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Case reports in pediatric rheumatology 2022

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Published in
Frontiers in Pediatrics

ISSN 1664-8714
ISBN 978-2-83251-711-6
DOI 10.3389/978-2-83251-711-6

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Case reports in pediatric rheumatology 2022

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Citation

Wu, J., Ziaee, V., eds. (2023). *Case reports in pediatric rheumatology 2022*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-711-6

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frontiers | Frontiers in Pediatrics

TYPE Editorial
PUBLISHED 06 February 2023
DOI 10.3389/fped.2023.1137843

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 04 January 2023
ACCEPTED 20 January 2023
PUBLISHED 06 February 2023

CITATION
Bakhtiari Koohsorkhi M, Wu J and Ziaee V (2023) Editorial: Case Reports in Pediatric Rheumatology 2022.
Front. Pediatr. 11:1137843.
doi: 10.3389/fped.2023.1137843

Editorial: Case Reports in Pediatric Rheumatology 2022

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KEYWORDS

monogenic lupus, a20 haploinsufficiency, kabuki syndrome, factor h deficiency, bardet-Biedl syndrome, lupus podocytopathy, knee lipoma, MIS-C

Editorial on the Research Topic
Case Reports in Pediatric Rheumatology 2022

The field of pediatric rheumatology is thriving and growing in science. the body of clinical knowledge and scientific work in this area has expanded exponentially and is receiving worldwide attention. the recently discovered field of autoinflammatory diseases describes disorders that are at the crossroads of immunology and rheumatology and the joint effort is shedding new light on the unclear pathogenesis, and helping in the identification of new treatment options. Systemic autoinflammatory diseases (SAIDs) consist of multisystem immune dysregulation disorders caused by the dysfunction of the innate immune system in the absence of infections or autoimmunity (1, 2).

For nearly 3 years, the main focus of the academic world has mostly been on COVID-19, presentations, complications, and treatment strategies. however, it seems like the appropriate time to attract attention and put emphasis on case reports, unusual presentations, and new and experimental treatment options for other rheumatologic diseases. Case reports count as a great source of new ideas and information in clinical medicine and it has the ability to report original discoveries and novel treatment strategies.

The present Special Issue entitled **"A Review on new Case Reports in Pediatric Rheumatology 2022"** aims to explore the advances in pediatric rheumatology and case reports chosen in this research topic represent some of the fresh advances in the field.

The recent discovery of monogenic inborn errors of immunity and the so-called subgroup of autoinflammatory disorders has broadened the field of pediatric rheumatology. Early age of presentation and familial tendencies are clues to the possibility of an underlying monogenic pattern. It is already known that autoimmunities are more common in relatives of children with SLE (3). Repetitive patterns in family members of lupus patients are in favor of underlying genetic causes. Mikhail M. Kostik et al. reported a case of 2 monozygotic twin brothers with simultaneous childhood SLE. This compelling case report emphasizes the possibility of monogenic origin in childhood SLE and justifies the need to perform WGS to study the spectrum of genetic variants associated with lupus.

Kwong et al. described a case of multiple autoimmune syndromes (MAS) comprising of type 1 diabetes, Hashimoto thyroiditis, and childhood-onset systemic lupus erythematosus (SLE). Although this is not a usual combination we expect to observe in polyautoimmunities, when repeated and reported, could help us integrate these new data into a more detailed

understanding of disease pathogenesis and genetics, as well as possible interactions with environmental factors.

In the past decade the scientific community has drawn more attention to A20 Haploinsufficiency which is a rare autoinflammatory disorder with Behçet disease (BD) like characteristics caused by loss-of-function mutations in TNFAIP3 gene. Some of the most common symptoms of the disease are recurrent mucosal ulcers, periodic fever, musculoskeletal symptoms, skin lesions, and recurrent infections (4, 5). Aslani et al. reported two patients with A20 haploinsufficiency and HLH (6). Zanatta et al. discussed a patient with novel heterozygous mutation in TNFAIP3 who developed intestinal BD. Considering that there are not enough published cases on this topic, reports on this matter should be encouraged to reach better understanding about symptoms and complications.

Mauro et al. described the first case of Bardet–Biedl syndrome (BBS) associated with recurrent pericarditis (RP). Congenital heart diseases are the most common cardiac finding in BBS and acquired disorders like pericarditis are usually not expected in these patients. what is even more interesting, is the excellent response to treatment with anakinra in this reported patient. Contextually, Tsyklauri et al. suggested that patients with BBS have a higher prevalence of autoimmune disorders (7) but there is no published data to support the correlation between BBS and rheumatological or autoinflammatory disorders. This association is particularly compelling as it shows a new possible feature associated with BBS and suggests a plausible unknown underlying autoinflammatory mechanism in BBS.

Li et al. described a *de novo* missense variant in the KMT2D gene in a boy with distinctive facial features consistent with Kabuki syndrome (KS) and pulmonary hemorrhage who was diagnosed with Goodpasture's syndrome. To our knowledge, no other similar case of KS with pneumorrhagia is described in the literature. Although we cannot be certain whether Goodpasture's syndrome is part of the KS presentation or if it occurred coincidentally, this case report does expand on the phenotype of KS and the possible associated autoimmune disorders.

Lunz Macedo et al. described a patient with homozygous Factor H (FH) Deficiency who started manifesting signs of childhood-onset SLE at age 15 while his primary immunodeficiency was diagnosed at 5. It's well worth the mention that Case reports that relate autoimmune diseases like lupus to the complement system are often related to the defects in the classical complement pathway (8). However, the association between SLE and deficiencies in the components of the alternative pathway is uncommon. There is no previously published case of a patient with an initial presentation of FH deficiency with normal components of the classical pathway, who develops childhood SLE later in life. What makes this report even more noteworthy is the experimental treatment with Curcumin. Falcão DA and her team previously described a patient with FH deficiency in 2008 who showed a promising response to *in vitro* treatment with curcumin resulting in increased secretion of FH from the endoplasmic reticulum of the patient's fibroblasts (9). However, *in vivo* treatment with CURCUMIN derivatives "Theracurmin", which was experimented with in this paper, did not result in an increase in the plasma levels of FH, C3, and FB in their patient and no change in the clinical and laboratory SLE parameters were observed.

Another interesting twist on Lupus is discussed by Li et al. which describes a case of SLE complicated with Lupus Podocytopathy (LP) and antiphospholipid syndrome (APS). We expect immune complex depositions in the mesangium, subepithelial or subendothelial regions in lupus nephropathy (10). However, Lupus podocytopathy is a non-immune complex-mediated type of lupus nephropathy. It is a newly described entity of non-immune complex-mediated lupus nephropathy and is not yet included in the updated 2018 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of LN (11). There are very few reported pediatric cases of LP in the literature. but the coexistence of APS and LP in the same patient with SLE has not ever been reported in children. Li et al. study reinforces the need to consider the potential co-occurrence of APS and LP.

The increasing knowledge of inflammation and immunological pathways helps with new therapeutic options for rheumatologic disorders. These advances help in further understanding disease pathophysiology and progression and its associated complications, which support the stratification of patients to treatment pathways. The introduction of biological drugs has revolutionized the management of pediatric rheumatologic diseases, primarily in juvenile idiopathic arthritis (JIA), and has led to dramatic changes in the treatment strategies.

In the observational study performed by Xu et al. the efficacy and safety of Etanercept biosimilar recombinant human TNF-α receptor II: IgG Fc fusion protein (rhTNFR-Fc) is evaluated in 60 Chinese children with JIA and entesithis related arthritis. Their study indicated that the combination of rhTNFR-Fc and methotrexate (MTX) significantly improved the symptoms and disease activity of children with JIA.

Frkovic et al. present a 16-year-old girl with psoriatic JIA and bilateral Lipoma arborescens (LA) of her knees. Her Diagnosis was confirmed when she was 13 and primarily received conservative medical treatment (MTX) and TNF inhibitor—adalimumab was added later as a step-up approach, Which resulted in an almost complete regression of LA. LA is a non-specific reactive response to chronic inflammation associated with the proliferation of synovial villi, causing intraarticular lesions. During the last decade, a growing number of reports suggest that LA has an underlying inflammatory property. However, most clinicians are doubtful about the success of anti-inflammatory therapy in these patients and recommend synovectomy as the definitive treatment (12). Even though chronic synovial inflammation is the main pathogenesis of JIA, there are only several reports of LA in JIA patients. This case report is the first case of successful use of the TNF inhibitor adalimumab for treating bilateral knee LA in a patient with psoriatic JIA.

The use of biological treatments in MIS-C (Multisystem inflammatory syndrome in children) is also a point of focus in recent literature. MIS-C is a potentially life-threatening condition triggered by SARS-COV-2 infection. Since its first description, a huge effort has been made worldwide to better understand the pathogenesis and the clinical features of this novel entity to optimize therapeutical approaches (13).

La Torre et al. discussed a rare case of pulmonary vasculitis in an MIS-C patient who was not primarily responsive to IVIG and high-dose corticosteroids. Their use of sildenafil and high-dose anakinra as rescue therapy provided amazing results. It's intriguing to think that MISC-associated pulmonary vasculitis can benefit from biological treatments but more extensive studies are required to confirm these preliminary results.

Most MIS-C cases are managed with high dose corticosteroid therapy and immunomodulatory medications (14). However, the recent revisions of ACR recommendation agree that "*in mild cases, after evaluation by specialists with expertise in MIS-C, some patients may be managed with only close monitoring without immunomodulatory treatment*" (15). In the case series provided by Meneghel et al. the absence of laboratory and instrumental findings of cardiac involvement was the key point for a conservative approach, although in other cohorts in which a self-limited course has been reported cardiovascular dysfunction was described.

In conclusion, all these research efforts have significantly contributed to increasing the knowledge of pathophysiological, diagnostic, and therapeutic aspects of rheumatologic disorders.

Author contributions

The concept was led by VZ provided the first draft. JW reviewed the manuscript. MB provided the first draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

The 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.

Publisher's note

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frontiers | Frontiers in Pediatrics

BRIEF RESEARCH REPORT
published: 16 June 2022
doi: 10.3389/fped.2022.929358

Simultaneous Onset of Pediatric Systemic Lupus Erythematosus in Twin Brothers: Case Report

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There are hundreds of twin adult patients with systemic lupus erythematosus (SLE), but male children with SLE are rarely affected. Two monozygotic twin brothers developed SLE at the age of 11 years during 1 month. The index brother manifested with Henoch-Shonlein purpura, accompanied by ANA positivity, and later developed critical left femoral arterial stenosis with high levels of anti-dsDNA, antiphospholipid antibodies, hypocomplementemia, and Coombs-positive hemolytic anemia. At that time his twin brother had only identical autoimmune findings and developed clinical manifestation (myositis and fasciitis) a month later. Both twins had increased IFN-score and shared a heterozygous variant in the RNASEL gene. Index patients developed scalp rash and nephritis 6 months after their parents refused the treatment which has been lasted for 1 year after disease diagnostics.

Conclusion: The simultaneous onset of the pediatric SLE in the male twin is a very rare situation suspected monogenic origin of the disease. Further functional studies are required to confirm the causative role of the mutation.

Keywords: pediatric systemic lupus erythematosus, twins, antiphospholipid syndrome, IFN-signature, RNASEL

OPEN ACCESS

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Specialty section:
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

Received: *26 April 2022*
Accepted: *23 May 2022*
Published: *16 June 2022*

Citation:
Raupov RK, Suspitsin EN, Imelbaev AI and Kostik MM (2022) Simultaneous Onset of Pediatric Systemic Lupus Erythematosus in Twin Brothers: Case Report. Front. Pediatr. 10:929358. doi: 10.3389/fped.2022.929358

INTRODUCTION

Familial cases of SLE are known, but just a few hundred cases of SLE in twins have been described in the world. Usually, SLE affects monozygotic female twins, while the descriptions of SLE in twin males are rare (1). Several genetic variants associated with lupus have been previously described. High penetrant single gene variants leading to complement deficiency (C1Q, C1R/S, C2, C4A, and C4B) are rare and mostly presented in patients with early-onset SLE while plenty of common low penetrant variants may only increase the risk of SLE. The following pathways are predominantly involved in SLE pathogenesis: TLR/IFN-I signaling, NF-κB signaling, T-cell signaling, B-Cell signaling, T- and B-Cell signaling and interaction, self-antigen clearance, IC clearance, DNA repair (2). This diversity explains the clinical and genetic heterogeneity of SLE. Some associations between gene defects and clinical manifestations have been found (3).

CASE DESCRIPTION

Two 11th years monozygotic twin boys developed SLE within 1 month. Family medical history is unremarkable, except cold-induced allergy of the maternal grandfather. No previous immune dysregulation diseases were observed in the twins.

Index Twin

Twin 1 had pain in the legs after physical activity for 6 months and pain in the groin during walking for the last month before the hospital admission. Then hemorrhagic rash on the legs, the left ankle, and the wrists edema, and fever appeared. He was admitted to the local hospital and Henoch-Schonlein purpura was diagnosed. Laboratory tests showed inflammation with mild leukocytosis and neutrophilia, ESR and CRP elevation, transaminase elevation, and positive direct Coombs test. Infections were ruled out. He was treated with antibiotics and heparin. Fever and rash were resolved, while the left ankle edema persisted. Due to ANA-positivity (1:5120, NR <1:160) he was transferred to our rheumatologic clinic. Suddenly he developed intermittent claudication, pain in the left calf muscle, and hypothermia on the left foot. The discrepancy in the blood pressure between the legs was detected on physical examination. He had mild ESR elevation, coagulopathy, hypocomplementemia, positive direct Coombs test without signs of hemolysis, and very high autoimmune activity with ANA positivity, anti-dsDNA, and antiphospholipid autoantibodies (**Table 1**). CT-angiography detected critical stenosis of the left femoral artery (**Figure 1A**). Doppler-ultrasound showed the difference in the blood flow pattern in the left iliac and the femoral arteries (**Figures 1B,C**). He was effectively treated with oral corticosteroid (prednisolone 1 mg/kg), hydroxychloroquine, IV prostaglandin E1, and low-weight heparin followed by warfarin. The symptoms resolved, signs of stenosis and arteritis partially improved and steroid tapering was recommended.

Twin 2

Twin 2 has no symptoms at the moment of Twin 1 clinical manifestation. The parents decided to examine him and identical laboratory and autoimmune changes as in Twin 1 were found (**Table 1**). The low dose of acetylsalicylic acid with hydroxychloroquine was started due to the presence of positive antiphospholipid antibodies for thrombotic events profilaxis. 1 month after Twin 1 clinical manifestation Twin 2 had acute severe pain in the left leg with hemorrhagic rash (petechiae) in the legs. The left lower leg circumference (mid-thigh) was +1.5 cm than the right one, painful on palpation. Laboratory tests showed the signs of inflammation (ESR 47 mm/h, CRP 20.1 mg/l), hypocomplementemia, and coagulopathy [APPT 45.1 sec (↑), D-Dimer 770 ng/ml (↑)]. Doppler ultrasound has not revealed any blood vessels pathology, except the fascia thickening of the quadriceps and fluid accumulation (**Figure 1D**). Corticosteroids (prednisolone 1 mg/kg) were immediately started with a resolution of clinical symptoms and laboratory parameters normalization and further tapered.

TABLE 1 | Laboratory characteristics of patients at the disease onset.

Studied parameter	Twin 1	Twin 2
Hemoglobin, g/dl (n.v 11.0–16.5)	11.4	11.5
Leucocytes, 10^9/l (n.v.<4.0–10.0)	4.3	5.5
Thrombocytes, 10^9/l (n.v.180–400)	141	182
ESR, mm/h (n.v.<20)	20	9
CRP, mg/l (n.v.<5)	1.4	3.4
Activated partial thromboplastin time, sec (n.v.25.1–36.3)	136	82.1
D-dimer, ng/ml (n.v.<250)	765	1,029
C3 complement, g/l (n.v. 0.82–1.73)	0.84	0.84
C4 complement, g/l (n.v.0.13–0.46)	0.05	0.06
Lupus anticoagulant (n.v.0.8–1.2)	3.06	2.86
Coombs test	Positive	Positive
Antinuclear antibody (n.v.<1:160)	1:5,120	1:5,120
Anti-dsDNA, IU/ml (n.v.<25)	>800	>800
Anticardiolipin antibody*, IgG, GPL-U/ml (n.v.<12)	45.8	109.5
Anticardiolipin antibody*, IgM, MPL-U/ml (n.v.< 12)	99.8	>120
Anti-β2-glycoprotein I*, MPL-U/ml (n.v.< 20)	>200	>200

*n.v., normal value, *all antiphospholipid antibodies were positive throw 12 weeks in both patients.*

GENETIC TESTING

IFN I-score was assessed by RT-PCR quantitation of 5 IFN I-regulated transcripts (IFI44L, IFI44, IFIT3, LY6E, MXA1); median relative expression of ≥ 2 was considered as a cut-off. Both twins had elevated blood IFN-I expression scores (9.9 and 10.0, normal range 0.57–1.9) in the second visit on corticosteroid treatment. Clinical exome sequencing of the twins revealed a shared heterozygous variant, RNASEL c.1880A>G (p.K627R), rs149964724. This substitution has a MAF (minor allele frequency) of 0.000378 (Genome Aggregation Database; gnomAD); it has not been reported in ClinVar. According to the ACMG (American College of Medical Genetics and Genomics) criteria the variant may be classified as Likely benign (BP1, BP4). The variant was inherited from an asymptotic mother.

