, but also in those with a long-standing history of psychiatric issues where an autoimmune entity could be at play.

CASE DESCRIPTION

A 67-year-old man with a 40-year history of schizophrenia was admitted to an inpatient psychiatric unit in January 2021 with a relapse of psychosis. His mental state deterioration followed the recent death of his mother and demonstrated increasing paranoia and thought disorder resulting in social withdrawal.

He was first diagnosed with schizophrenia at the age of 25 years following the development of acute psychosis characterised by paranoid delusions, thought disorder, and auditory hallucinations. Though this was a *de novo* illness, it had been preceded by premorbid loner behaviours and potential schizoid personality traits. Over the next 20 years, he relapsed every 3–4 years with episodes characterised by prolonged, treatment-refractory events of highly disorganised and fluctuating psychosis. In several of these relapses, he required electroconvulsive therapy (ECT), which he responded well to.

After a 10-year period of being lost to follow-up between 1999 and 2010, he presented to the emergency department in early 2011 with a psychotic relapse and a first reported generalised seizure. A brain CT scan showed a small old left caudate infarct and an EEG performed was normal. A similar episode occurred in 2015 where a second tonic-clonic seizure occurred, and he again was diagnosed as having had a psychiatric relapse and subsequently had a prolonged inpatient psychiatric admission. Following a protracted psychiatric episode in 2018 that failed to respond to the psychotropic treatment, he underwent 9 sessions of ECT that appeared to reduce some of his psychiatric symptoms. During these relapses, he demonstrated substantial cognitive decline. In between episodes, he maintained a relatively high functioning baseline (see **Appendix 1**) whilst on antipsychotics although he was unable to participate in paid employment. Prior to the 2021 relapse, he was living independently in the community and in previous periods had been a carer for his late mother.

On admission to the psychiatric unit in January of 2021, his symptoms were characterised by thought disorder and hypomania. His affect and behaviour were highly labile demonstrating perceptual disturbances (auditory and visual) and psychomotor agitation, occasionally physical aggression towards staff and later appearing lethargic, dazed, and withdrawn. Moreover, he had multiple low-grade fevers and developed several autonomic and dyskinetic symptoms including hypersalivation, speech disturbance, and unsteady, widened shuffling gait. These symptoms were not correlated with medication changes, but appeared to spontaneously fluctuate (**Table 1**).

Due to ongoing fluctuations in his psychiatric and behavioural symptoms with no improvement in trend, the decision was made for referral to the tertiary medical hospital site to undergo more extensive investigation for reconsideration of diagnosis.

Haematological, biochemical, and septic screens were performed and yielded unremarkable results (**Table 2**). An EEG was normal and a CT brain demonstrated no acute findings, noting only the known small old left caudate infarct. Microbiological and biochemical analysis of a CSF sample

TABLE 1 | Inpatient unit (IPU) admission summary.

Timeline	Event/Assessment and medication changes
D1 Admission	Mental State Examination (MSE)[a]: psychotic with prominent thought disorder and hypomanic symptoms. Noted unusual wide based quick stepping gait. Admission medications: Olanzapine 10 mg three times a day, Atorvastatin 40 mg daily, Thiamine 100 mg daily Aspirin 100 mg daily, Perindopril 8 mg daily, Amlodipine 10 mg daily, Monoxidine 400 mg morning, and 200 mcg at night.
D10	Appearing improving affect, denying perceptual disturbance, stabilising without change to psychotropic regimen
D11	Cognitive assessments completed: MoCA[b] 23/30
D17	Requiring excessive reassurance from staff, thought disordered but no psychomotor agitation or perceptual disturbance. Alteration to olanzapine from 10 mg three times a day to 10 mg in the morning, 25 mg at night.
D18	Start of slurred speech development, significantly labile affect
D23	Low-grade fever, 37.7, No infective symptoms
D26	Mild sore throat. Isolated and COVID swab sent, returning negative.
D27	Commenced new Lorazepam 1 mg twice daily to assist with agitation
D29	2nd low-grade fever 37.7. No infective symptoms. Creatine Kinase (CK) tested returning 65 u/L (reference range 40–200)
D31	Lithium dose increased to 250 mg in the morning/375 mg at night. Sodium valproate 400 mg at night commenced.
D36	Sodium valproate dose increased from 400 mg at night to 200 and 400 mg at night
D38	MSE AM: sedated, slurred speech, hypersalivating, unsteady slightly wide based gait MSE PM: highly driven with significant psychomotor agitation, limited sleep
D41	Repeat MOCA 16/30
D42	Morning lithium dose further reduced to 125 mg
D45	MSE: ongoing prominent thought disorder and slurred speech but improving agitation
D46	3rd low grade fever to 37.5, however MSE improving, more settled, less irritable.
D52	MSE deterioration: increased agitation, irritability, and thought disorder. Recurrence of auditory perceptual disturbance and cognitive deterioration.
D55	Acute worsening of agitation with physical aggression and sexual inhibition. Commenced cross titration of olanzapine to Paliperidone.
D59	4th low-grade temperature to 37.8 degrees. No infective symptoms
D66	Ongoing highly fluctuating symptoms. Paliperidone increased to 6 mg, olanzapine weaning.
D72	Repeat MOCA 20/30
D82	Repeat MOCA 15/30
D90	Affect improving but fluctuations ongoing in cognition. Sodium valproate dose weaning commenced Paliperidone increased to 9 mg.
D101	Behaviours worsening with aggression, impulsivity. Noted auditory and visual perceptual disturbances and prominent thought disorder. Slurred speech again noted. Paliperidone dose reduced. Delirium screen including CT brain completed with no new findings.
D123	Transferred to acute medical hospital. MSE on arrival: flattened affect with slurred mumbling speech. Labile behaviours from withdrawn, sedated, quiet, to later significant psychomotor agitation, aggression towards staff. Noted hypersalivation, shuffling wide-based gait. Psychotropic medications on admission to Acute Medical Hospital: Paliperidone 6 mg at night, Lithium 375 mg at night, Lorazepam 1 mg at night and 1 mg in the morning as needed, Zopiclone 7.5 mg at night. This medication regimen had been stable for several weeks and did not change during his Tertiary Medical Hospital Admission.