FURTHER FOLLOW-UP

Corticosteroids have been tapered up to 0.2 mg/kg during the following 6 months without flare in both twins. Both patients also had migraine headaches, the levels of anti-dsDNA and antiphospholipid antibodies still had increased in several scheduled testing in the following 18 months. Brain MRI was normal. Rituximab was recommended, but the parents refused it as well as any other treatment. In the 24 months from the onset, the parents refused the following treatment in both twins. Twin 1 developed intensive skin and scalp rash, thrombocytopenia (PLT 72 x 10^9/l), and lupus nephritis (proteinuria 1,1 g/24 h) 6 months after the treatment ceased (**Figure 2**). Despite clinical and laboratory deterioration, his IFN-I score was lower (5.7) than in the disease onset (9.9). Oral corticosteroids 1 mg\kg were initiated, but parents have been against the kidney biopsy and any

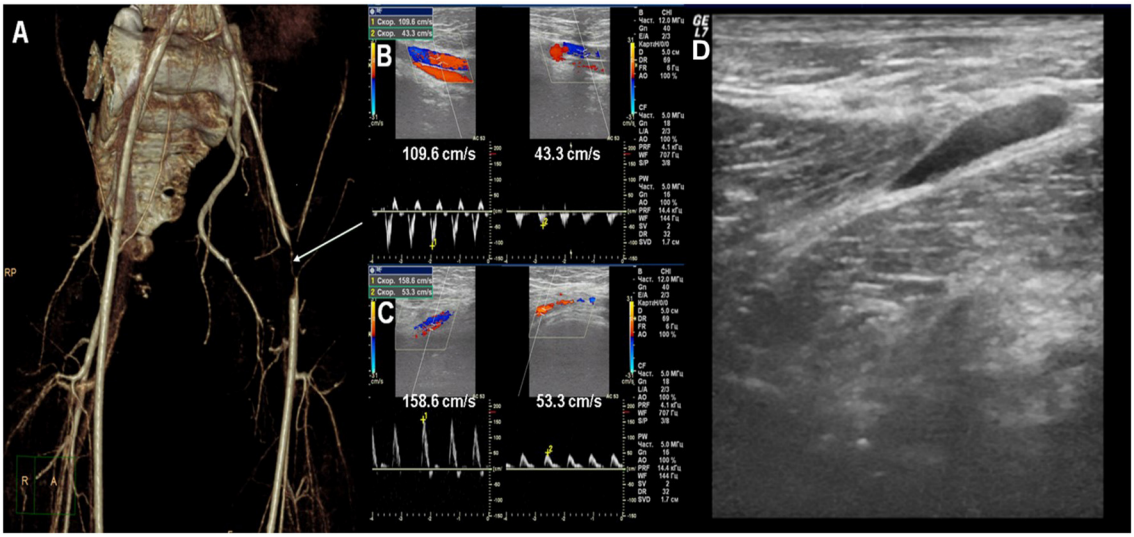

FIGURE 1 | (A) CT-angiography: critical stenosis of the left femoral artery. **(B)** Doppler ultrasound: the difference of blood flow velocity in the iliac arteries. **(C)** Doppler ultrasound: the difference of blood flow velocity in the femoral arteries. **(D)** Ultrasound: fascia thickening of the quadriceps and sub-fascial fluid accumulation.

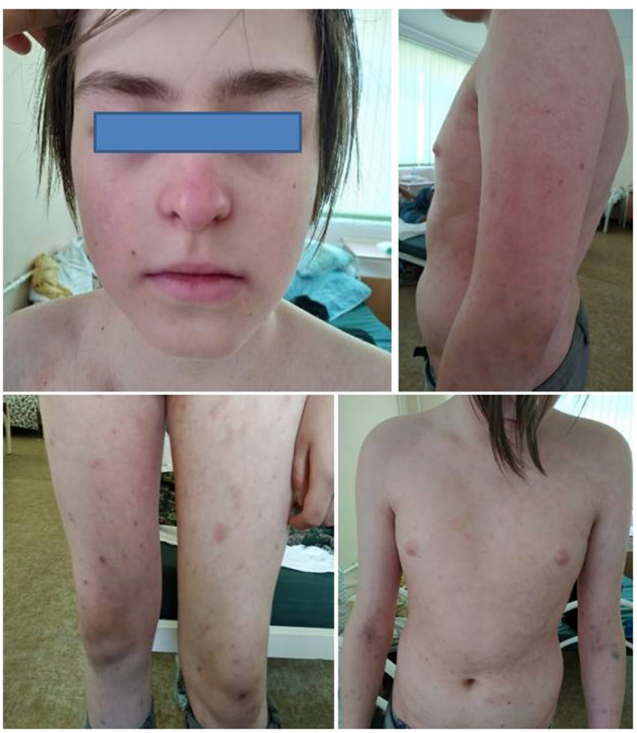

FIGURE 2 | The rash in Twin 1 during the flare (Month 30 from the onset).

additional treatment (rituximab or synthetic DMARDs). Twin 2 hasn't developed the symptoms of SLE for the following 3 years.

DISCUSSION

We described a rare case of the simultaneous onset of pediatric SLE in male monozygotic twins: Twin 1 has developed a typical SLE with antiphospholipid syndrome and his brother Twin 2 has not realized yet full-blown SLE possibly due to early diagnostics and treatment intervention. Local arterial involvement is a rare phenomenon in lupus. It was difficult to distinguish local femoral arteritis from arterial thrombosis without distal ischemic lesions in Twin 1. Twin 2 manifested with similar local thigh changes, but it is unclear whether the early treatment of Twin 2 prevented vascular lesions or not. According to ACR/EULAR 2019 Twin1 meets SLE criteria (totally 19 points). Twin 2 scored 11 points by only immunologic features without pronounced clinical manifestation.

The first investigations proposing the genetic background of SLE were performed for twins in the second part of the XX century (4). The presence of SLE and autoantibodies production in concordant and discordant twins were analyzed. The literature review showed 60/151 concordant SLE cases in monozygotic twins while only 4/96 dizygotic (1). Population-based Danish study demonstrated concordance rates of 25% in monozygotic and 7.7% in dizygotic SLE twins. Only 2/22 (9.1%) were male twins with SLE. The majority of twins (19/22) developed clinical manifestations of SLE within the same year (5). Serologic studies were performed on 7 pairs of identical twins: three were concordant and four were discordant for SLE. Concordant twins had similar autoantibodies and anti-RNA profiles, whereas affected twins had higher titers than unaffected discordant pairs. The profile of anti-RNA proteins (e.g., Ro/SS-A, La/SS-B, U1 RNP, and Sm) was identical in 3/4 of discordant twins (6). First-degree relatives of SLE patients had higher ANA autoantibodies levels than healthy controls (7). Autoantibodies against a panel of 21 autoantigens (excluding anti-dsDNA and antiphospholipid autoantibodies) were analyzed in discordant twin patients with SLE ($n = 9$) and idiopathic inflammatory myositis ($n = 22$). Only 3/31 (10%) unaffected twins were seropositive against single autoantigens not observed in twins with the disease (8). The

results of these studies indicate SLE heterogeneity and the role of genetic and epigenetic factors.

Our patients have a variant in the gene which might play role in the interferon type I signaling. The hyperactivation of the interferon I signaling pathway plays a major part in lupus pathogenesis and several medications affecting IFNI hyperproduction had been recently tested (tofacitinib, baricitinib, anifrolumab, sifalimumab, IFN-αkinoid, BIIB059) (9). Type I IFNs stimulate both the innate and adaptive immune systems, which contribute to loss of tolerance and a sustained autoimmune disease process (10). There are many variants in genes that encode components of the IFNI pathway associated with SLE. Some single gene variants (SAMHD1, RNASEH2ABC, ADAR1, IFIH1, ISG15, ACP5, TMEM173) can cause monogenic lupus (11). They are characterized by early SLE onset and severe disease manifestation. Monogenic lupus has similar features to type I interferonopathies and some interferonopathies, such as CANDLE, SPENCD, SAVI, Aicardi-Goutières syndrome has lupus as a part of the disease (12).

In the recent paper, the whole-exome sequencing (WES) was performed in 52/281 pediatric SLE cases who fulfilled one of the following criteria: early onset of the disease (<5 years), family history of autoimmune disease and complicated conditions, and causative mutations in 5 genes (SLC7A7, NRAS, TNFAIP3, PIK3CD, and IDS) were identified in 12 patients (23.1%) (13).

Seven children with SLE who had a disease onset ≤5 years and a family history consistent with an autosomal recessive inheritance were enrolled in the next study. WES revealed two novel and three previously reported homozygous variants in genes coding early complement proteins (C1QA, C1QC, and C1S), and one patient had a DNASE1L3 variant, which might activate interferon type I signaling (14).

Tirosh, et colleagues performed WES in 6/15 newly diagnosed childhood-onset SLE with severe (life-threatening or organ-threatening presentation), atypical presentation (out of the typical clinical classification criteria for SLE), close-married parents, or additional comorbidities (i.e., immunodeficiency). Four unrelated severe cases of childhood-onset SLE were secondary to mutations in five different genes, the last three of them are working in interferon type I signaling: C1QC, SLC7A7, MAN2B1, PTEN, and STAT1 (15). Ultra-rare (≤0.1%) missense and non-sense variants in 22 genes, known to cause monogenic forms of SLE were identified in 71 SLE patients and their healthy parents with WES. Only one homozygous mutation in C1QC and seven heterozygous variants in five genes (C1S, DNASE1L3, DNASE1, IFIH1, and RNASEH2A), associated with monogenic SLE were identified (16). All genes, except for C1S are involved in interferon type I signaling.

In a recent Chinese study, WGS were analyzed in three families where 7 of 16 members had SLE. There was one discordant for SLE female pair. The pathogenic risk of rare missense variants in WNT 16 and ERVW-1 genes was identified in five and two patients, respectively. Whereas, none of the healthy family members has mutations (17). Genome-wide DNA methylation changes in sorted CD4 + T-cells, monocytes, granulocytes, and B-cells were analyzed in 15 SLE-affected twin pairs. All cell types had hypomethylation in interferon-regulated genes, such as IFI44L, PARP9, and IFITM1. Notably, hypomethylation was more pronounced in patients who had disease flare within the past 2 years. In contrast to the other cell types, differentially methylated CpGs in B -cells were predominantly hypermethylated, were the most important upstream regulators included TNF and EP300 (18). The case of monozygotic twins discordant for SLE was described. A total of 8 putative discordant variants in the DNA were selected out for validation by Sanger sequencing, but all of them were ultimately non-diagnostic (19).

It's known that IFN type I hyperactivation leads to endothelial dysfunction and activates the coagulation cascade, which may explain arterial involvement (10). A recent study demonstrated that type I IFN score was increased in all the patients with primary antiphospholipid syndrome and antiphospholipid syndrome in SLE (20). RNASEL gene encodes a ribonuclease participating in IFN induction. While RNA/DNA-modulating enzymes are known to play a role in lupus pathogenesis (2), it is unclear whether the RNASE variant, which has been found in our twins is associated with our patients' phenotype or not.

CONCLUSION

SLE in male twins is a rare and unique phenomenon. Genetic factors probably play a crucial role in such cases. There're only a few studies where WGS/WES were performed in twins with SLE. It is necessary to study the spectrum of genetic variants associated with SLE.

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. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MK and RR had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

FUNDING

This work was supported by the RSF Grant No: 20-45-01005.

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Conflict of Interest: The 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 | Frontiers in Pediatrics

TYPE Case Report
PUBLISHED 19 August 2022
DOI 10.3389/fped.2022.950576

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 23 May 2022
ACCEPTED 02 August 2022
PUBLISHED 19 August 2022

CITATION
Li G-m, Li Y-f, Zeng Q-q, Zhang X-m, Liu H-m, Feng J-y, Shi Y, Wu B-b, Xu H and Sun L (2022) Lupus podocytopathy and antiphospholipid syndrome in a child with SLE: A case report and literature review. *Front. Pediatr.* 10:950576. doi: 10.3389/fped.2022.950576

Lupus podocytopathy and antiphospholipid syndrome in a child with SLE: A case report and literature review

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Lupus podocytopathy is a glomerular lesion in systemic lupus erythematosus (SLE) characterized by diffuse podocyte foot process effacement (FPE) without immune complex (IC) deposition or with only mesangial IC deposition. It is rarely seen in children with SLE. A 13-year-old girl met the 2019 European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) Classification Criteria for SLE based on positive ANA; facial rash; thrombocytopenia; proteinuria; and positive antiphospholipid (aPL) antibodies, including lupus anticoagulant (LAC), anti-β2 glycoprotein-I antibody (anti-β2GPI), and anti-cardiolipin antibody (aCL). The renal lesion was characterized by 3+ proteinuria, a 4.2 mg/mg spot (random) urine protein to creatinine ratio, and hypoalbuminemia (26.2 g/l) at the beginning of the disease. Kidney biopsy findings displayed negative immunofluorescence (IF) for immunoglobulin A (IgA), IgM, fibrinogen (Fb), C3, and C1q, except faint IgG; a normal glomerular appearance under a light microscope; and diffuse podocyte foot process effacement (FPE) in the absence of subepithelial or subendothelial deposition by electron microscopy (EM). Histopathology of the epidermis and dermis of the pinna revealed a hyaline thrombus in small vessels. The patient met the APS classification criteria based on microvascular thrombogenesis and persistently positive aPL antibodies. She responded to a combination of glucocorticoids and immunosuppressive agents. Our study reinforces the need to consider the potential cooccurrence of LP and APS. Clinicians should be aware of the potential presence of APS in patients with a diagnosis of LP presenting with NS and positivity for aPL antibodies, especially triple aPL antibodies (LCA, anti-β2GPI, and aCL).

KEYWORDS

antiphospholipid syndrome, foot process effacement, lupus podocytopathy, systemic lupus erythematosus, aPL antibodies

Introduction

The podocyte is a visceral epithelial cell that is the core component of the glomerular filtration barrier (1). Podocytopathies are kidney diseases in which direct or indirect podocyte injury drives proteinuria or nephrotic syndrome (2, 3). The most frequent histopathologic findings of primary injury to podocytes are minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) (2–4). However, MCD and FSGS are morphologic descriptions that can be caused by various pathogenic pathways (2, 4). Systemic lupus erythematosus (SLE) is a chronic immune complex-mediated disease characterized by disseminated inflammation that may affect multiple organs (5). Renal nephritis (LN) occurs in 30 to 70% of patients with SLE, and there is compelling evidence to suggest that glomerular epithelial cells, and podocytes in particular, are also involved in glomerular injury in patients with SLE (6–8). Lupus podocytopathy (LP) is also a glomerular lesion in SLE characterized by proteinuria or nephrotic syndrome (NS), demonstrating MCD, mesangial proliferation (MsP) or FSGS. Meanwhile, by electron microscopy (EM), diffuse podocyte FPE is observed in the absence of subepithelial or subendothelial deposition (9–11). Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the occurrence of venous and/or arterial thrombosis and pregnancy morbidity in the presence of pathogenic autoantibodies known as antiphospholipid (aPL) antibodies (12, 13). APS may be associated with other diseases, mainly SLE. Herein, we report a child suffering from SLE with LP and APS.

Case presentation

The patient, a 13-year-old Chinese girl, presented with fever and persistent right upper abdominal pain in Sep 2020. She was admitted to the surgery department of her local hospital, and computed tomography (CT) of the upper abdomen revealed cholecystitis. Laboratory findings suggested thrombocytopenia (77.0×10^9/l, normal range $100–300 \times 10^9$/l), mildly elevated serum (91 U/l, normal range 40–85 U/l) and urine (1,329 U/l, normal range 400–1,000 U/l) amylase, abnormal alanine aminotransferase (ALT; 72 U/l, normal range 7–40 U/l) and aspartate aminotransferase (AST; 42 U/l, normal range 13–35 U/l), elevated D-dimer (4,140 ng/ml, normal range 0–500 ng/ml), and positive anti-nuclear antibodies (ANA; 1:320) and perinuclear antineutrophil cytoplasmic antibody (p-ANCA; 1:10). She was diagnosed with cholecystitis and acute biliary pancreatitis and was treated with antibiotics and supportive treatment, such as fasting, rehydration, parenteral nutrition, and anticoagulation. Although the symptoms were relieved after treatment, the thrombocytopenia did not improve. However, the persistent thrombocytopenia and positive ANA in the patient did not attract sufficient attention from surgeons, and the symptoms of fever and abdominal pain relapsed after 2 months. She was readmitted to the surgery department of her local hospital. Magnetic resonance cholangiopancreatography (MRCP) was normal, abdominal ultrasound revealed that the gallbladder wall was rough and thickened, and lung CT showed pleural and pericardial effusion. Laboratory findings revealed thrombocytopenia (52.0×10^9/l, normal range $100–300 \times 10^9$/l), proteinuria (3+), decreased serum albumin (26.2 g/l, normal range 40–55 g/l), low levels of complement 4, and positive ANA (1:320). The spot (random) urine protein to creatinine ratio (UPr/Cr ratio) was 4.2 mg/mg (normal <0.2 mg/mg), which suggests nephrotic range proteinuria (UPr/Cr ratio>2.0 mg/mg). She was diagnosed with cholecystitis and was treated with antibiotics. The abdominal pain was relieved, but the fever was not improved. Moreover, she had a rash (Figures 1A,B) in face and neck accompanied by swelling and pain of the right auricle (Figure 1B), which became necrotic (Figure 1C). The right auricle had to be removed, and new skin had to be grafted on from her neck (Figure 1D). Pathological changes from the auricle and its surrounding skin displayed microvascular thrombogenesis (Figures 1E–G). She was treated with oral prednisolone (2 mg/kg/day) and aspirin because she may have had connective tissue disease and a hypercoagulable state after a physician consultation. The fever was relieved after treatment with prednisolone, and the proteinuria was reduced.

She was referred to our hospital for evaluation because of persistent thrombocytopenia and proteinuria. Physical examination revealed a rash on the face and neck, absence of the right pinna, and surgical scarring on the area of the right pinna. Other physical findings were unremarkable. Her medical history and family history were unremarkable. Laboratory testing showed mild anemia (hemoglobin 95 g/l, normal range 110–160 g/l), 2 + proteinuria (0.96 g/24 h, normal <0.15 g/ 24 h), mildly elevated ALT and AST, and decreased serum albumin (34.2 g/L, normal range 39–45 g/L). The UPr/Cr ratio was 2.2 mg/mg. Autoantibodies were positive for ANA (1:640), p-ANCA (1:10), lupus anticoagulant (LAC), anti-β2 glycoprotein-I antibody (anti-β2GPI), anti-cardiolipin antibody (aCL) immunoglobulin G (IgG) and immunoglobulin M (IgM), and the others were negative. Kidney biopsy was performed because of persistent haematuria and proteinuria, and the findings displayed negative immunofluorescence (IF) for immunoglobulin A (IgA), IgM, fibrinogen (Fb), C3, and C1q, except faint IgG (Figure 2); a normal glomerular appearance under light microscopy (Figure 2); and diffuse podocyte foot process effacement in the absence of subepithelial or subendothelial deposition on EM (Figure 2). Whole exon sequencing (WES) in the core family was performed, and no disease-causing mutations in any genes associated with SLE or APS were detected. The patient was diagnosed with SLE accompanied by LP and APS.

She was treated with intravenous pulse methylprednisolone followed by oral prednisolone (60 mg/day) and hydroxychloroquine (5 mg/kg/day) combined with monthly

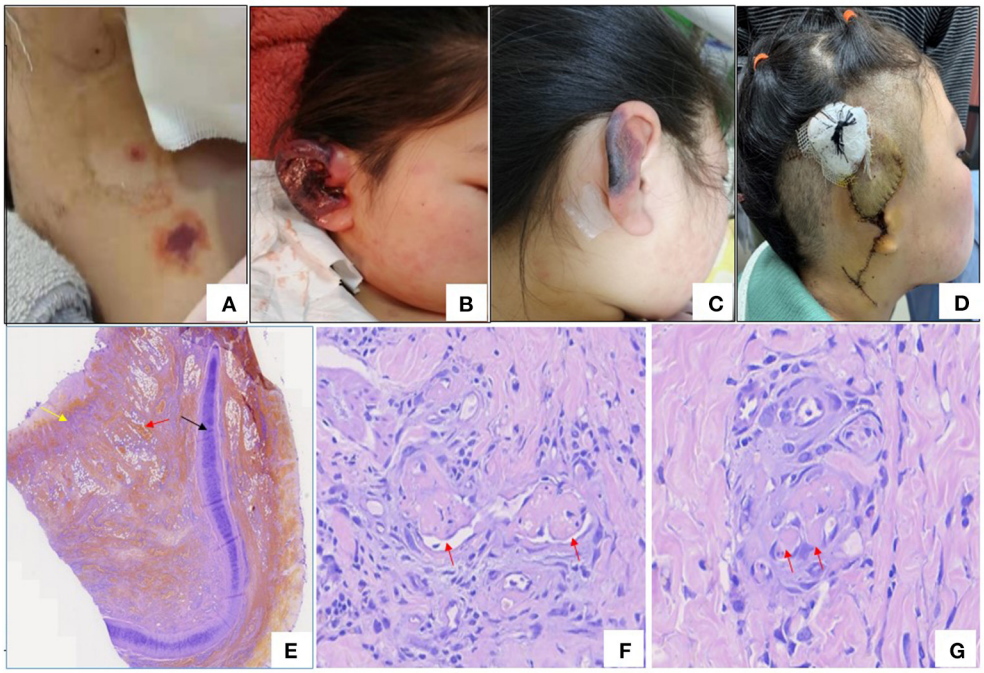

FIGURE 1
(A) Rash in neck. **(B)** Congestion and edema of right auricle. **(C)** Necrosis of right auricle. **(D)** Right auricle excision and flap transplantation. **(E)** Histopathology of right ear (Hematoxylin –Eosin staining×40), black arrow: cartilage, yellow arrow: necrosis and red arrow: necrosis and red arrow: hemorrhage. **(F,G)** The histopathologic examination of skin of right ear revealed microthrombi in small vessel (red arrows) (Hematoxylin-Eosin staining).

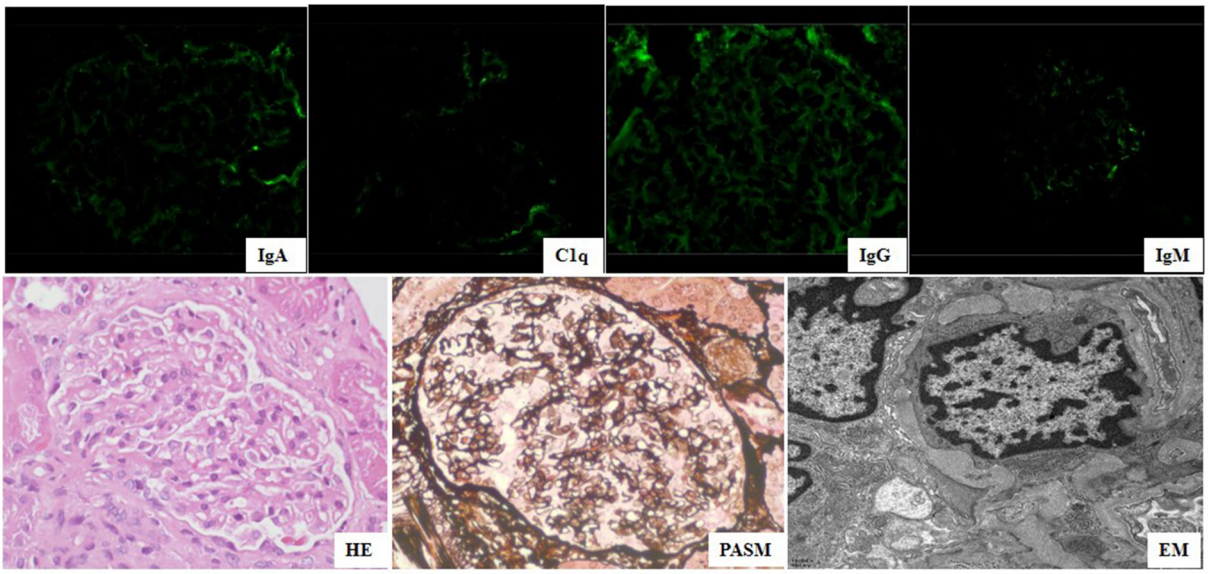

FIGURE 2
Kidney biopsy of findings showed negative IgA, IgM, Clq, and faint IgG under immunofluorescence (×400) microscopy, normal glomerular change (HE&PASM: periodic acid-silver metheramine) under light microscopy (×400), diffuse podocyte foot process effacement (FPE) in absence of sub-epithelial or sub-endothelial deposition under electron microscopy (×11,600).

TABLE 1 Coagulation function and aPL antibodies in the patient during following up.

Testing items	29/1/2021	17/2/2021	9/3/2021	12/5/2021	9/7/2021	11/9/2021	15/11/2021	Normal ranges
D-dimer	4.4	1.98	0.63	0.45	0.76	0.89	0.33	0–0.5
FIB(g/L)	7.44	3.90	1.95	4.04	3.54	2.93	2.87	2–4
FDP(g/L)	20.01	8.51	1.28	1.54	1.19	1.30	0.10	0–5
RLACST	3.57	2.68	1.58	1.31	1.54	1.15	1.53	0.8–1.2
Anti-β2GP1(RU/ml)*	82.2	45.0	50.7	47.8	26.9	39.8	26.9	<20
aCL-IgA*	4	<2	<2	<2	<2	5.5	<2	<12-PL-IgA
aCL-IgG*	14.6	2.5	2.6	2.2	<2	2.4	2.5	<12-PL-IgG
aCL-IgM*	16.3	5.9	10.7	4.5	4.7	3.9	4.0	<12-PL-IgM

*Was tested by Enzyme-Linked ImmunoSorbent Assay (ELISA).
FIB, Fibrinogen; FDP, fibrin degradation product; RLACST, Ratio of lupus anticoagulant screening test; anti-β2GP1, anti-β2 glycoprotein-1 antibody; aCL, anti-cardiolipin antibody.

intravenous cyclophosphamide (CTX) pulses (500 mg/m^2) as induction therapy. Other treatments included oral enalapril and subcutaneous injection of low molecular weight heparin sodium for 2 weeks followed by oral aspirin. After 6 pulses of CTX, she started maintenance therapy with mycophenolate mofetil (MMF) and continued to gradually taper doses of oral prednisolone. The proteinuria gradually decreased, and she achieved clinical remission and complete remission at 2 and 7 months of follow-up, respectively. Although the aCL antibody turned negative soon after treatment, LAC and anti-β2GPI were persistently positive (Table 1).

Informed written consent was obtained from the patient's parents for publication of this case report and accompanying images. Ethics board approval and consent were obtained for this work from the Ethics Committee at the Children's Hospital of Fudan University, Shanghai, China.

Discussion and conclusion

Herein, we report an SLE patient complicated with LP and APS. The patient met the 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for SLE (14) based on positive ANA (1:640); facial rash (six points); thrombocytopenia (four points); proteinuria (4 points); and positive aPL antibodies (two points), including LAC, anti-β2GP1, aCL antibody IgG and IgM. The renal lesion presented with NS: 3+ proteinuria, a 4.2 mg/mg UPr/Cr ratio, and hypoalbuminemia (26.2 g/l) at the beginning of the disease. The patient presented with acute abdominal pain as the first symptom, which led to a misdiagnosis of acute abdominal disease in the surgery department of the local hospital. Abdominal pain should be vigilant against gastrointestinal vasculitis in children with SLE.

LN has a large impact on SLE prognosis, resulting in a risk of end-stage kidney disease (ESKD) of 10% after 5 years of follow-up (15, 16). It is thought to be a typical immune-complex-mediated kidney disease that displays a "full house" model on IF and various electron dense deposits in the mesangium, subepithelial or subendothelial regions (6, 17). However, LP is characterized by diffuse epithelial cell FPE without immune complex deposition or with only mesangial immune complex deposition (9–11). It is a newly emerging entity of non-immune complex-mediated lupus nephropathy and is not yet included in the updated 2018 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of LN (18, 19). LP was coined by Kraft in 2005 when he described eight SLE patients with nephrotic range proteinuria and diffuse FPE on EM but no immune deposits in glomerular capillaries or endocapillary proliferation of glomeruli (20). Although there are no formalized guidelines for the diagnosis of LP, the diagnostic criteria established by Hu were taken as the most commonly used diagnostic criteria of LP, which are the following: clinical presentation of NS or nephrotic range proteinuria in a patient with SLE; kidney biopsy findings of normal glomeruli or minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) (with or without mesangial proliferation) on light microscopy and diffuse and severe FPE on EM; and the absence of subendothelial or subepithelial immune deposits on light, IF, and electron microscopy (9). The renal lesions in our patient met the diagnostic criteria for LP established by Hu based on nephrotic range proteinuria; MCD without mesangial proliferation on light microscopy and diffuse FPE on EM; and the absence of immune deposits under the endothelium and epithelium by light, IF, and electron microscopy.

LP accounts for 1.33% of all LN biopsies in adults (9), representing 8.14% in children (21). Our data showed LP in <1% of all children with LN biopsies (unpublished). To date, eleven pediatric cases of LP have been reported in PubMed. Four were case reports including our patient (Table 2), and a cohort study included seven patients (21–24), which suggests that it is a very rare complication of SLE in children. All children with LP have been girls and present with NS (21–24). Kidney biopsy findings revealed MCD in eight patients and FSGS in three patients (21–24). All patients achieved remission after treatment with a combination of prednisolone and immunosuppressive agents, including mycophenolate mofetil

TABLE 2 clinical features of SLE cases with LP in children.

Case	Gender	Age at diagnosis (years)	Renal manifest ations	Extra-renal manifestations	Positive auto-antibody	Pathologic changes	Immunosuppressive therapy		Treatment response
							Induction	Maintenance	
1. Wang et al. (22)	Female	14.1	Nephrotic syndrome	Fever, abdominal pain, arthritis, cutaneous lesions	ANA Anti-dsDNA	MCD	Prednisolone CTX	Prednisolone	Remission
2. Ito et al. (23)	Female	11	Nephrotic syndrome	Fever, cutaneous lesions, Raynaud's phenomenon, hematologic involvement	ANA Anti-dsDNA	FSGS	Prednisolone Cyclosporine/MMF	Prednisolone MMF	Remission
3. Pilania et al. (24)	Female	3	Nephrotic syndrome	Alopecia, chylous ascites, serositis, Hematologic and neurological involvement	ANA Anti-dsDNA	MCD	Prednisolone CTX	Prednisolone MMF	Remission
4	Female	13.2	Nephrotic syndrome	Fever, abdominal pain, serositis, cutaneous lesions, hematologic involvement, APS	ANA, anti-β2GPI, aCL, LCA.	MCD	Prednisolone CTX	Prednisolone MMF	Remission
Groups (seven cases) Abdelnabi (21)	Female	13.60 ± 2.30	Nephrotic syndrome	-	-	MCD(N = 5)/FSGS(N = 2)	Prednisolone MMF (N = 3) Aza (N = 2) CsA (N = 2)	-	Remission

ANA, anti-nuclear antibodies; Anti-dsDNA, anti-double stranded DNA; APS, antiphospholipid syndrome; Aza, azathioprine; CsA, cyclosporine A; CTX, cyclophosphamide; FSGS, focal segmental glomerulosclerosis; MMF, mycophenolate mofetil; N, numbers; RP, Raynaud's phenomenon.

10.3389/fped.2022.950576

(MMF, n = 4), CTX (n = 3), cyclosporine (n = 2), and azathioprine (n = 2) (21–24). One of these 11 patients (patient 2) with FSGS resisted prednisolone treatment alone, but she responded to a combination of prednisolone and cyclosporine, which was switched to MMF because of posterior reversible encephalopathy syndrome (PRES) associated with cyclosporine treatment (23). As of the time of case reporting, three patients relapsed (21). Thirty-four percent of patients with LP developed acute kidney injury (AKI) in adults, but no AKI was reported in children with LP (9, 21–24).

APS is an autoimmune disease characterized by the occurrence of venous and/or arterial thrombosis and pregnancy morbidity in the presence of pathogenic autoantibodies known as aPL, including aCL, anti-β2GPI antibodies and LCA (12, 25). APS may be associated with other diseases, mainly SLE. The prevalence of aCL, anti-β2GPI and LCA antibodies was 44, 40, and 22% in children with SLE, respectively (26). It has been estimated that APS may develop in up to 50–70% of patients with both SLE and aPL after 20 years of follow-up (27). Our patient met the current consensus criteria for APS based on microvascular thrombosis in the auricle and positive anti-β2GPI antibodies and LCA lasting for more than 12 weeks. Both APS and SLE have renal involvement. The former is characterized by hypertension, renal artery stenosis, renal infarction, and renal vein thrombosis, and the latter can reveal proteinuria, haematuria and hypertension and sometimes renal failure (27–29). Thus, renal involvement in the patient is caused by SLE. To the best of our knowledge, the coexistence of APS and LP in the same patient with SLE has not been reported in children. However, comorbidities of APS and LP in adults with SLE are very rare (30, 31).