[a]*Mental State Examination (MSE): A structured examination approach that assesses patients' appearance, behaviour, speech, mood and cognition (32).*
[b]*Montreal Cognitive Assessment (MoCA): a clinician administered 30 questions designed to detect and monitor cognitive impairment (33).*

returned results within normal limits. However, his serum and CSF returned positive tests for anti-NMDAR Abs.

Due to concerns of acute behaviour exacerbation, particularly with uncertainties regarding the clinical significance of the positive antibodies, it was felt that methylprednisolone pulsing would be inappropriate. In preference, he completed a 5-day course of 0.4 mg/kg/day of intravenous Ig (IVIg) (days 145–150 of his combined psychiatric and medical inpatient admissions).

For the following 7 days, his mental state remained persistently labile with ongoing thought disorder and agitation. However, on days 9–12 post-IVIg, there was marked, sustained improvement in his mental state. On review day 14 post-IVIg, he was observed to be lucid with a reactive affect, speaking and behaving politely, and demonstrating both capacities to understand medical discussions and recall conversations.

Computed tomography chest, abdomen, and pelvis and PET scan, MRI brain, and second lumbar puncture day 12 post-IVIg failed to identify a paraneoplastic source of NMDAR antigens such as a teratoma or any neurodegenerative disorders. His second CSF sampling day 12 post-IVIG again returned positive for NMDAR Abs.

He later underwent a 5-day course of 500 mg daily IV methylprednisolone as it was felt his mental state had improved enough to be safe for a trial of steroid therapy and that this would align with the more aggressive treatment approach increasingly recommended in the literature (26, 36). This was tolerated well and he continued small progressive daily improvements in his mental state and cognition.

He was then discharged home postcommencement of rituximab, with the plan to continue rituximab on a 6-monthly basis. At outpatient review 6 months posttreatment,

TABLE 2 | Results table.

Test	Result	Test	Result
Anti-NMDAR Antibodies*	CSF 09/06/21 detected CSF 12/7/21 Detected (no discernible difference in staining intensity) Serum 24/6/21 detected	CSF 12/7/21	Protein 0.39 (ref <0.45 g/L), glucose 3.6 Erythrocytes 74, polymorphs 0, lymphocytes 2 No oligoclonal IgG bands Culture negative Cryptococcal antigen negative
Voltage Gated Potassium Channel Antibodies	Not detected	CSF 9/6/21	Protein 0.31 (<0.45g/L) glucose 3.7 Erythrocytes 0, Polymorphs 0, lymphocytes 0
AMPA receptor antibodies	Not detected	Viral CSF PCR	Serum HSV1 IgG positive, IgM negative CSF HSV 1/2, VZV, CMV, Adenovirus no detected
Neuronal antibodies	Negative	Alpha-feto protein	Not elevated
Mitochondrial antibodies	Not detected	Syphilis serology	Negative
HIV serology	Negative	Hepatitis B + C serology	Negative
CASPR2 antibodies	Not detected	CMV serology	IgG positive, IgM negative
Non-contrast MRI brain 19/07/21	No acute intracranial pathology. In particular no imaging features of autoimmune encephalitis.	CT chest, abdomen, pelvis 14/07/21	No evidence of solid malignancy. Long-standing occlusion of infrarenal abdominal aorta.
Non-contrast MRI brain 19/07/21	No acute intracranial pathology. In particular no imaging features of autoimmune encephalitis.	PET 22/07/21	No FDG evidence of malignancy. Increased metabolism of the parietal, temporal and to lesser frontal cortices. Although non-specific, this is reported as a finding seen in anti-NMDA-receptor encephalitis.