In conclusions, LP is rarely described in children with SLE, and it responds to a combination of glucocorticoids and immunosuppressive agents. Our study reinforces the need to consider the potential co-occurrence of APS and LP. Clinicians should be aware of the potential presence of APS in patients with a diagnosis of LP presenting with NS and positivity for aPL antibodies, especially triple aPL antibodies (LCA, aCL, and anti-β2GPI).

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 the Ethics Committee at the Children's Hospital of Fudan University, Shanghai, China. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

G-mL, Y-fL, Q-qZ, J-yF, YS, and B-bW performed the experiments and collected data. X-mZ, H-mL, and HX analyzed the data. G-mL wrote the manuscript. LS conceived and supervised the project. All authors contributed to the article and approved the submitted version.

Conflict of interest

The 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.

Publisher's note

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frontiers | Frontiers in Pediatrics

TYPE Case Report
PUBLISHED 26 August 2022
DOI 10.3389/fped.2022.933693

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 01 May 2022
ACCEPTED 09 August 2022
PUBLISHED 26 August 2022

CITATION
Li S, Liu J, Yuan Y, Lu A, Liu F, Sun L, Shen Q and Wang L (2022) Case report: A study on the *de novo KMT2D* variant of Kabuki syndrome with Goodpasture's syndrome by whole exome sequencing.
Front. Pediatr. 10:933693.
doi: 10.3389/fped.2022.933693

Case report: A study on the *de novo KMT2D* variant of Kabuki syndrome with Goodpasture's syndrome by whole exome sequencing

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Kabuki syndrome (KS) is a rare genetic disorder characterized by dysmorphic facial features, skeletal abnormalities, and intellectual disability. *KMT2D* and *KDM6A* were identified as the main causative genes. To our knowledge, there exist no cases of KS, which were reported with pneumorrhagia. In this study, a 10-month-old male was diagnosed to have KS with typical facial features, skeletal anomalies, and serious postnatal growth retardation. Whole exome sequencing of the trio family revealed the presence of a *de novo KMT2D* missense variant (c.15143G > A, p. R5048H). The child was presented to the pediatric emergency department several times because of cough, hypoxemia, and anemia. After performing chest CT and fiberoptic bronchoscopy, we found that the child had a pulmonary hemorrhage. During research on the cause of pulmonary hemorrhage, the patient's anti-GBM antibodies gradually became positive, and the urine microalbumin level was elevated at the age of 12-month-old. After glucocorticoids and immunosuppressant therapy, the patient became much better. But he had recurrent pulmonary hemorrhage at the age of 16 months. Therefore, the patient underwent digital subtraction angiography (DSA). However, the DSA showed three abnormal bronchial arteries. This single case expands the phenotypes of patients with KS and Goodpasture's syndrome, which were found to have a *de novo KMT2D* missense variant.

KEYWORDS

Kabuki syndrome, *KMT2D* gene, whole exome sequencing, Goodpasture's syndrome, missense variant

Introduction

Kabuki syndrome (KS; OMIM #147920) is a rare, multiple malformation syndrome characterized by distinctive facial features combined with skeletal abnormalities, immunological defects, and intellectual disability (1, 2, 3). The prevalence of KS is around 1 in 32,000 live births (1).

The major causes of KS are variants in lysine methyltransferase 2D (*KMT2D*) and lysine demethylase 6A (*KDM6A*) (4, 5). *KMT2D* (also called *MLL2*, *ALR*, or *MLL4*) encodes a histone methyltransferase protein that contains 5,537 amino acids in length and methylates the LYS-4 position of histone H3 (6). Studies using the Xenopus model system found that loss-of-function of *Kmt2d* impedes neural crest development (7). *KDM6A* (formerly known as *UTX*) is a well-known epigenomic regulator that interacts with KMT2D and encodes a protein that eliminates the trimethylation of histone 3 lysine 27. Pathogenic *KDM6A* variants can cause KS (8).

Kabuki syndrome has been associated with several genetic variants. In this case report, we described a single case with clinical characteristics compatible with KS. We used a whole exome sequencing to find a *de novo* missense variant in *KMT2D* that explained the phenotype.

Goodpasture's syndrome, which is often used synonymously to refer to anti-glomerular basement membrane (GBM) disease, is a severe and extremely rare autoimmune disorder characterized by the presence of circulating autoantibodies directed against the non-collagenous domain of the α3 chain of type IV collagen (9, 10). The majority of patients were present with features of rapidly progressive glomerulonephritis and 40% to 60% have concurrent alveolar hemorrhage because of antibodies deposited in both glomerular and alveolar basement membranes (10). Very few studies of childhood Goodpasture's syndrome are available. We reported a 10-month-old male baby with KS and pulmonary hemorrhage. Whole exome sequencing (WES) of his trio family revealed a *KMT2D* missense variant (NM_003482: exon 48: c.15143G > A, p. R5048H). During the search for the cause of pulmonary hemorrhage, we found that pulmonary hemorrhage in the patient was caused by Goodpasture's syndrome, which is rare in a patient with KS.

Case presentation

This study was approved by the Ethics Board of the Children's Hospital of Fudan University. Written informed consent was obtained from the patient's parent before submission. The CARE guidelines were followed in the reporting of our case.

A 10-month-old boy was delivered at 35 and 6/7 weeks *via* normal spontaneous vaginal delivery. His mother and father aged 33 and 31 years, respectively, and were non-consanguineous. The boy's birth weight was 3,145 g, and his height was 49 cm. The child was admitted to the NICU ward as he was suffering from aspiration pneumonia and neonatal necrotizing enterocolitis. At the time of birth, no facial or phenotypic abnormalities were described. Anal stenosis deformity was found during NICU hospitalization, and atrial septal defect (ASD) and ventricular septal defect (VSD) were found using echocardiography. At 21 days of age, he underwent an anoplasty and perineal fistula repair because of congenital anal stenosis and rectal perineal fistula. Afterward, he had VSD repair, patent ductus arteriosus amputation, and patent foramen ovale repair under cardiopulmonary bypass at the age of 4-month-old. The patient has feeding difficulties after birth, easy choking, and spitting up, hence, supplementary food was added at 7 months old. The child lagged in growth and development could not turn over until 10 months. His family history was unremarkable.

At 10 months of age, he visited our hospital due to pneumonia with anemia for the first time. His chest X-ray showed exudation of both lungs with interstitial changes, and the hemoglobin decreased from 11.0 to 6.4 g/dl. After antibiotic treatment, transfusion of red blood cells, and intravenous immunoglobulin support, his chest x-ray became better and hemoglobin rose to 11.0 g/dl, therefore, he was discharged home. His facial examination showed arched eyebrows, long palpebral fissures with lateral eversion of the lower eyelids, inverse epicanthus, wide nasal bridge, lower lip concave, and large ears (**Figures 1A,C**). Other characteristics, including brachydactyly and prominent fetal finger pads, are shown in **Figures 1B,D**. In addition to these facial phenotypes, the patient also had post-natal growth deficiency, motor delay, joint hypermobility, hypotonia, and feeding problem. He had abnormal dentitions and an abnormal genitourinary system due to which he underwent surgery. A head computed tomography (CT) showed that part of the extracerebral space was widened, bilateral ventricles were full, and there were multiple low-density shadows on the skull. Abdominal ultrasonography showed no abnormalities. Abdominal CT suggested the possibility of stones in the right kidney.

Our patient showed typical characteristics of KS as mentioned. We performed WES on the trio family. The patient showed a missense variant of c.15143G > A (p. R5048H) in exon 48 in the *KMT2D* gene. The variant was compared with dbSNP,[1] 1000 Genomes,[2] as well as Exome aggregation consortium (ExAc) database.[3] The variant was not reported as polymorphism and was neither found in ExAC nor 1000G. It is a known disease mutation in Human Gene Mutation Database (HGMD CM 138442) which has been reported in Makrythanasis et al's (11) study. Sanger sequencing confirmed that the child's

1 http://www.ncbi.nlm.nih.gov/projects/SNP/
2 http://www.1000genomes.org
3 http://exac.broadinstitute.org/

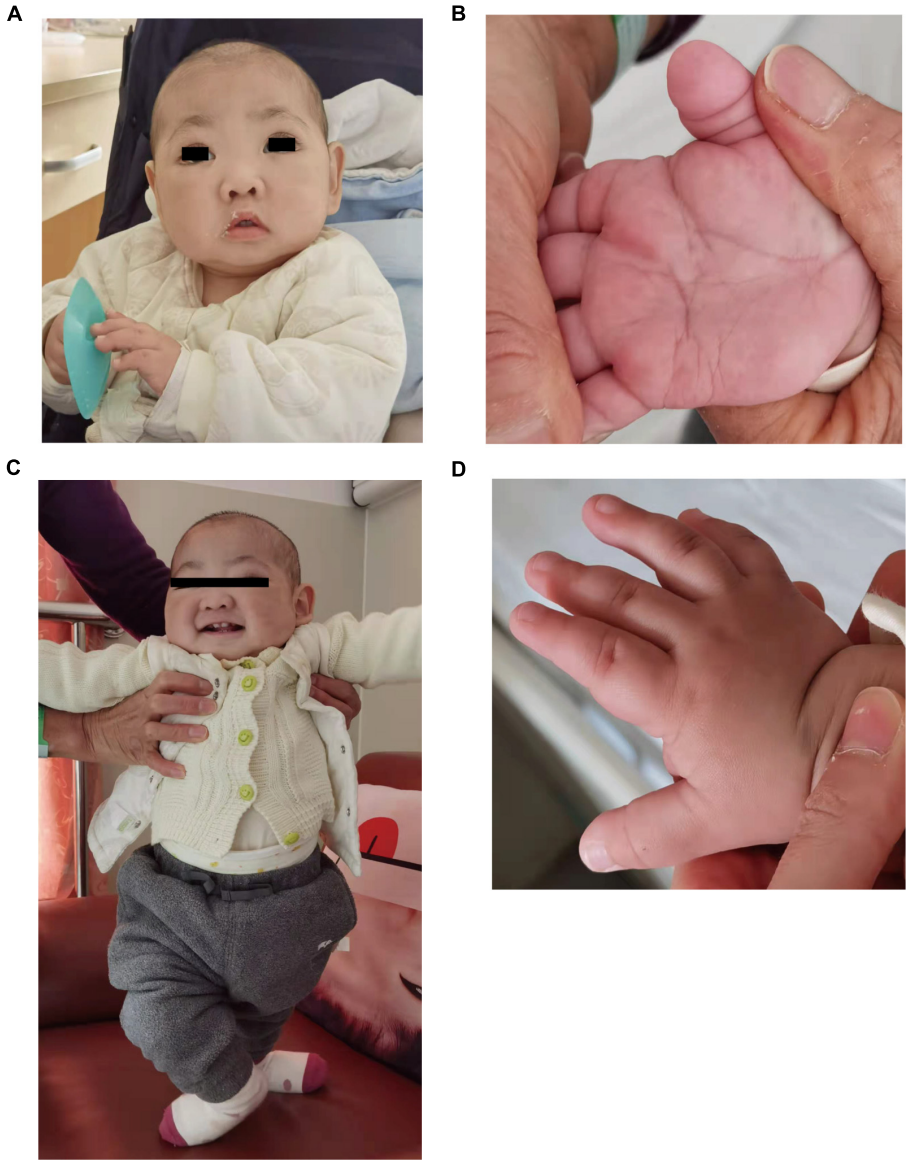

FIGURE 1
Photographs of the patients in this study. **(A,B)** Showed makeup appearance. **(C,D)** Showed short fingers.

parents did not carry the variant, so we determined it as a *de novo* heterozygous variant (**Figure 2**). Meanwhile, the variant c. 15143G > A was predicted to be probably a disease caused by Polyphen-2[4] and MutationTaster.[5] According to the ACMG guideline (12), the pathogenesis of the variant c.15143G > A (p. Arg5048His) should be pathogenic strong (PS1).

After a short time, at 12-month-old, the patient was admitted to our pediatric pneumology department after recurring fever (37.9–39.4°C), cough accompanied by tachypneic, tachycardia, severe dyspnea, blood from the nasogastric tube, and anemia (hemoglobin level, 7.6 g/dl). At the time of hospital admission, the physical findings were reported as follows: body weight: 7.1 kg (<3rd percentile); body temperature: 37.9°C; blood pressure: 86/58 mmHg; heart rate: 136 beats/min; respiratory rate: 38 breaths/min; oxygen saturation at room air: 76%. He was dyspneic and withdraw blood from the nasogastric tube. Laboratory tests revealed anemia, a mean corpuscular volume of 80.3 fl, a reticulocyte count of 3.9%, and serum iron around 5.4 μg/dl. Ferritin (113.8 μg/L) and total iron binding capacity (49.2 μmol/L) were normal. The C-reactive protein was found to be increased (26.92 mg/L; normal value, <8 mg/L). Liver and kidney

4 http://genetics.bwh.harvard.edu/pph2/
5 http://www.mutationtaster.org/

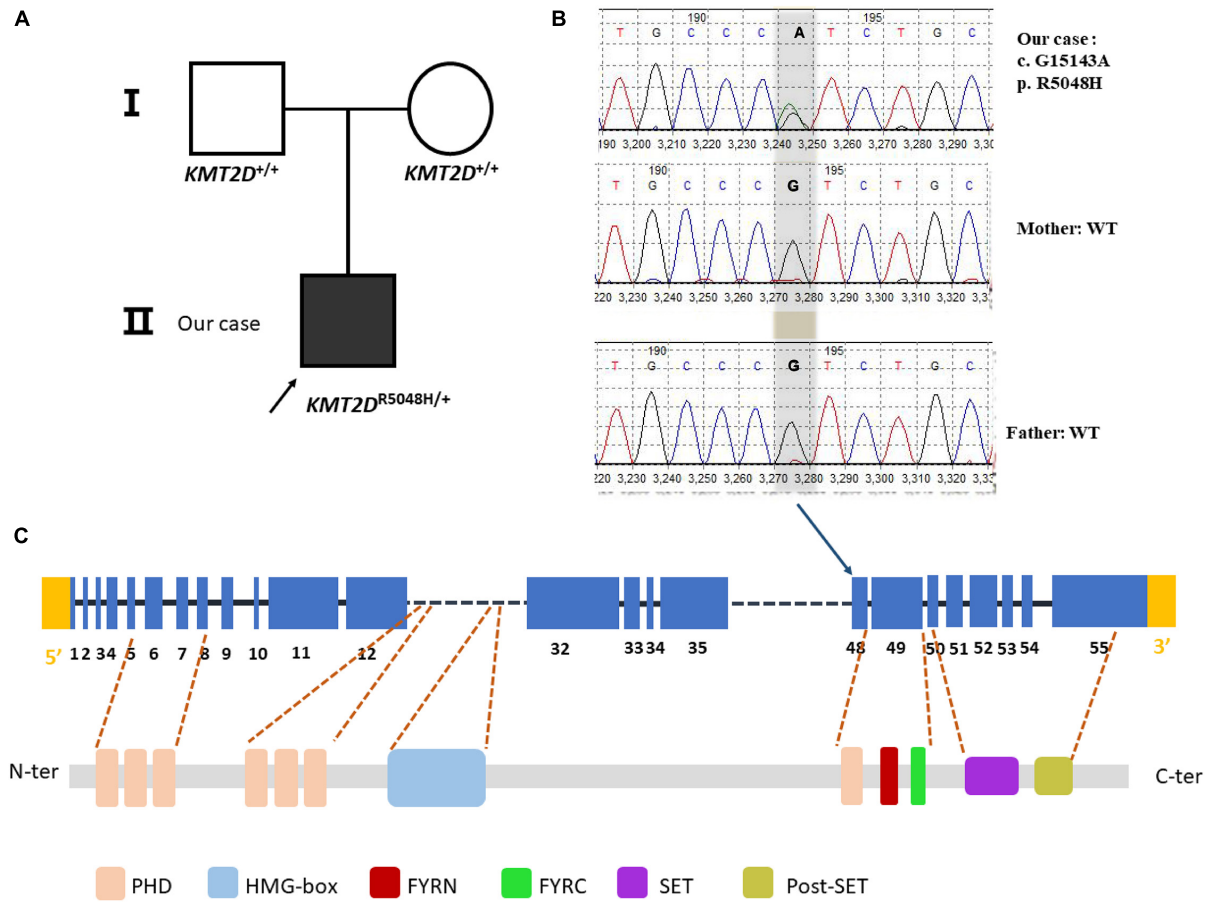

FIGURE 2
Sanger sequencing of the case family. **(A)** Showed pedigree of the family. **(B)** A heterozygous G > A substitution was confirmed by sanger sequencing at position c.15143, changing an arginine codon into a histidine codon at amino acid position 5,048 (p.R5048H). **(C)** The variant is at the exon 48 of the *KMT2D* gene (NM_003482.3) but not at any domain of the KMT2D protein. PHD, plant homeotic domain; HMG-box, high mobility group-box; FYRN, FY- rich N-terminal domain; FYRC, FY-rich C- terminal domain; SET, Su (var) 3-9, enhancer-of-zeste and Trithorax domain.

function indexes were within the normal range. Serologic tests for autoimmune diseases were negative on 9 August 2021. After several times screen, the anti-glomerular basement membrane antibody (anti-GBM) was shown to be high (71.1 RU/ml; normal value, <20 RU/ml) while urine microalbumin was elevated (NAG/CR 12.59, normal range, 0.3–1.2; IGGU/CR 40.7, normal range, <14; A1MU/CR 615.3, normal range, <14; ALBU/CR 152.9, normal range < 26.5). Oxygen with high-flow nasal cannulae was administered and a prompt blood transfusion was performed. Intravenous infusion of cefotaxime (100 mg/kg/day, 3 times daily for 8 days) was also performed.