CSF, cerebrospinal fluid; HSV, herpes simplex virus; VZV, varicella zoster virus; CMV, cytomegalovirus.

**Antibody testing was carried out by Pathology Queensland (NATA/RCPA Corporate Accreditation Number 2639) with Health Support Queensland. Anti-NMDA-receptor IgG antibodies were detected in serum and cerebrospinal fluid (CSF) by indirect immunofluorescence using a commercial assay containing four biochips of primate hippocampus, primate cerebellum, fixed NR1-transfected human embryonic kidney 293 (HEK293) cells, and fixed non-transfected control HEK293 cells (IIFT: Glutamate Receptor Mosaic 3, Euroimmun, Lübeck, Germany, UK) (34, 35). When the second sample was received the CSF was tested in parallel with the earlier CSF specimen with no discernible difference in intensity of the staining identified. Dilution base or titre testing is not available in Australian laboratories.*

he maintained his improved psychiatric state and is living independently in the community. He reported no hallucinations or delusions and denied any new neurological symptoms. He reported improvements in his memory. He was continued on the same psychiatric drug regimen. However, his stability has meant the psychiatric team has started weaning his lorazepam and assuming ongoing stability with treatment on rituximab, there may be scope to further reduce his antipsychotics. As it is impossible to determine when he developed the anti-NMDAR Ab, ongoing management must be considered for the likelihood of an overlap syndrome of a background schizophrenia with superimposed anti-NMDAR Ab-mediated encephalitis, both now well-controlled with antipsychotic therapy and rituximab.

DISCUSSION

This is an unusual case of anti-NMDAR Ab-mediated encephalitis in a patient with a preexisting diagnosis of chronic atypical treatment-refractory schizophrenia. This case fulfils all the diagnostic criteria for anti-NMDAR Ab-mediated encephalitis:

(1) Presence of NMDAR antibodies in CSF: *This case demonstrated positive NMDAR Abs in CSF sampling on two separate occasions.*
(2) Consistent clinical symptoms: *This case demonstrated disorganised psychiatric and behavioural disturbance, speech disturbance (mumbling, non-sensical), hypersalivation, and intermittent fevers. These were not correlated with medication changes.*
(3) Treatment response: *This case demonstrated acute improvement in behaviour, orientation, resolution of autonomic dysfunction, and hypersalivation in appropriate timeframe post-IVIg. This acute improvement was out of keeping with his pattern of symptom recovery in previous psychiatric relapse* (6).

What remains ambiguous is whether his current and past psychiatric disturbance are explainable by the anti-NMDAR Ab-mediated encephalitis alone or whether it reflects an anti-NMDAR Ab encephalitis superimposed on a prior schizophrenia. It is impossible to retrospectively determine when he developed the anti-NMDAR Abs and there is always the possibility of diagnostic assay error. However, the reproducibility of the anti-NMDAR Ab in his CSF on two occasions adds validity to the diagnosis, as studies demonstrating the specificity of CSF antibodies when applied to general and psychiatric patient groups, unlike serum testing (3, 37, 38).

This case may represent sporadic anti-NMDAR Ab-mediated encephalitis developing in 2021 mimicking his typical psychiatric episodes. Alternatively, this may represent a long-term relapsing-remitting anti-NMDAR Ab-mediated encephalitis, where the lack of appropriate treatment has led to prolonged medication-resistant episodes. This would be supported by his previous responsiveness to ECT, which is known to be efficacious in anti-NMDAR Ab-mediated encephalitis in addition to treatment-refractory psychotic illnesses (39–41). Moreover, this would explain as to his fluctuating disease course as well as the two previous episodes of seizures in 2011 and 2015.

Anti-NMDAR Ab-mediated encephalitis was only identified 15 years ago and most cases involve short periods (weeks to months) between symptom onset and diagnosis. Examples of prolonged symptom onset to diagnosis periods are rare and case descriptions are limited. This case raises the possibility of a group of patients with long-standing relapsing-remitting anti-NMDAR Ab-mediated encephalitis who remain undiagnosed as their symptoms developed prior to when the condition was first identified. Additionally, the difficulty in distinguishing anti-NMDAR encephalitis symptoms from psychiatric psychosis supports the hypothesis of NMDA deregulation as a contributing mechanism in the development of schizophrenia.