Chest X-ray showed a massive, diffuse bilateral large pulmonary consolidation (**Figure 3A**). Chest CT showed increased patchy and flaky shadows, which were evident in both the lungs; with this, local thickening of bilateral pleura was seen (**Figure 3E**).

To find the reason why this patient has anemia and pulmonary hemorrhage, fiberoptic bronchoscopy was performed early after admission showing that active diffuse bleeding was objectified and there existed no foreign body in the bronchus and tumor. A bronchoalveolar lavage (BAL) revealed increasingly hemorrhagic returns and abundant hemosiderin-laden macrophages. The etiologic assessment was conducted, which was not contributive, except revealing the presence of *Hemophilus influenzae* in BAL culture and identification of bocavirus from the virus test. Isotope lung inhalation test and gastroscopy that had been performed showed no apparent abnormality. Cardiac ultrasound indicated no regurgitation after ventricular defect repair, bicuspid aortic valve, and pulmonary hypertension (36 mmHg).

After multidisciplinary consultation and discussion with the pediatric rheumatology, cardiology, respiratory, and imaging departments, the diagnosis of Goodpasture's syndrome was performed. Immunosuppressive therapy was initiated with high-dose methylprednisolone (30 mg/kg per day for 3 days) and intravenous immunoglobin supporting

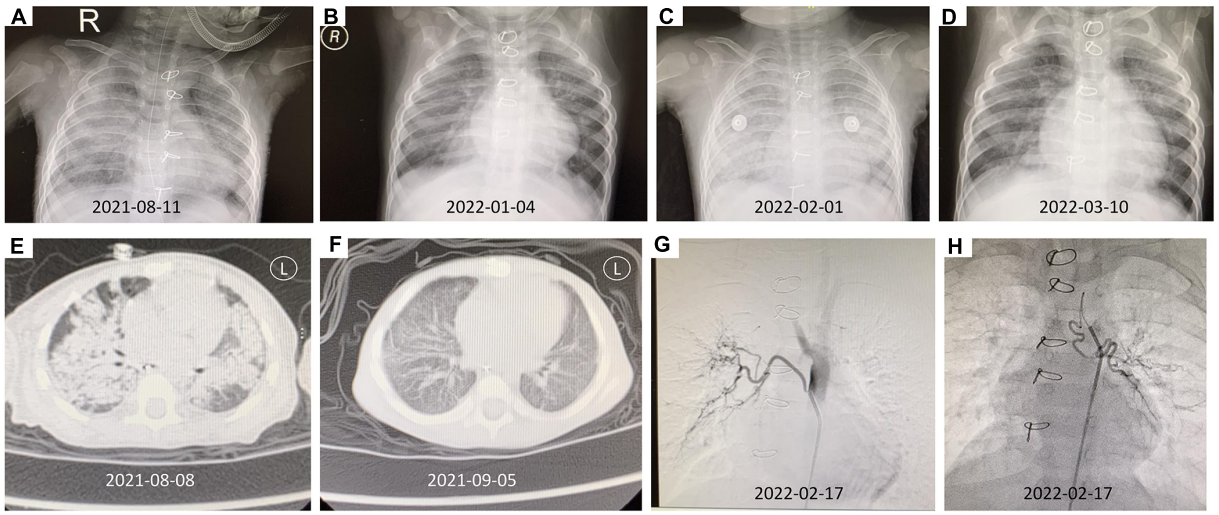

FIGURE 3
The imaging findings of this patient. **(A)** Chest X-ray (2021-08-11) showed a massive, diffuse bilateral large pulmonary consolidation. **(B)** The chest X-ray after therapy (2022-01-04). **(C)** The chest X-ray (2022-02-01) suggested extensive exudate. **(D)** After abnormal bronchial artery was embolized, the follow-up chest X-ray (2022-03-10) was significantly better than before. **(E)** Chest CT (2021-08-08) revealed increased patchy and flaky shadows were evident in both lungs, and a local thickening of bilateral pleura was seen. **(F)** The chest CT after therapy showed better than **Figure 3E** (2021-09-05). **(G)** The DSA showed right bronchial artery originated from the thoracic aorta. **(H)** The DSA showed left bronchial artery originating from the aortic arch.

therapy for 3 days. During the hospital admission, his respiratory symptoms have been improved, and his hemoglobin raised to 10.7 g/dl. A review of autoimmune antibodies showed that anti-GBM antibodies were negative, and urinary microproteins were significantly reduced. Hence, plasmapheresis has not been indicated. The patient was discharged in good general conditions with the following drugs: Prednisone 2 mg/kg/day, 1 time a day; Mycophenolate mofetil dispersible tablets 30 mg/kg/day (0.125 g), two times a day. The patient was in good general condition at the follow-up examination. The chest X-ray and chest CT have shown better than before (**Figures 3B,F**). At the moment, the patient is in good condition, being treated with oral corticosteroids.

During the outpatient follow-up, the child again developed anemia and dyspnea at the age of 16-month-old. The chest X-ray suggested extensive exudate (**Figure 3C**) with a drop in hemoglobin (7.3 g/dl). At the same time, the anti-GBM antibody showed a value of 24.4 RU/ml. Considering the possibility of repeated pulmonary hemorrhage, combined with the fact that the child is with KS, and has a history of VSD and ASD, digital subtraction angiography (DSA) is recommended to check whether there is abnormal pulmonary circulation. After undergoing DSA, it was observed that the left bronchial artery originates from the aortic arch, the right bronchial artery originates from the thoracic aorta, and the left and right trunk inferior phrenic arteries originate from the right renal artery (**Figures 3G,H**). Abnormal bronchial artery embolization was done successfully.

After discharge, the patient (weight 8.5 kg) was given oral methylprednisolone 16 mg, 1 time a day, and mycophenolate mofetil dispersible tablets 0.25 g, 1 time every 12 h, and iron, calcium supplementation, and omeprazole to prevent corticosteroids side effects. The follow-up chest X-ray examination was significantly better than before (**Figure 3D**), the hemoglobin was elevated (10.2 g/dl), and there were no symptoms of dyspnea as found recently.

Discussion

A *de novo* missense variant in the *KMT2D* gene was described in a boy with distinctive facial features and pulmonary hemorrhage diagnosed with Goodpasture's syndrome. The patient showed classical clinical features of KS, including arched eyebrows, long palpebral fissures with lateral eversion of the lower eyelids, depressed nasal tip, large ears, lower lip concave, ASD, VSD, postnatal growth retardation, hypotonia, intellectual disability, poor feeding and nutrition, congenital anal stenosis, and rectal perineal fistula.

To date, KS is caused due to pathogenic variants in *KMT2D* or *KDM6A* genes (13, 14). Variants in the *KMT2D* gene have been most frequently identified and are present in 55–80% of KS (15). Different *de novo KMT2D* variants have been reported in sporadic patients with KS (16). In familiar cases, an autosomal dominant inheritance has been observed. We identified a missense *de novo* variant in exon 48 of *KMT2D* (c.15143G > A, p. R5048H). This variant was not reported

from the 1000 Genomes Database and the Exome Variant Server, suggesting that it is not a common variant. This variant c.15143G > A was also found in Makrythanasis et al's (11) study in *KMT2D* (also known as *MLL2*) variant detection done on 86 patients with KS (17). Consistent with our study, Banka et al. (18) have also shown that the pathogenic missense variants were commonly located in exon 48. Although this variant does not belong to any domain of the KMT2D protein, it was predicted to be probably a disease caused by Polyphen-2 and MutationTaster. According to the ACMG guideline (12), the pathogenesis of the variant c.15143G > A (p. Arg5048His) should be pathogenic strong (PS1).

In the laters years of childhood, patients with KS develop an immune dysfunction, including susceptibility to infection and autoimmune disorders (19). Studies about immune deficiency in KS demonstrated that low immunoglobulin levels were a more common manifestation (20, 21) so many cases are susceptible to infections, including recurrent otitis and pneumonia (22). In addition, the most common autoimmune disease were hematological disorders, such as autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and autoimmune hepatitis (19, 22, 23). Matsushima et al. (24) have reported the first patient with KS and pernicious anemia. However, our understanding of the mechanisms underlying autoimmune disorders related to KS is limited. In this study, we review the immunological phenotypes of KS as shown in **Table 1**. So far, no patient with KS has been reported with Goodpasture's syndrome.

Goodpasture's syndrome is a severe and extremely rare autoimmune disorder characterized by the presence of circulating autoantibodies directed against the non-collagenous domain of the α3 chain of type IV collagen (9, 10). Antibodies found in both glomerular and alveolar basement membranes resulting in glomerulonephritis (GN) and acute pulmonary hemorrhage are usually from the IgG class, with IgG1 and IgG3 subclasses predominating, while rare cases of IgA- and IgG4-mediated disease have been reported (10, 25, 26). Unlike reports in adults, very few cases of childhood Goodpasture's syndrome are available. In Menzi's retrospective analysis, pulmonary fundings are not present commonly before puberty and the minimum age at diagnosis is 2 years old (27). However, the age of symptom onset in our case report was 12-month-old, which may be related to KS.

Abnormal persistence of germinal centers, along with a defect in class switch recombination and reduced antibody production was seen in *Kmt2d* knockdown mice (28). Missense variants in the terminal region of the *KMT2D* gene may increase the risk for autoimmune disorders (22). Laboratory tests showed that patients with *KMT2D* variants displayed defective B cell differentiation (22, 24). A defective B cell differentiation may lead to humoral immune deficiency and autoimmune disorders. Although we cannot determine whether Goodpasture's syndrome is part of the KS phenotypic spectrum or if it occurs coincidentally, this case report does expand on the phenotype of KS and the possible associated autoimmune disorders. Current treatment protocol by the Hammersmith group remains at the cutting edge of therapy. Patients with Goodpasture's syndrome should be started on prednisolone (1mg/kg tapered over 6–9 months) and cyclophosphamide for 2–3 months in combination with daily plasmapheresis for 14 days or until the anti-GBM antibody is no longer detectable (10). These drugs decrease the immune system's production of antibodies. Although after immunosuppressive treatment, the patient's antibody declined rapidly, anti-GBM antibody levels, pulmonary hemorrhage condition, and renal function must be monitored at regular intervals.

TABLE 1 Immunological phenotypes of KS in pediatric patients in literature.

References	Infection susceptibility	Hypogammaglobulinemia	↓ IgA	↓ IgG	↓ IgM	Autoimmune disease	ITP	AIHA	AITD	VT	AIN	Others
Di Candia et al. (21)	2/5	2/5	5/5	3/5	2/5	–	–	–	2/5	0/5	–	–
So et al. (29)	3/21	0/21	0/21	–	–	–	2/21	1/21	1/21	–	–	–
Margot et al. (19)	57/134	31/58	–	–	–	13/134	6/134	4/134	0/134	6/134	–	–
Lindsley et al. (22)	9/13	3/13	9/13	5/13	4/13	–	–	–	–	1/13	1/13	AIH 1/13
Stagi et al. (23)	51/59	–	36/54	21/51	–	–	17/59	7/59	3/59	4/59	2/59	–
Armstrong et al. (30)	–	2/48	–	–	–	–	1/48	–	–	–	–	–
Hoffman et al. (20)	–	–	15/19	8/19	2/19	3/19	–	–	–	–	–	–
White et al. (31)	14/27	–	–	–	–	–	–	–	–	–	–	–
matsumoto et al. (32)	73/116	1/116	–	–	–	–	1/116	1/116	–	–	–	–
Wessels et al. (33)	114/24	–	–	–	–	–	–	–	–	–	–	–

"–" Not reported;↓ decreased.
AIHA, autoimmune hemolytic anemia; AITD, autoimmune thyroid disease; AIN, autoimmune neutropenia; AIH autoimmune hepatitis; ITP, Immune thrombocytopenic purpura; VT, vitiligo.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Children's Hospital of Fudan University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

SL and JL collected the data and wrote the manuscript. LW revised the manuscript. YY collected the patient information. AL, FL, LS, and QS diagnosed the disorder, performed the experiments, and emended the manuscript. All authors read and approved the final version of this manuscript.

Conflict of interest

The 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 | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 10 October 2022
DOI 10.3389/fped.2022.992932

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 13 July 2022
ACCEPTED 15 September 2022
PUBLISHED 10 October 2022

CITATION
Xu X, Liu X, Zheng W, Xiao J, Li X, Wu L, Zou L, Ouyang Q, Shangguan Y, Lin K, Dai X, Chen Y, Xu Y, Wu J and Lu M (2022) Efficacy and safety of etanercept biosimilar rhTNFR-Fc in Chinese patients with juvenile idiopathic arthritis: An open-label multicenter observational study. Front. Pediatr. 10:992932. doi: 10.3389/fped.2022.992932

Efficacy and safety of etanercept biosimilar rhTNFR-Fc in Chinese patients with juvenile idiopathic arthritis: An open-label multicenter observational study

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Background: Etanercept biosimilar recombinant human TNF-α receptor II: IgG Fc fusion protein (rhTNFR-Fc) has showed its efficacy and safety in Chinese patients with rheumatoid arthritis. However, data on rhTNFR-Fc's application in juvenile idiopathic arthritis (JIA) is limited.

Methods: A prospective, observational, multicenter study was performed at 6 institutes in China from July 2020 to December 2021. In a 24-week follow-up, patients with JIA including polyarticular JIA and enthesitis related arthritis received rhTNFR-Fc plus methotrexate (MTX) treatment. The primary outcome parameters were improvements of cJADAS-10 (clinical Juvenile Arthritis Disease Activity Score), and the secondary outcome parameter was an inactive disease.

Results: 60 patients completed at least 12-week follow-up, and 57 completed 24-week follow-up. They had high C reactive protein values (11.6 mg/L) and cJADAS-10 (14.6) at baseline. Thirteen patients had morning stiffness. 33 patients showed synovial thickening, and 34 showed bone marrow edemas on MRI. Ultrasonography demonstrated significant joint effusions in 43 patients. The cJADAS-10 sharply decreased from 14.66 at the baseline to 2.4 at 24 weeks of rhTNFR-Fc therapy, respectively ($P < 0.01$). About half of patients achieved inactive disease at 24 weeks of therapy. Compared with the baseline, the number of patients with morning stiffness, joint effusions, bone marrow edema and synovial thickening on MRI significantly decreased at 24 weeks. Adverse events were consistent with known side effects of biologic agents.

Conclusions: The present study indicated that the combination of rhTNFR-Fc and MTX significantly improve symptoms and disease activity of children with JIA. This study suggests etanercept biosimilar rhTNFR-Fc as an effective and safe therapy for children with JIA.

KEYWORDS

juvenile idiopathic arthritis, etanercept biosimilar, disease activity, efficacy, safety

Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous collection of inflammatory arthritis of unknown etiology, and is also the most common chronic autoimmune disease in children (1, 2). According to International League of Associations for Rheumatology (ILAR) classification criteria, JIA is categorized into seven subtypes, including polyarticular course JIA (pJIA) and enthesitis related arthritis (ERA) (3, 4). The majority of children with JIA experienced continuously ongoing disease activity (5). Extended disease developed in one-third of the patients with oligoarticular JIA, and the outcomes of these patients were similar to those of children with pJIA (5). Furthermore, children with pJIA have a more treatment-resistant disease course than those with fewer joints affected, and they have longer periods of active disease associated with higher risk of joint damage (5, 6). Although some children with ERA appear to respond well to conventional synthetic disease-modifying anti-rheumatic drugs (cDMARDs) such as methotrexate or sulfasalazine monotherapy, most of children with peripheral joint disease still require the escalation of therapy to a biologic DMARDs (bDMARDs) (7, 8). Accordingly, recent treatment recommendations for pJIA or ERA suggest the bDMARDs as initial treatment or escalating therapy after 3–6 months' use of cDMARDs without response (3, 9). Tumor necrosis factor inhibitor (TNFi) has been recommended as a first-line biologic agent for the treatment of pJIA and ERA, including adalimumab and etanercept (3, 9).