In cases involving long-standing diagnoses, clinicians are prone to diagnostic error from premature closure bias and subsequently exclude explanations that do not align with their current beliefs. This case highlights the importance of recognising red flags such as neurological symptoms, autonomic disturbances or failure to respond to appropriate antipsychotic treatment in the treatment of patients with psychiatry. The decision for invasive investigations requires a high index of clinical suspicion to justify. However, by nature of their symptoms, this patient group may be unreliable historians, and as such rigorous history can be limited unless substantive collateral history is available. Moreover, with prolonged hospitalisation superimposed disorders such as delirium, or complications such as neuroleptic malignant syndrome, can act as confounders in clinical assessment (42). However, conclusive diagnosis remains challenging due to the pervasive risk of false positives and negatives, even with the gold standard investigation with CSF testing.

Seeking medical consultation for reconsideration of diagnosis and completion of the extensive investigation were ultimately judicious decisions by the psychiatric and neurology teams that proved critical for his treatment and ongoing care.

CONCLUSION

Further research is needed to guide if screening for anti-NMDAR Ab-mediated encephalitis should be considered for patients with long-standing treatment-refractory schizophrenia with atypical symptoms or syndromes. Clinicians must balance the risks of invasive investigation and acute- and long-term side effects of treatment, against the potential of an alternate diagnosis and effective treatments. This case highlights the importance of maintaining clinical vigilance in patients who fail to respond to treatment and the pervasive risk of diagnostic error through premature closure bias.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AV prepared the first draft of the manuscript with a contribution from BS who provided a summary of the most recent psychiatric inpatient stay of the individual. AV, KR, BS, NC, TK, AE, and MM were all involved in the clinical care of the patient and critically reviewed the manuscript drafting for its factual accuracy, assessments, and conclusions. All authors provided approval for the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.810926/full#supplementary-material

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CASE REPORT
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Posterior Reversible Encephalopathy Syndrome in Guillain-Barré Syndrome: Just a Problem of Immunoglobulins? Controversy From Two Atypical Case Reports

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Background: Posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS), or the coexistence of these two entities shares similar risk factors and clinical features. For these conditions, a common origin has been supposed. Even if the majority of patients show a favorable course and a good prognosis, a small percentage of cases develop neurological complications. Up to date, only about 30 cases of PRES associated with Guillain-Barré syndrome (GBS) have been reported in the literature.

Cases: Here, we present two cases of a particularly aggressive PRES/RCVS overlap syndrome, associated with acute motor axonal neuropathy (AMAN) and acute inflammatory demyelinating polyneuropathy (AIDP) variants of GBS, respectively, presenting with similar initial clinical aspects and developing both an atypical and unfavorable outcome. On MRI examination, the first patient showed typical aspects of PRES, while, in the second case, radiological features were atypical and characterized by diffusion restriction on the apparent diffusion coefficient (ADC) map. The first patient demonstrated rapid worsening of clinical conditions until death; the second one manifested and maintained neurological deficits with a permanent disability.

Conclusions: We suggest that PRES may conceal RCVS aspects, especially in most severe cases or when associated with a dysimmune syndrome in which autoimmune system and endothelial dysfunction probably play a prominent role in the pathogenesis. Although the role of IVIg treatment in the pathogenesis of PRES has been proposed, we suggest that GBS itself should be considered an independent risk factor in developing PRES.

Keywords: posterior reversible encephalopathy syndrome, neuroimaging, immunoglobulins, clinical neurology, endothelial dysfunction

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinical-radiological entity characterized by a potentially reversible subcortical vasogenic brain edema and acute neurological symptoms (1).

Reversible cerebral vasoconstriction syndrome (RCVS) is a group of clinical entities characterized by prolonged, reversible vasoconstriction of the cerebral arteries that resolve within 3 months, associated with a rapid or gradual onset of severe headache, and complicated by other neurological symptoms (stroke, hemorrhage, encephalopathy, concomitant PRES, and seizures) in up to one-third of patients (2).

The pathophysiology of PRES, RCVS, or their rarer co-existing syndrome is still a matter of debate. In light of similar risk factors and clinical features, a common origin has been supposed.

In most patients, a prognosis is generally favorable due to the reversibility of those syndromes; however, permanent disability or even death can be found in about 3–10% of cases (3).

CASE DESCRIPTION

Patient 1

A 45-year-old woman was referred to the emergency room (ER) with a 4-day history of leg paresthesia. Two weeks before, she had a gastroenteritis-like illness. The remaining personal history was unremarkable. Neurological examination revealed walk impairment, reduction in pinprick sensation and sense of position in the distal part of legs, diffuse absence of osteotendinous reflexes, mild reduction of strength, cranial nerves were spared, and no sphincter dysfunction was present. Blood pressure (BP), heart rate (HR), and other vital signs were within normal range. The CSF examination showed high proteins (1,7 gr/L) with a normal leukocytes count.

A neurophysiological examination was performed, including motor nerve conduction studies, F-waves evaluation (Median, Ulnar, SPE, and SPI nerves bilaterally), and sensory nerve conduction studies (sural, superficial radial, median, and ulnar nerves bilaterally), leading to the diagnosis of an acute motor axonal neuropathy (AMAN) variant of Guillain-Barré syndrome (GBS) (4).

Immunomodulatory therapy with intravenous immunoglobulins (IVIg) was started (0.4 g/Kg/die for 5 consecutive days); however, 12 h after terminating the first infusion of IVIg, the patient complained of blurred vision and headache, soon after a convulsive seizure occurred. Continuous monitoring of BP and HR in the stroke unit did not reveal any alteration preceding the events.

The electroencephalogram showed multifocal epileptiform discharges mainly in the central and posterior regions.

The patient underwent magnetic resonance (MR) examination that showed the typical aspect of PRES lesions with bilateral, relatively symmetric, cortical, and subcortical parieto-occipital hyperintensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (**Figures 1A,B**), without diffusion restriction in the affected areas on the ADC map (**Figure 1C**) due to vasogenic edema. After Gadolinium administration, a mild and patchy enhancement, especially on the left side, was noted. An MR angiography with a 3D-time of flight (TOF) revealed multifocal segmental areas of narrowing and dilatation of both the anterior and posterior arterial cerebral circulation (**Figure 1D**).

The PRES was, therefore, suspected.

In the absence of autonomic dysfunction (no fluctuation of BP or HR was observed during continuous monitoring in the stroke unit), the immunomodulatory therapy was changed from IVIg to 5 sessions of plasma exchange (PEX) to arrest the rapid clinical worsening of a patient's conditions.

Due to the unfavorable course, 8 days after admission, a new MRI was performed, which revealed a hemorrhagic evolution of the lesion in the left occipital lobe (**Figure 1E**), associated with massive ischemic brain damage in the left frontal, temporal, and parietal lobes, and with the persistence of diffuse caliber reduction of all large vessels (**Figure 1F**).

A new diagnostic work-up was started; 11 days later, a CSF examination showed again marked albumin-cytological dissociation (2.3 gr/L with 5 lymphocytes at Nageotte); PCR for Varicella Zoster Virus (VZV) and Herpes simplex virus (HSV) 1–2, tick borne encephalitis (TBE) and Lyme serology, as well as standard microbiological cultures on cerebrospinal fluid (CSF), were negative.

Blood tests revealed an IgG title compatible with remote exposition to VZV, Citomegalovirus (CMV), Epstein Barr Virus (EBV), and Borrelia, while the IgM title was negative; screening for HIV, West Nile Virus (WNV), Hepatitis Viruses (A, B, C), and Toxoplasma was negative.

Autoimmune screening [antinuclear antibodies (ANA), extractable nuclear antigen (ENA), anti-neutrophil cytoplasmic antibodies (ANCA), complement C3, C4, cryoglobulins, antiphospholipid and anti-cardiolipin, Rheumatoid Factor, lupus anticoagulant] and systemic indices of inflammation [C-reactive protein (RCP) and Erythrocyte Sedimentation Rate (ESR)] were normal.

After PEX, the patient was treated with high-dose steroids (1-gr methylprednisolone for 2 days). Despite treatment, the evolution was unfavorable, and the patient needs to be transferred to the intensive care unit, where she died 15 days after the admission due to massive brain ischemia.

Patient 2

A 59-year-old woman, with a history of mild hypertension and depression, treated with angiotensin-converting enzyme (ACE)-inhibitor and sertraline, arrived at our ER for symmetrical numbness and weakness in all limbs, which began 4 days earlier.

Abbreviations: PRES, posterior reversible encephalopathy syndrome; RVCS, reversible cerebral vasoconstriction syndrome; GBS, Guillain-Barré syndrome; ER, emergency room; BP, blood pressure; HR, heart rate; AMAN, acute motor axonal neuropathy; IVIg, intravenous immunoglobulins; MR, magnetic resonance; FLAIR, fluid-attenuated inversion recovery; TOF, time of flight; PEX, plasma exchange; AIDP, acute inflammatory demyelinating polyneuropathy; MFV, mean flow velocity; CNS, central nervous system.