Different from a TNF monoclonal antibody adalimumab, etanercept is a soluble receptor fusion protein consisting of the extracellular ligand-binding portions of human TNF p75 receptor, which binds and neutralize soluble and transmembrane TNF as well as lymphotoxin (10, 11). However, the high cost of etanercepts and the lack of national medical insurance coverage limited their use in China. The biosimilars of TNFi had an overall comparable efficacy and safety profile compared to their reference agents in rheumatoid arthritis and ankylosing spondylitis (12). Etanercept biosimilar recombinant human TNF-α receptor II: IgG Fc fusion protein (rhTNFR-Fc) has been widely used for more than 10 years as well as reduces the medical burden in China (13–17). rhTNFR-Fc has also showed its efficacy and safety in Chinese patients with rheumatoid arthritis, ankylosing spondylitis, and psoriasis (13, 14, 18, 19). Although rhTNFR-Fc has been approved and administered in Chinese children with pJIA and ERA, we lack a multi-center clinical study to further assess their efficacy and safety.

Here, we performed a prospective observational, open-label and multi-center study of rhTNFR-Fc in Chinese children with pJIA and ERA. The purpose of this study was to further evaluate the efficacy and safety of rhTNFR-Fc.

Methods

Study subjects

A prospective observational, open-label and multi-center study of etanercept biosimilar rhTNFR-Fc (trade name Yisaipu, 3SBio Inc., China) was carried out at 6 institutes (Zhejiang University School of Medicine Children's Hospital, Wenzhou Medical University Yuying Children's Hospital, Jiangxi Provincial Children's Hospital, Xiamen University Affiliated First Hospital, Soochow University Children's Hospital, Ningbo Women and Children's Hospital) in China from July 2020 to December 2021. The study protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the ethics committee institutional review board (2020-IRB-096). This trial was registered in the Chinese Clinical Trial Registry database (ChiCTR2000035016).

All the children with JIA were followed up to assess the efficacy and safety of rhTNFR-Fc within 6 months of recruitment. Inclusion criteria were as follows: (1) age: 2–17 years old; (2) meet the classification criteria of pJIA and ERA by the ILAR (4); (3) children with pJIA and ERA were still moderately active after 3 months of methotrexate (MTX) or still low activity after 6 months of MTX; (4) MTX medication needs to meet one of the following conditions: MTX-free time before taking MTX or baseline visit ≥4 weeks; MTX medication time before baseline ≥12 weeks, and stable dose (10–15 mg/m^2) for 8 weeks, and taking folic acid; (5) children who did not take oral corticosteroids, or the hormones have been discontinued for 4 weeks; (6) Children who did not receive non-steroidal anti-inflammatory drugs (NSAIDs); or are taking one kind of NSAIDs, but the stable dose should be applied for ≥2 weeks before the baseline visit. Exclusion criteria were as follows: (1) suffering from other autoimmune or rheumatic diseases other than JIA; (2) accompanied by serious infectious diseases, including but not limited to active tuberculosis, latent tuberculosis infection, active viral hepatitis; (3) severe gastrointestinal disease or previous medical history, such as ulcer, perforation or inflammatory bowel disease, Crohn's disease, ulcerative colitis; (4) a history of macrophage activation syndrome within 3 months before the screening visit; (5) previous history of demyelinating syndrome or multiple sclerosis; (6) received intra-articular, intramuscular,

intravenous, or long-acting glucocorticoids (CS) treatment within 28 days before the baseline visit; (7) received other cDMARDs (except MTX) within 6 weeks before the baseline visit; (8) received cyclophosphamide treatment within 90 days before the baseline visit; (9) received live or attenuated vaccination within 4 weeks before the baseline visit, or plan to receive live or attenuated vaccination during study drug administration; (10) peripheral blood leukocyte count $<4.0 \times 10^9$/L, or peripheral blood neutrophil count $<1.5 \times 10^9$/L, or peripheral blood platelet count $<100 \times 10^9$/L, or serum creatinine >1.5 times the upper limit of reference value, or serum ALT >2 times the upper limit of reference value. The patient's clinical information including age, gender, laboratory tests, magnetic resonance imaging (MRI) and ultrasonography results were recorded.

Drug administration

At treatment initiation, children with JIA received rhTNFR-Fc at a dose of 0.8 mg/kg per week (up to 50 mg/week) plus MTX at a dose of 10 mg/m^2/week by subcutaneous injection and orally, respectively. The patients also received oral once-weekly folic acid on the second day of oral methotrexate and oral daily non-steroidal anti-inflammatory drugs (NSAIDs). When symptoms improved, NSAIDs were tapered. The therapeutic course was 24 weeks.

Outcome criteria

The primary outcome parameters of the study were improvements of cJADAS-10. The cJADAS-10 was calculated by assessing the following variables: (1) physician's global rating of overall disease activity measured on a 0–10 visual analog scale (VAS), where 0 = no activity and 10 = maximum activity; (2) parent/child ratings of well-being assessed on a 0–10 VAS, where 0 = best and 10 = worst; and 3) counts of active joints assessed in 10 joints (the number of active joints of included patients <10) (20). The secondary outcome parameter was an inactive disease. The definition of inactive disease included no active uveitis or arthritis; no fever, rash, splenomegaly, serositis, generalized lymphadenopathy or elevation of ESR/CRP (erythrocyte sedimentation rate/C reactive protein); best physician's VAS; and duration of morning stiffness of ≤15 min (21). The cJADAS-10 cutoff value ≤1 was considered as inactive disease for pJIA and ERA (20). All the clinical assessments were performed at baseline and at week 4, 8, 12, and 24 after study initiation.

Safety assessment

Safety was evaluated according to the frequency of adverse events (AEs) and laboratory abnormality. AEs were recorded in detail including the date and time of onset, description, severity, time course, duration and outcome, and relationship of the AE to the study drug. Severe AEs were defined as events that were fatal or life threatening and resulted in a persistent or major disability or incapacity requiring prolonged inpatient hospitalization (22).

Statistical analysis

All the statistical analysis and graphics were performed with R statistical software packages (R version 4.0.3). Statistical analysis was performed using descriptive statistics. The continuous variables between groups were compared by Student's *t*-test or Mann-Whitney *U* test. For categorical variables, Pearson's chi-squared test was applied. A repeated measures analysis of variance was performed between children with pJIA and ERA. A *P* value of less than 0.05 was considered statistically significant.

Results

Characteristics of included children

The flow chart showed information for patient screening (**Figure 1**). 60 patients completed at least 12-week follow-up, and 57 completed 24-week follow-up. Detailed baseline clinical characteristics of children with JIA were listed in **Table 1**. These children included 30 boys and 30 girls, and their mean age was 8.6 ± 3.6 years with an average duration of symptoms of seven months. They had high CRP values (11.6 ± 17.5 mg/L) and cJADAS-10 (14.6 ± 5.7). Thirteen patients had morning stiffness; 33 patients showed synovial thickening, 34 showed bone marrow edemas, and 27 had surrounding soft swelling on the MRI. Ultrasonography demonstrated significant joint effusions in 43 patients. In addition, two subgroups of pJIA and ERA were also analyzed. At baseline, no significant differences were observed in age, duration of symptom, WBC (white blood cell) counts, platelets (PLT) counts, ESR, CRP, alanine transaminase (ALT), and creatinine (CREA) between the pJIA and ERA groups. Overall, there was a trend towards a higher cJADAS-10 with a more pronounced joint involvement in the pJIA group, as well as a significant female predominance.

Efficacy

The significant improvements were observed from the baseline to the last visit in the majority of patients. During the follow-up, three children withdrew this study after 12 weeks due to poor efficacy. Overall, these patients

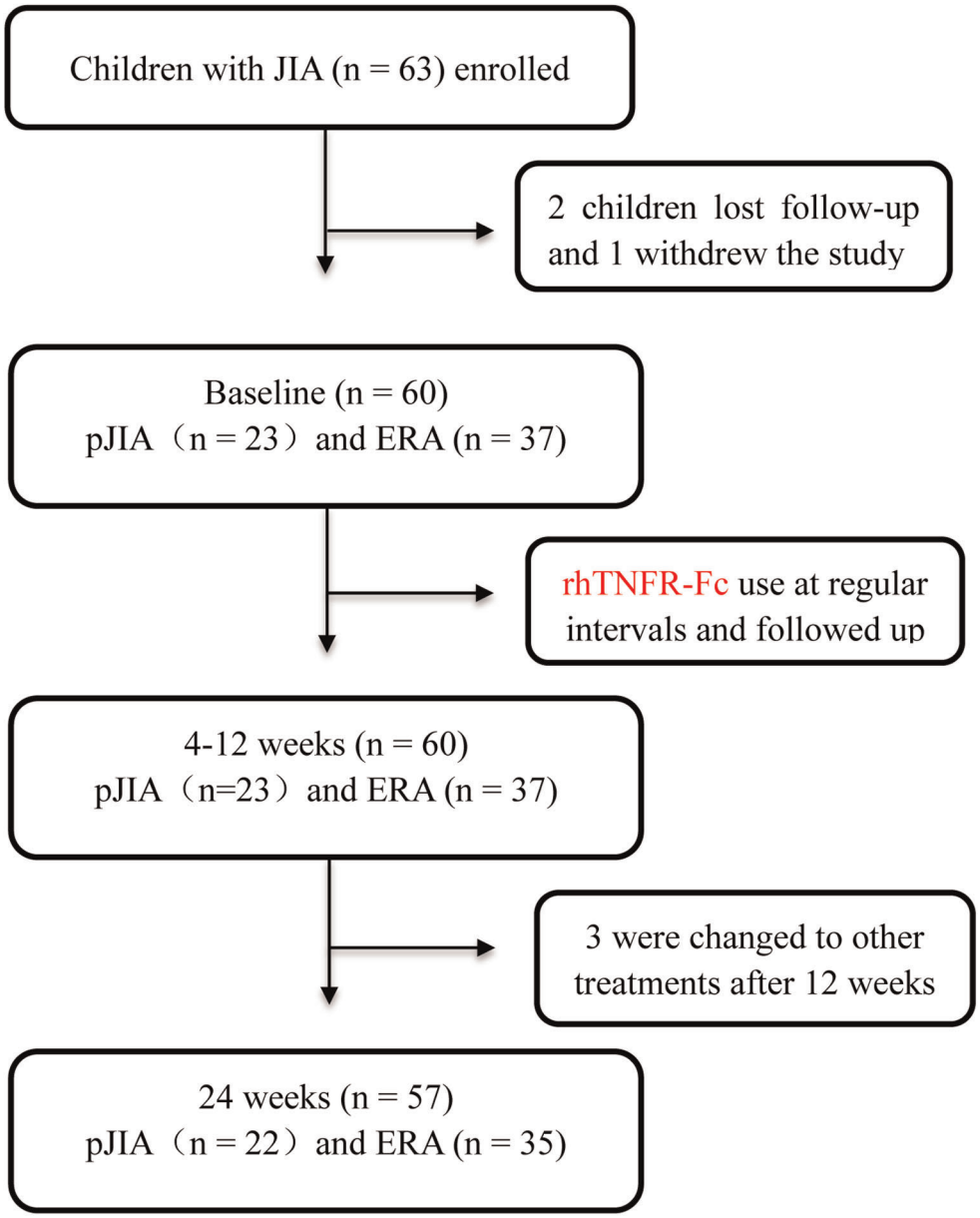

FIGURE 1
Participant selection flowchart. JIA, juvenile idiopathic arthritis; pJIA, polyarticular course JIA; ERA, enthesitis related arthritis.

demonstrated clinical benefits by the decrease in cJADAS-10 ($P < 0.01$), erythrocyte sedimentation rate (ESR, $P < 0.01$), and C reactive protein (CRP, $P < 0.01$) throughout the follow-up period (**Figures 2A,B**). At 4 weeks, the three indicators showed a clear downward trend, especially cJADAS-10. Notably, the cJADAS-10 sharply decreased from 14.66 to 5.81 at the baseline and 4 weeks, respectively ($P < 0.01$). However, the cJADAS-10 declined slowly from 3.97 at 8 weeks to 2.40 at 24 weeks. Additionally, the cJADAS-10 subgroups were set up based on high disease activity and mean of cJADAS-10 at 4, 8, and 12 weeks after treatment (**Figures 2C–F**, **Table 2**). The repeated measures analysis of variance revealed that there were significant statistical differences between subgroups ($P < 0.001$). Similar to total cJADAS-10 trend (**Figure 2A**), various cJADAS-10 subgroups also demonstrated a clear decreasing trend from baseline to 4 weeks (**Figures 2C–F**). Furthermore, the number of children with inactive disease of cJADAS-10 ≤ 1 significantly increased from zero at baseline to 19 at 4 weeks (**Table 2**), indicating that 4 weeks of rhTNFR-Fc treatment contributed to significant improvements in the cJADAS-10 and clinical manifestations.

The subgroup analysis showed that patients with pJIA had higher cJADAS-10 score, CRP and ESR values compared with

TABLE 1 Clinical characteristics of children with JIA.

Clinical variables	Total, no. (%) ($n = 60$)	ERA, no. (%) ($n = 37$)	pJIA, no. (%) ($n = 23$)	*P* value
Demographics				
Age (years), mean (SD)	8.6 (3.9)	9.2 (3.8)	7.6 (3.9)	0.122
Male/female (male%)	30/30 (50%)	26/11 (70.3)	4/19 (17.4)	<0.01**
Height, mean (SD), cm	133 (24.9)	138.3 (23.9)	124.6 (24.7)	0.037*
Weight, median (IQR), kg	27.9 (18.5-38.9)	30 (23.5-42.4)	25 (15.5-36.8)	0.092
Disease characteristics				
Symptom duration, Median (IQR), months	7 (4-14.25)	8 (4-14)	6 (4.5-14)	0.882
WBC				
Median (IQR), 10^9/L	7.61 (6.64-8.60)	7.60 (6.81-8.84)	7.67 (6.31-8.17)	0.68
In reference range	54 (90.0)	33 (89.2)	21 (91.3)	0.79
Outside reference range	6 (10.0)	4 (10.8)	2 (8.7)	
Hgb				
Mean (SD), g/L	120.3 (15.5)	124.2 (14.4)	113.8 (15.6)	0.015*
In reference range	58 (96.7)	36 (97.3)	22 (95.7)	0.73
Outside reference range	2 (3.3)	1 (2.7)	1 (4.3)	
PLT				
Mean (SD), 10^9/L	372.6 (11.5)	375.7 (11.7)	367.6 (20.5)	0.73
In reference range	31 (68.3)	25 (67.6)	16 (69.6)	0.87
Outside reference range	19 (31.7)	12 (32.4)	7 (30.4)	
ESR				
Median (IQR), mm/h	20 (10.5-41.5)	19 (12-38)	22 (9-44.5)	0.486
In reference range	31 (51.7)	20 (54.1)	11 (47.9)	0.16
Outside reference range	29 (48.3)	17 (45.9)	12 (52.1)	
CRP				
Mean (SD), mg/L	11.6 (17.5)	9.0 (13.0)	15.9 (22.6)	0.19
In reference range	39 (65.0)	25 (67.6)	14 (60.9)	0.60
Outside reference range	21 (35.0)	12 (32.4)	9 (39.1)	
ALT				
Mean (SD), IU/L	17.3 (11.7)	19 (12.9)	14.5 (9.1)	0.118
In reference range	59 (98.3)	36 (97.3)	23 (100)	0.43
Outside reference range	1 (1.7)	1 (2.7)	0 (0)	
CREA				
Mean (SD), μmol/L	48.7 (7.23)	53.8 (11.4)	40.6 (4.1)	0.38
In reference range	59 (98.3)	36 (97.3)	23 (100)	0.43
Outside reference range	1 (1.7)	1 (2.7)	0 (0)	
Physician's global rating, Mean (SD)	5.3 (2.2)	5.1 (2.2)	5.6 (2.2)	0.40
Parent/child rating, mean (SD)	5.5 (2.4)	5.5 (2.5)	5.5 (2.3)	0.96
Counts of active joints, Mean (SD)	4.1 (3.5)	2.4 (1.5)	6.9 (3.9)	< 0.01**
cJADAs				
Mean (SD)	14.6 (5.7)	13 (5)	17.3 (5.8)	< 0.01**
≤2.5	0 (0)	0 (0)	0 (0)	
>2.5 & ≤8.5	9 (15.0)	7 (18.9)	2 (8.7)	0.28
>8.5	51 (85.0)	30 (81.1)	21 (91.3)	
Morning stiffness	13 (21.7)	4 (10.8)	9 (39.1)	< 0.01**
MRI synovial thickening	33 (55)	23 (62.2)	10 (43.5)	0.1572
MRI: bone marrow edema	34 (56.7)	19 (51.4)	15 (65.2)	0.292
MRI: peripheral soft tissue swelling	27 (45)	16 (43.2)	11 (47.8)	0.7286
Ultrasound joint effusions	43 (71.7)	25 (67.6)	18 (78.3)	0.3715