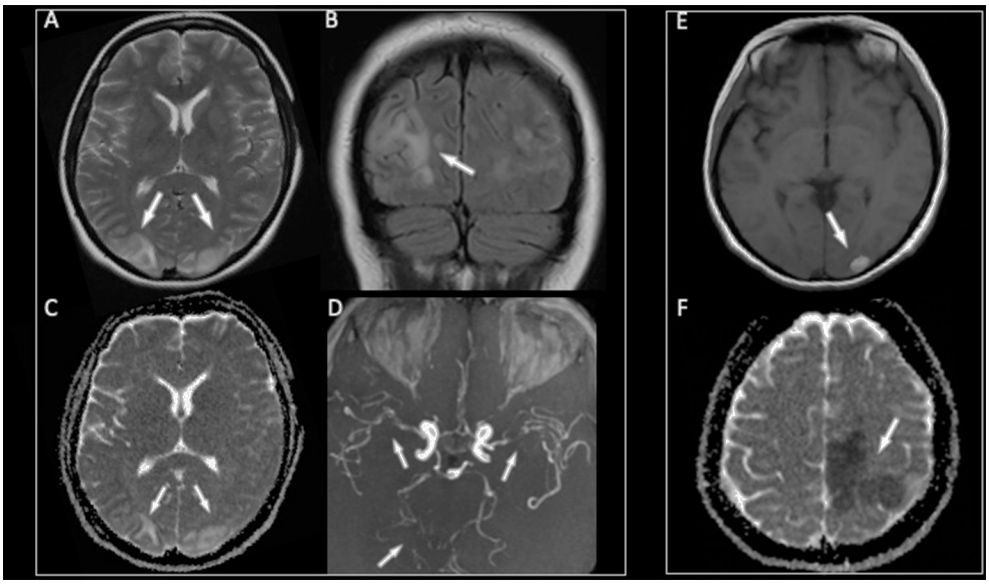

FIGURE 1 | The MR examination showing symmetric bilateral cortical and subcortical hyperintensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images **(A,B)** in the parieto-occipital lobes with a high signal in the same areas on the ADC map **(C)** due to vasogenic edema. The 3D-TOF MR angiography **(D)** demonstrating multifocal segmental areas of narrowing and dilatation of both the anterior and posterior arterial circulations. After 1 week, a hemorrhagic complication characterized by a bright signal on T1-weighted images **(E)** has appeared in the left occipital lobe, while a new ischemic lesion with a low signal on the ADC map **(F)** was noted in the frontal lobe.

One month before, she had experienced fever for 3 days without other symptoms.

The neurological examination revealed flaccid paraparesis in the lower limbs and reduced muscle strength in the upper limbs; deep tendon reflexes were diffusely absent; distal deep sensitivity was abnormal. Cranial nerves were spared, and no sphincter dysfunction was present. On admission, her BP and HR were normal.

The CSF analysis showed an albumin-cytological dissociation with 0,4 cells and 1.1 gr/L of protein.

An extensive neurophysiological examination was performed, including motor nerve conduction studies, F-waves evaluation (median, SPE, and SPI nerves bilaterally and right ulnar nerve), and sensory nerve conduction studies (sural nerves bilaterally, right superficial radial, median and ulnar nerves, and left median nerve), which led to the diagnosis of an acute inflammatory demyelinating polyneuropathy (AIDP) variant of GBS (4).

Treatment with IVIg was started (0.4 g/Kg/die for 5 consecutive days). No fluctuations of BP or HR were reported during continuous monitoring of vital parameters in the stroke unit, and the patient did not experience any symptom of autonomic dysfunction.

The clinical status remained unchanged, but 5 days after IVIg therapy, she developed a bilateral loss of vision.

The patient underwent an MR examination that demonstrated the presence of cortical and subcortical T2 weighted and FLAIR hyperintensities with mild mass effect in both parietal lobes and the occipital horns of lateral ventricles (**Figures 2A,B**).

The lesions were characterized by diffusion restriction on the ADC map (**Figure 2C**), consistent with cytotoxic edema; no hemorrhage or calcification was present (**Figure 2D**). Diffuse leptomeningeal enhancement was noted after a contrast medium (**Figure 2E**), and MR angiography with a 3D-TOF sequence showed slight narrowing of a P2 segment of the left posterior cerebral artery (in this case, with fetal origin) of the basilar trunk and the M1 segment of the right middle cerebral artery (**Figure 2F**).

The PRES showing atypical imaging characteristics was, therefore, suspected.

Transcranial doppler ultrasound evaluation was compatible with cerebral vasospasm; mean flow velocity (MFV) in the right middle cerebral artery was 140 and 160 cm/s in the left one; the Lindegaard ratio was 4. The BP and HR values were normal during continuous monitoring. Cerebral vasospasm was treated with nimodipine, and, after 1 week, MFV was decreased to 65 cm/s bilaterally.

Due to the persistence of visual deficit and paraplegia, the patients underwent treatment with five sessions of PEX.

On clinical examination, performed 4 months after the discharge, the patient showed a mild improvement in motor function with residual moderate paresis in both legs; visual acuity was only partially recovered.