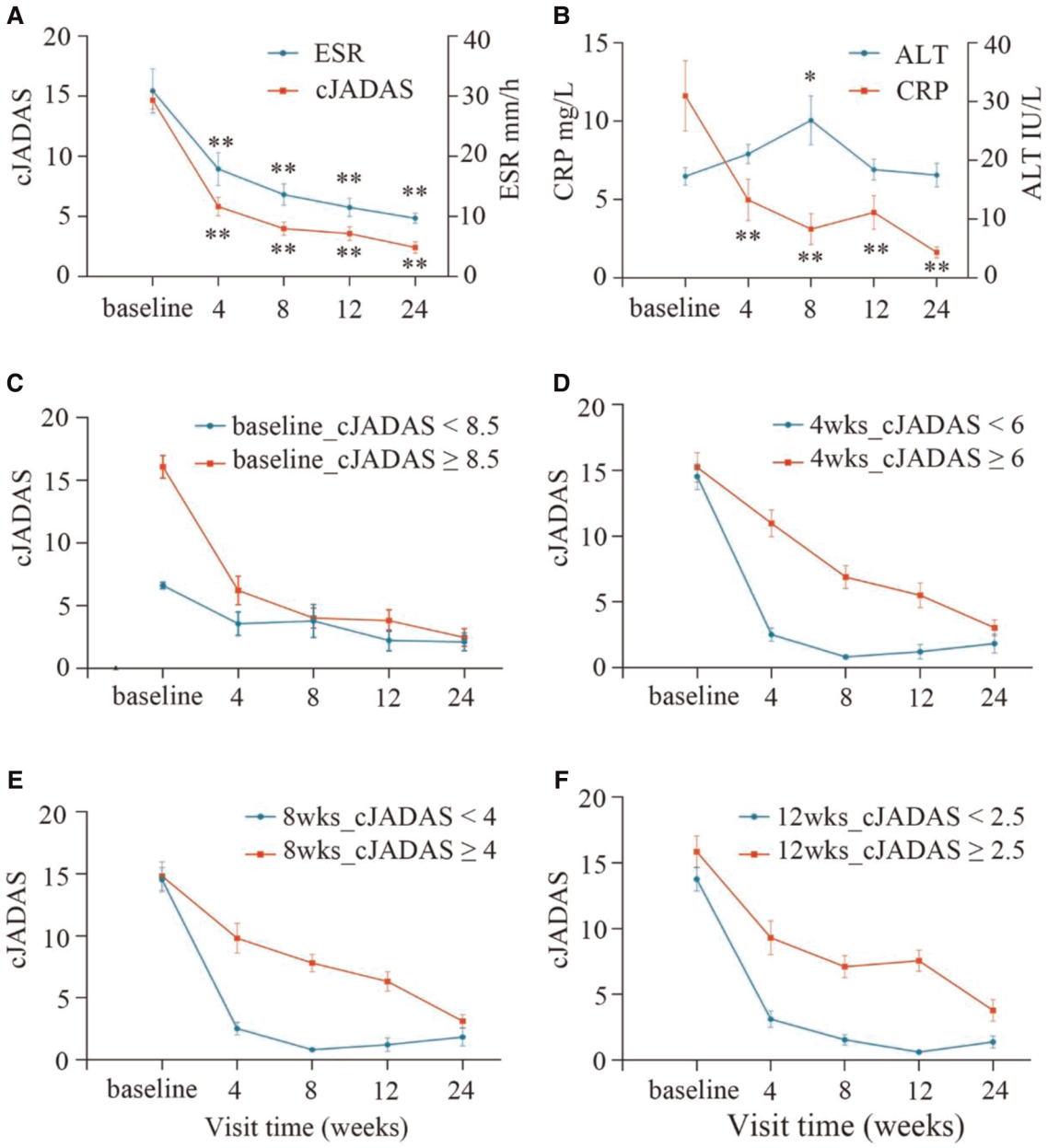

FIGURE 2
Clinical response at baseline and after 4, 8, 12, 24 weeks of rhTNFR-Fc therapy. (A) The cJADAS-10 sharply decreased from 14.66 at the baseline to 5.81 at 4 weeks ($P < 0.001$), and the cJADAS-10 decline slowly from 3.97 to 2.40 at 8 weeks and 24 weeks; the similar trend exists in ESR. (B) The decreased trend was observed in CRP; ALT were within normal ranges with moderately elevation at week 8. The similar trend to the total cJADAS-10 (A) was showed in various cJADAS-10 subgroups based on the baseline (C), and mean cJADAS-10 of 4 (D), 8 (E), and 12 (F) weeks after treatment ($P < 0.01$). cJADAS, clinical Juvenile Arthritis Disease Activity Score; ESR, erythrocyte sedimentation rate; CRP, C reactive protein.

those with ERA (Figure 3). The repeated measures analysis of variance revealed that there were significant statistical differences in the cJADAS-10 ($P = 0.023$), CRP ($P < 0.001$), and ESR ($P = 0.001$) between the two groups (Figures 3A–C). Consistent with total cJADAS-10 and cJADAS-10 subgroups, 4 weeks of rhTNFR-Fc treatment also contributed to a significant improvement in the cJADAS-10 regardless of pJIA or ERA, as well as in CRP and ESR.

Compared with the baseline, the number of patients with morning stiffness ($P < 0.001$) and joint effusions (ultrasonography, $P < 0.001$) significantly decreased at 24 weeks. Furthermore, the number of children with bone

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TABLE 2 Clinical characteristics of various cJADAS-10 subgroups.

cJADAS-10 subgroups	Baseline ($n = 60$)	4 weeks ($n = 60$)	8 weeks ($n = 60$)	12 weeks ($n = 60$)	24 weeks ($n = 57$)
cJADAs ≤ 1, no. (%)	0 (0)	19 (31.67)	22 (36.67)	26 (43.33)	29 (53.70)
Total cJADAs, mean (SD)	14.66 (5.71)	5.81 (5.93)	3.97 (4.34)	3.56 (4.42)	2.40 (3.59)
Subgroup based on baseline data					
cJADAs <8.5, no. (%)	9.00 (15.00)	9.00 (15.00)	9.00 (15.00)	9.00 (15.00)	9.00 (15.79)
cJADAs <8.5, mean (SD)	6.61 (0.78)	3.56 (2.79)	3.78 (3.96)	2.22 (2.49)	2.11 (2.09)
cJADAs ≥8.5, mean (SD)	16.08 (4.96)	6.21 (6.25)	4.00 (4.44)	3.80 (4.66)	2.46 (3.83)
Subgroup based on 4-week data					
cJADAs <6, no. (%)	34.00 (56.67)	34.00 (56.67)	34.00 (56.67)	34.00 (56.67)	33.00 (57.89)
cJADAs <6, mean (SD)	14.22 (5.65)	1.85 (1.97)	1.74 (2.50)	2.03 (3.35)	1.94 (3.87)
cJADAs ≥6, mean (SD)	15.23 (5.85)	10.98 (5.35)	6.88 (4.53)	5.50 (4.89)	3.04 (3.14)
Subgroup based on 8-week data					
cJADAs <4, no. (%)	33.00 (55.00)	33.00 (55.00)	33.00 (55.00)	33.00 (55.00)	32.00 (56.14)
cJADAs <4, mean (SD)	14.53 (5.55)	2.53 (2.82)	0.82 (1.10)	1.22 (3.14)	1.84 (4.06)
cJADAs ≥4, mean (SD)	14.81 (5.99)	9.81 (6.29)	7.81 (3.64)	6.33 (4.13)	3.12 (2.80)
Subgroup based on 12-week data					
cJADAs <2.5, no. (%)	34 (56.67)	34 (56.67)	34 (56.67)	34 (56.67)	33 (57.89)
cJADAs <2.5, mean (SD)	13.75 (5.17)	3.13 (3.52)	1.56 (2.30)	0.62 (0.85)	1.39 (2.65)
cJADAs ≥2.5, mean (SD)	15.85 (6.25)	9.31 (6.64)	7.12 (4.38)	7.56 (4.15)	3.79 (4.27)

marrow edema ($P < 0.001$) and synovial thickening ($P = 0.018$) on MRI also significantly decreased at 24 weeks (**Figure 4**).

Safety

Treatment safety was evaluated separately at each visit, including complete blood counts, liver and kidney functions. At the last visit (24 weeks), infections including hepatitis virus and tuberculosis were detected. AEs and severe AEs were also recorded at each visit. Overall, both MTX and rhTNFR-Fc were well tolerated, and the majority of AEs were mild or moderate. During the 24-week follow-up period, a transient decrease of leucocyte counts ($<4 \times 10^9$/L) in 4 patients, an elevation of liver enzyme (ALT > 40 IU/L) in 4 patients and increased uric acid levels (range 420–639 μmol/L) in 8 patients were observed. Although a transient elevation of liver enzyme was observed at 8 weeks after therapy, their levels were still within normal range (**Figures 2B**, **3D**), indicating the importance of liver function monitoring, especially within 8 weeks after therapy.

AEs were consistent with known side effects of biologic agents, including transient reaction of the injection site, skin rash, and gastrointestinal symptom. Upper respiratory tract infections occurred in seven patients. There were no infections requiring hospitalization or intravenous administration of antibiotics. AEs were mild, not requiring interruption of the rhTNFR-Fc, DMARDs, and NSAIDs therapy. No severe AEs and deaths occurred during the course of our study. One patient had a positive PPD test and received prophylactic antituberculosis drugs.

Discussion

Tumor necrosis factor-α (TNF-α) is a naturally occurring cytokine that produced by T-cells and macrophages, integrally involving in both the physiologic and pathologic processes of the inflammatory and immune responses (23). Many biologic agents that target against TNF-a have been developed and are now increasingly used in clinical practice (1, 2). TNFi is effective against disease activity and improves the physical functionality of patients with ankylosing spondylitis. Furthermore, TNFi may retard the progression of spinal mobility dysfunction and maintain spinal mobility (14). Several biosimilars of TNFi have been approved and marketed in various countries. Furthermore, TNFi biosimilars had been shown to have an overall comparable efficacy and safety profile compared to their reference agents in rheumatoid arthritis and ankylosing spondylitis (12). Etanercept is a fusion protein consisting of a Fc portion of immunoglobulin G linked to human TNF-α receptor with potent anti-inflammatory activities, competitively inhibiting the binding of TNF-α to cell surface receptors and attenuating its biological effects. A number of studies have revealed the good effect and safety of etanercept for the treatment of rheumatoid arthritis, JIA, psoriatic arthritis, ankylosing spondylitis and psoriasis (10, 24–27).

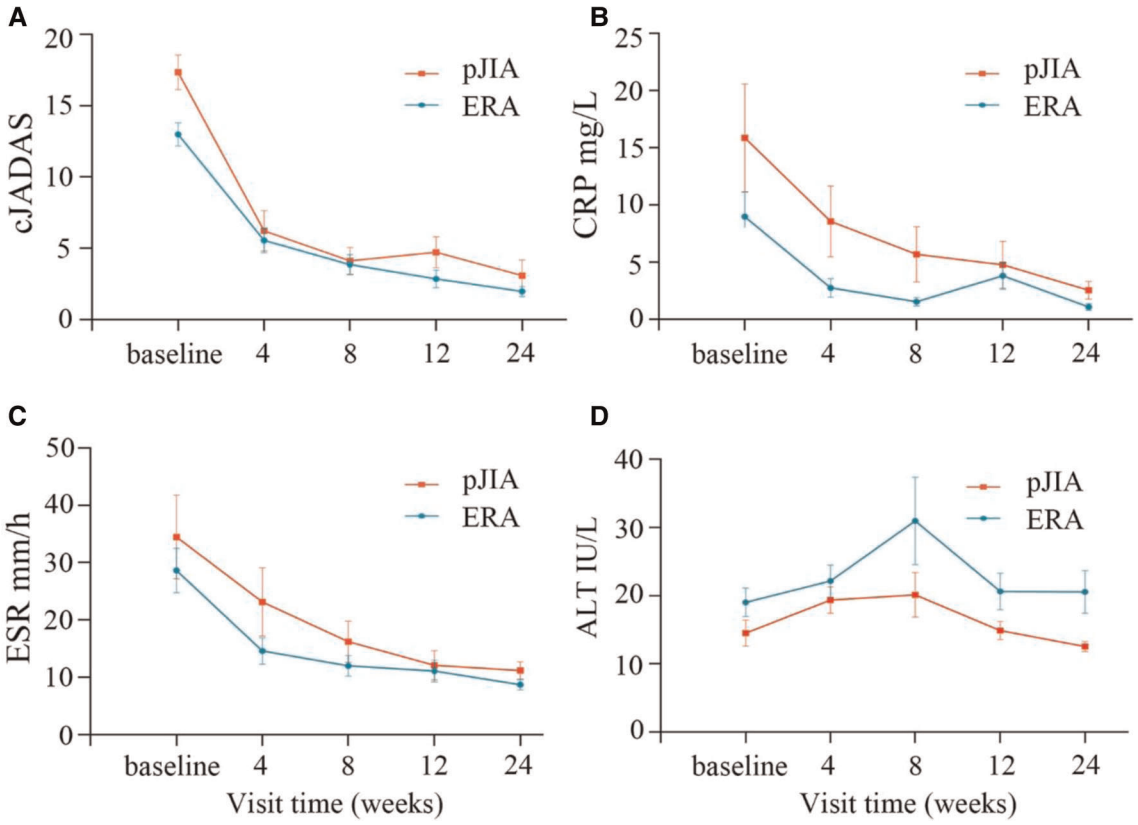

FIGURE 3
Comparison of children with pJIA and ERA. There were obvious decreased trends in cJADAS-10 (**A**), CRP (**B**) and ESR (**C**) between children with pJIA and ERA. The repeated measures analysis of variance revealed significant statistical differences in the cJADAS-10 (**A**), CRP (**B**), and ESR (**C**) between the two groups. The ALT levels were still within normal range regardless of pJIA or ERA (**D**). pJIA, polyarticular course JIA; ERA, enthesitis related arthritis; cJADAS, clinical Juvenile Arthritis Disease Activity Score; ESR, erythrocyte sedimentation rate; CRP, C reactive protein.

Etanercept biosimilar recombinant human TNF-α receptor II: IgG Fc fusion protein (rhTNFR-Fc) is a TNF-α inhibitor targeting soluble TNF-α to inhibit its interaction with cell–surface receptors. Currently, rhTNFR-Fc has been widely used in clinical practice for more than 10 years in China (15, 17, 19). The efficacy and safety of rhTNFR-Fc have been also confirmed in Chinese patients with rheumatoid arthritis, plaque psoriasis, ankylosing spondylitis, and axial spondyloarthritis (13, 14, 16–19). Our study also showed that the combination of rhTNFR-Fc and MTX significantly improve symptoms of children with pJIA and ERA, and nearly half of patients achieved inactive disease at 24 weeks of therapy. This study further supported the role of rhTNFR-Fc in immune-mediated inflammatory conditions, regardless of adult rheumatoid arthritis or JIA. A randomized, double-blind multicenter study reported that adalimumab was shown to reduce signs and symptoms of ERA at week 12 (28). Our multi-center study demonstrated that a significant improvement in cJADAS-10 was observed at the fourth week of rhTNFR-Fc therapy, suggesting an available early time window suitable for observing efficacy. Although three patients failed to respond to 12-week treatment and switched to other treatments, most of patients achieved better clinical improvement such as morning stiffness, bone marrow edema, synovial thickening, and joint effusions, further supporting an efficacy of rhTNFR-Fc.