DISCUSSION

Although rare, the association between GBS and PRES has been previously described in the literature, with PRES preceding or following GBS diagnosis (5). Autonomic dysfunction with pressure changes, altered permeability of the blood-brain

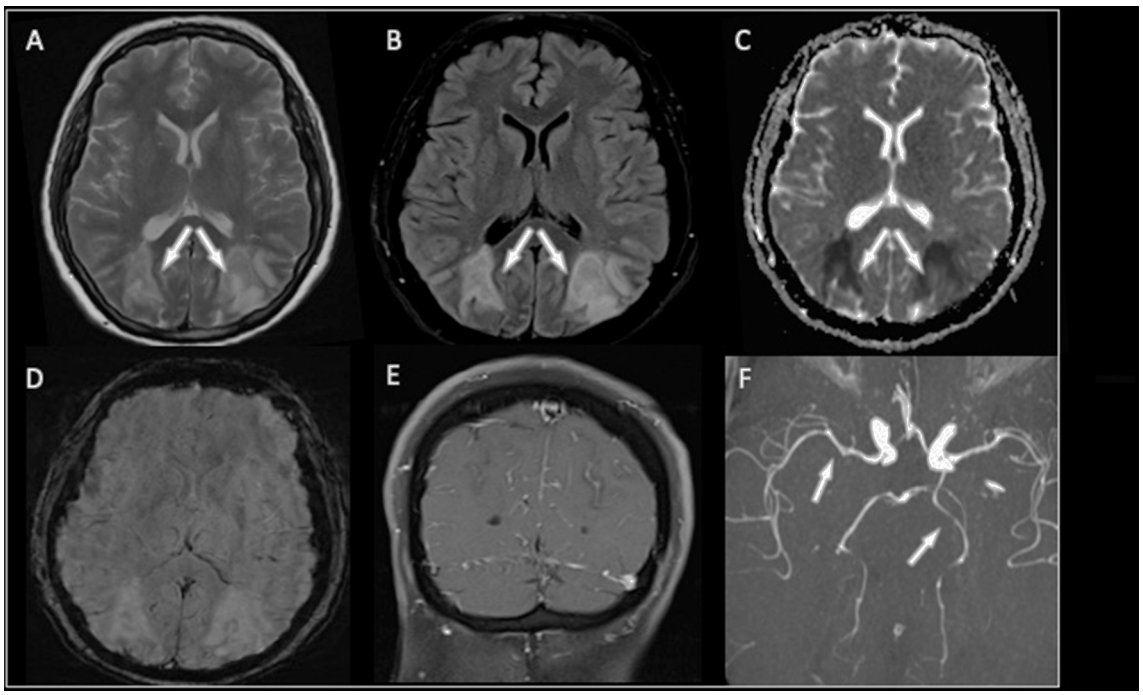

FIGURE 2 | The MR examination demonstrated the presence of cortical and subcortical T2-weighted and FLAIR hyperintensities involving both parieto-occipital lobes **(A,B)**. In this case, the lesions were characterized by diffusion restriction on the ADC map **(C)** findings consistent with cytotoxic edema. No hemorrhagic transformation or calcifications on SWI were seen **(D)**. After contrast medium administration, diffuse leptomeningeal enhancement was noted **(E)**. The MR angiography with 3D-TOF sequence **(F)** showed slight narrowing of the P2 segment of the left posterior cerebral artery and the M1 segment of the right middle cerebral artery.

barrier in the central nervous system, and increased risk of encephalopathy after IVIg treatment are believed to be involved in the pathogenesis of PRES associated with GBS (6).

Up to date, about 30 cases of PRES associated with GBS have been reported (7). All but one of them demonstrated autonomic dysfunction, with high levels of BP [except for the case following Miller–Fisher syndrome (8)].

Even if IVIg therapy is believed to be associated with PRES, its pathogenetic role is questionable. Several cases of PRES are reported to occur before the administration of IVIg therapy (5). In addition, no case report of PRES has been reported after IVIg treatment performed for another disease aside from GBS or Miller–Fisher, except for a patient with end-stage renal failure and hematologic disease treated with chemotherapy, which are typical risk factors in developing PRES (9).

On the other side, a high prevalence of autoimmune disorders as risk factors in PRES has been identified. As reported by Pilato and colleagues, the presence of a systemic immune impairment should be considered in the pathogenesis of PRES, especially in normotensive patients; this possibility is supported by the fact that both our patients were suffering from GBS, which is strongly associated with a dysregulation of immune system response (3). In addition, the hypothesis of an altered endothelial function has been supposed, especially in patients with autoimmune diseases (10).

Moreover, the release of several cytokines in GBS (tumor necrosis factor-α, interleukin-6, interferon-γ, and IL-17) (11) is responsible for systemic immune activation, which, in our hypothesis, could lead to endothelial dysfunction and altered vascular permeability is seen in PRES.

As responsible for systemic inflammation, GBS should be considered a risk factor in the pathogenesis of PRES, independently of the presence of autonomic dysfunction.

Based on these considerations, we suggest the alternative possibility that PRES (and the coexistence of PRES-RCVS) might be caused by the altered endothelial function and by the immune system dysregulation that is present in GBS, supported by the fact that, in our patients, the continuous monitoring of vital parameters permitted the exclusion of hypertension, HR alteration, or other dysautonomic features that, if present, could have justified PRES.

Reversibility of the lesions and clinical aspects are a hallmark of PRES; however, several studies report a poor outcome, with permanent structural or clinical deficits, or even death in 26–37% and 8–19% of cases, respectively (12).

Up to 85% of patients presenting with PRES show some characteristics of RCVS-like cerebral vasoconstriction (13). We suggest the coexistence of RCVS syndrome both for some neuroradiological aspects (such as the segmental areas of narrowing and dilatation of several cerebral arteries) and for the poor clinical outcome, that it is reported to affect about 1/3 of patients with RCVS (3).

Even if vasoconstriction features could be demonstrated in some patients with PRES (14), the coexistence of these two

syndromes has been previously reported. Nonetheless, more studies are needed to provide a more detailed description of this entity.

Due to the atypical clinical and neuroradiological features of our patients, the absence of BP alterations or other preexisting risks factors in intracerebral hemorrhage (such as hypertension or use of anticoagulants), as well as diffuse caliber reduction of all large cerebral vessels shown on MRI (first case) and an altered MFV, found on transcranial doppler ultrasound evaluation (second case), we hypothesize that PRES was associated with the simultaneous presence of a malignant RCVS-like cerebral vasoconstriction syndrome.

In literature, few cases are reporting an association between PRES and RCVS in patients with predisposing conditions (3), characterized by a more aggressive and sometimes unfavorable course, but no one after GBS.

In light of the prominent role of immune system activation and the systemic inflammatory status in GBS, we suggest the hypothesis of a central role of the immune system in the pathogenesis of PRES, or even of PRES/RCVS co-existing syndrome, and, subsequently, to endothelial dysfunction (15). This interpretation could justify the Gadolinium enhancement on MRI present in our two cases. The hypothesis of an altered endothelial function has been already proposed in previous studies, and it is believed to explain, at least partially, the pathogenesis of cytotoxic transformation and irreversibility of cerebral lesions seen in some atypical cases (3, 16).

Primary central nervous system (CNS) vasculitis is a rare but severe condition that affects cerebral and spinal cord vessels. For its clinical and neuroradiological characteristics, it is one of the main challenging differential diagnoses of RCVS. Calabrese and Mallek proposed diagnostic criteria for primary CNS vasculitis (17). Neuroradiological and angiographic imaging can increase the probability of a correct clinical diagnosis, although CNS biopsy remains mandatory to confirm the diagnosis of definite vasculitis.

In our two patients, vasculitis was considered among possible alternative diagnoses. However, the rapid onset of symptoms (headache, blurred vision, and altered mental status) in both the patient and the negativity of serological findings and cerebrospinal fluid analysis (except for mild elevation of proteins value, explained by GBS) is better explained by RCVS.

The MR angiography demonstrated areas of narrowing and dilatation of several cerebral arteries in both patients. Despite these findings, the differential diagnosis between vasculitis and RCVS cannot be done only on imaging data, without considering clinical and laboratory findings. This difficulty in distinguishing the two entities also remains for vessel-wall MRI, a new advanced technique to detect inflammation in the cerebral vessel (18).

CONCLUSIONS

Our two cases show typical initial symptoms of PRES who successively developed permanent neurologic deficit and ischemia, leading to an unfavorable outcome.

We suggest that, in our cases, GBS may have generated a multifactorial condition of systemic inflammation, leading to endothelial dysfunction, in which insidious aspects, similar to RCVS, had complicated a typical clinical picture of PRES. In this scenario, GBS itself should be considered a risk factor in PRES/RCVS, independent of the presence of autonomic dysfunction. The exact mechanism underlining PRES/RCVS co-occurrence is still debated and crucial for therapeutic strategy. Although the role of IVIg treatment in the pathogenesis of PRES has been proposed, it remains debatable (5, 9). In conclusion, in the cases presented here, we highlight the hypothesis that autoimmune dysregulation, following GBS, and endothelial dysfunction could be responsible for the development of PRES/RCVS.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

EB, ID, SL, GM, and GG were involved in the management of the patients and drafting the manuscript. DB carried out the neuroradiological study. MV and GG were responsible for the project and the final revision of the text. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.817295/full#supplementary-material

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