Compared to those treated with the standard step-up regimen, more patients treated with a combination of etanercept plus MTX reached better response and achieved inactive disease and remission more rapidly (26). The majority of children with JIA can attain inactive disease within 2 years, even many being able to discontinue treatment (6). In general, patients with JIA did not used biological DMARDs until they were treated with cDMARD at adequate dose for at least 3 months (3, 9). However, such a recommendation would prolong the time with active arthritis, reduce the life quality of patients and increase the risk of developing irreversible osteoarticular changes (26). According to 2019 Arthritis Foundation Guideline, initial biologic therapy may be considered for patients with risk factors and

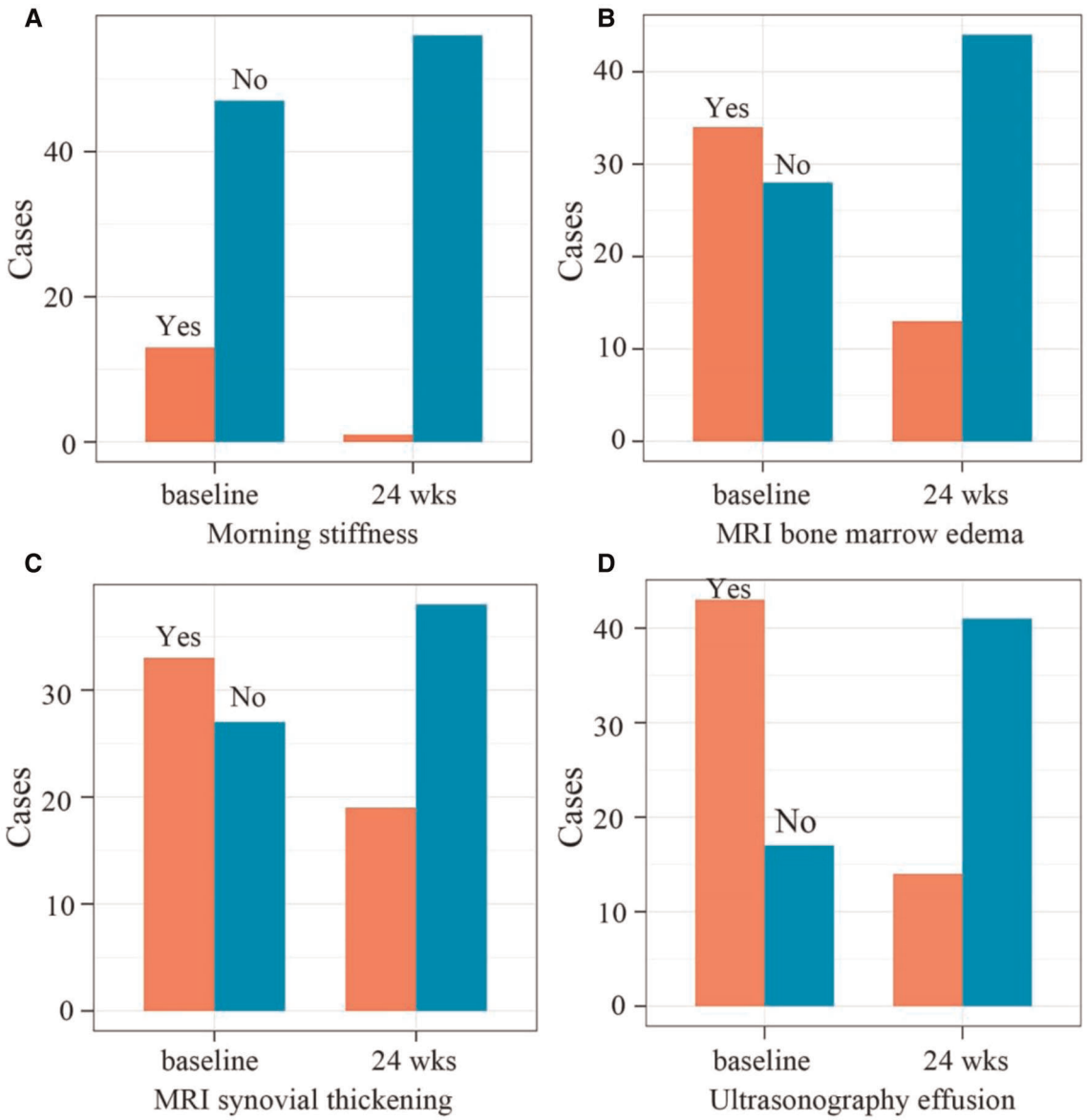

FIGURE 4
(A) the number of patients with morning stiffness significantly decreased from 13 to 1 at the baseline and 24 weeks after therapy, respectively ($P < 0.001$). (B) The number of patients with bone marrow edema on MRI significantly decreased from 34 to 13 at the baseline and 24 weeks after therapy, respectively ($P < 0.001$). (C) the number of patients with synovial thickening on MRI significantly decreased from 33 to 19 at the baseline and 24 weeks after therapy, respectively ($P = 0.0184$). (D) The number of patients with ultrasonography effusions significantly decreased from 43 to 14 at the baseline and 24 weeks after therapy, respectively ($P < 0.001$). MRI, Magnetic Resonance Imaging.

involvement of high-risk joints, high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage (9). Furthermore, most patients have concerns about corticosteroids side effects, they prefer biologics as the first-line choice. In the present study, some patients directly chose biologic agents as their initial treatment due to high-risk factors. Different from a longer duration in adult rheumatic diseases, the duration of JIA in our study was relatively short. We observed a high response rate, with 50% of patients with JIA achieving inactive disease after 24 weeks of rhTNFR-Fc treatment. These results allowed us to speculate that early biologic agents or combination treatment could contribute to improvement of symptoms and control of disease. On the other hand, the safe use of biosimilars depends on informed and adequate administration by medical professionals and regulatory agencies (29). In the field of pediatric rheumatology, further education about biosimilars and real-life experiences is required to better understand

treatment options in children (30). There is evidence that adalimumab biosimilar is a suitable and effective treatment option for patients with JIA and has a gradual increase in prescription in pediatric rheumatology (31), which further indicating that these biosimilars had similar efficacies to reference agents.

Notably, cJADAS-10 was frequently used to assess the condition of pJIA patients (20). However, for ERA, there are currently no widely accepted scoring criteria. In the view of convenience and operability of cJADAS-10, we adopted cJADAS-10 as scoring criteria for pJIA and ERA. Especially in the multi-center study, consistency is very important for different hospitals. Our study indicated that cJADAS-10 was also feasible in evaluating ERA.

Regarding the safety assessment, we found that the combination regime had an acceptable safety and tolerability profile. AEs were consistent with known side effects of biologic agents, including transient reaction of the injection site, skin rash, and gastrointestinal symptom. Additionally, the most common AEs were upper respiratory tract infections, elevation of liver enzyme, and increased uric acid levels. Overall, AEs were mild or moderate, not requiring interruption of the rhTNFR-Fc therapy. No severe AEs and deaths were observed during the course of our study. Notably, a transient elevation of liver enzyme was observed at 8 weeks after therapy, suggesting the importance of liver function monitoring within 8 weeks after therapy. In addition to adult rheumatic diseases, our study also supported the safety of rhTNFR-Fc in patients with JIA.

Additionally, we also need to focus on the nocebo effect of biosimilars. Nocebo effects were considered as new or worsening symptoms or adverse events that occur largely as a consequence of patients' negative expectations rather than by the mechanism of the treatment itself (32). The nocebo effect could further inhibit biosimilar adoption, especially those patients previously discomfort with switching to a biosimilar product (31). In this study, the enrolled patients were the first to use biologics, we did not find significant nocebo effect. There was evidence that systematic switch from reference to biosimilar etanercept was not associated with changes in disease activity or function (33). Current evidence is insufficient to confirm a biosimilar nocebo effect (34).

The present study has some limitations that should be considered. First, our study did not use the control group and double-blind method. Second, this study enrolled Chinese children and no other ethnicities were included. Therefore, the present findings may not be completely applicable to other ethnicities. Third, the sample size was relatively small due to difficulty in recruiting pediatric patients. Although our results are derived from only 24-week follow-up records, this can still reflect the true efficacy and safety of rhTNFR-Fc. In addition, we are also performing a longer follow-up to further make a more comprehensive assessment of rhTNFR-Fc's efficacy and safety.

Conclusion

This prospective, observational, open-label and multi-center study indicated that the combination of rhTNFR-Fc and MTX significantly improve symptoms and disease activity of children with pJIA and ERA. Furthermore, nearly half of patients achieved inactive disease at the end of follow-up. Throughout the follow-up, AEs were consistent with known side effects of biologic agents. These findings suggest rhTNFR-Fc as an effective and safe therapy for children with pJIA and ERA, especially for those patients with involvement of high-risk joints (cervical spine, wrist, or hip) and/or high disease activity. Further multicenter randomized controlled trial should be conducted on rhTNFR-Fc in patients with JIA or other rheumatic diseases.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by The studies involving human participants were reviewed and approved by the Ethic Review Board of Children's Hospital, Zhejiang University School of Medicine (2020-IRB-096). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

XFX, and MPL designed the study, interpreted the data, drafted the initial manuscript, and critically reviewed and revised the manuscript. LXZ, QO, YYS, KZL, XMD, and YLC undertook data collection and provided technical, or material support. XFX, XHL, WJZ, JHX, XZL and LW undertook data collection, contributed to analyses and data interpretation, and critically reviewed and revised the manuscript. XFX, XHL, WJZ, JHX, XZL, LW and MPL had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by fund from the National Natural Science Foundation of China (82070027). The funder had no

role in study design, data collection and interpretation, or the decision to submit the work for publication.

Conflict of interest

The 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.

Publisher's note

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frontiers | Frontiers in Pediatrics

TYPE Case Report
PUBLISHED 04 November 2022
DOI 10.3389/fped.2022.1039291

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 08 September 2022
ACCEPTED 04 October 2022
PUBLISHED 04 November 2022

CITATION
Lunz Macedo AC, Santisteban Lores LE, Albuquerque JAT, Duarte NJC, Romano P, Ebner PAR, Rezende VM, Silva CA, Andrade LEC, Vasconcelos DM and Isaac L (2022) A rare association between factor H deficiency and lupus: Case report and experimental treatment with curcumin.
Front. Pediatr. 10:1039291.
doi: 10.3389/fped.2022.1039291

A rare association between factor H deficiency and lupus: Case report and experimental treatment with curcumin

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Factor H (FH) is one of the most important regulatory proteins of the alternative pathway of the complement system. FH deficiency is a rare condition that causes unregulated C3 consumption, leading to an increased susceptibility to infections and glomerulopathies. Our previous studies have demonstrated a FH deficient patient carrying a c.452G > A, *p*.R127H FH mutation which leads to a misfolded protein and its retention in the endoplasmic reticulum. In his cultured fibroblasts, FH-delayed secretion was partially rescued when treated with curcumin, and once secreted, exhibited normal regulatory function. Here, we report a childhood-onset systemic lupus erythematosus (cSLE) in this FH deficient patient and the results of experimental treatment with curcumin aiming to rescue FH secretion and regulatory activity.

KEYWORDS

FH deficiency, lupus, curcumin, experimental treatment, translational medicine, case report

Introduction

Factor H (FH) is a central regulator of the complement system that inhibits excessive alternative pathway activation by acting as a cofactor for Factor I in the cleavage of C3b into iC3b. FH also competes with Factor B (FB) for binding to C3b, resulting in the dissociation of Bb from C3- and C5-convertases. FH deficiency is related to C3 deficiency owing to the acceleration of C3 consumption. Complete homozygous FH deficiency is a rare condition, and to date a few cases have been described (1, 2). In humans, a single gene on chromosome 1q32 codes for FH. Mutations in the human

FH gene can result in the lack of protein in the plasma due to misfolding and impaired protein secretion or in normal range detection but with defective regulatory functions (3). FH deficiency is mainly associated with an increased susceptibility to infections, and patient's defective regulatory functions can lead to C3-glomerulopathy, atypical haemolytic uraemic syndrome, and age-related macular degeneration (1–5). FH- and C3-deficient patients are treated constantly with antibiotics and when in critical conditions, they are plasma infused to replace complement proteins levels. Clearly, new options of treatment are required. In experimental models, the use of mini-FH (containing domains 1–4 and 19–20) offer promising results in the regulation of the alternative pathway (6). However, so far this has not been tested in FH-deficient patients.

We have previously described the case of a patient with FH deficiency diagnosed after two episodes of complicated pneumonia (7). The homozygous variant c.452G > A in CFH determining *p*.R127H was found in the patient by Sanger sequencing analysis (7). *In vitro*, the patient's fibroblasts retain FH in the endoplasmic reticulum, resulting in delayed secretion. These cells, when treated with curcumin, showed increased secretion of the mutant FH, which once transported, had normal regulatory function in the alternative pathway of the complement system (8).

Curcumin is a hydrophobic polyphenol derived from the rhizome of the *Curcuma longa* plant with a broad spectrum of antioxidant, anti-inflammatory, antimicrobial, and anticancer effects. It is well accepted that curcumin has low bioavailability in humans, chemical instability, and rapid metabolism, even when administered orally at doses as high as 12 g/day (9). A formulation of curcumin in nanoparticles (Theracurmin®) has been used in clinical trials, presenting better absorption and bioavailability (10, 11). Based on these observations, we hypothesised that Theracurmin® could be used to treat FH deficiency *in vivo*.

Before the experimental treatment, the patient presented unexpected signs and symptoms of childhood-onset systemic lupus erythematosus (cSLE). SLE is a rare autoimmune disorder that affects multiple organs and systems (12–14). Deficiencies in the first components of the classical pathway C1q/r/s, C4, and C2 are frequently associated with early onset SLE or lupus-like disease (15). However, deficiency of alternative pathway proteins has rarely been associated with SLE development (1).

In this case report, we discuss the diagnosis of cSLE in this patient and the results of treatment with Theracurmin® for his FH deficiency.

Case description

A 2-year-old Brazilian boy, the second child of first-degree cousins with Japanese ascendance, was hospitalised in the intensive care unit because of complicated pneumonia with bilateral pleural effusion. The patient was treated with antibiotic therapy and bilateral thoracic drainage with complete resolution. At the age of 3 years, he presented with a new episode of pneumonia that required invasive ventilation and antibiotic therapy, and was discharged after three weeks. He was fully vaccinated according to the public health schedule available when he was a child, which at that time did not include pneumococcal vaccine. After hospitalisation, prophylactic amoxicillin was prescribed. Immunological evaluation revealed FH deficiency, associated with reduced levels of C9, C3, and FB owing to the lack of regulation of the alternative pathway. The variant c.452G > A in CFH, which determines *p*.R127H, was found in the homozygous patient by Sanger sequencing analysis, and this variant was found in both parents in heterozygosis (7). He had chickenpox with no complications at 6 years of age, despite not vaccinated. At 15 years of age, he presented with a malar rash and photosensitivity, with periods of improvement and worsening. One year later, the patient developed persistent rashes on the posterior cervical and thoracic region. At the age of 17, he reported episodes of acute and painful oligoarthritis involving the right elbow, right ankle, and right fourth finger (proximal interphalangeal joint). These episodes lasted two to four days, and improved after a short course of non-steroidal anti-inflammatory drugs.

At 18 years of age, when he was invited to participate in the experimental treatment protocol, he had a malar rash, photosensitivity, and posterior cervical and thoracic rash, and had reported episodes of oligoarthritis. Ultrasound examination performed during a new episode of acute arthritis revealed normal radiographic findings and small joint effusion with synovial thickening in the olecranial fossae of the elbow. Despite the distribution of the rashes in the posterior cervical and thoracic region, the lesions were not compatible with dermatomyositis, and skin biopsies confirmed the immunofluorescence pattern characteristic of the skin lesion in SLE. Thoracic lesion skin biopsy showed lupus band test with immunofluorescence of continuous cross-linked IgM and focal granular IgG, with the absence of IgA and C3 along the dermoepidermal junction. IgG fluorescence was also observed in the keratinocyte nuclei. Ophthalmic exam did not reveal any abnormalities or pigmentary changes in the retina. The laboratory findings showed haemoglobin, 14.6 g/dl; white blood cell count, 6,560/mm^3 (47% neutrophils, 32% lymphocytes, 5% eosinophils, 1% basophils, and 15% monocytes); and platelet count 300,000/mm^3. C reactive protein was 2.18 mg/dl, C3 < 4 mg/dl (reference 67–149 mg/dl), C4 26,7 mg/dl (reference 10–38 mg/dl), C1q 389 mg/dl (reference 100–250 mg/dl), and C2 14,1 (reference 14–25 mg/dl). Anti-C1q 32 U/ml (reference <9 U/ml). Immunological tests showed antinuclear antibodies on HEp-2 cells (HEp-2 ANA) 1:1,280 thick speckled pattern, positive ENA (anti-Sm

42,8 U/ml, anti-RNP >200 U/ml, anti-Ro/SSA >200 U/ml, anti-La/SSB 35,92 U/ml—reference values <15 U/ml) IgG 21.58 GPL/ml anticardiolipin (reference <10 GPL/ml) and IgM anticardiolipin 26.11 MPL/ml (reference <7 MPL/ml) autoantibodies. Rheumatoid factor was positive, with 219.2 U/ml (reference value <14 U/ml). Anti-double-stranded DNA (anti-dsDNA) antibodies, ANCA (antineutrophil cytoplasmic antibodies), anti-JO1 (anti-histidyl T-RNA synthetase), and anti SCL-70 (anti-topoisomerase I) were negative. Urinalysis did not indicate the presence of leukocytes or erythrocytes and the albumin/creatinine ratio was 9.2 mg/g. The serum urea and creatinine levels were 18 mg/dl and 0.79 mg/dl, respectively.

Treatment description

Theracurmin® was kindly provided by Theravalues Corporation (Tokyo, Japan). After obtaining informed consent and local ethical committee approval, we initiated the regimen of a 2-g dose of Theracurmin® powder (containing 200 mg curcumin), diluted in water, orally every 12 h for 106 days. The dosage was subsequently increased to a 4-g dose of Theracurmin® every 12 h for an additional 29 days. As indicated in **Figure 1**, during treatment with Theracurmin®, the patient was not treated with standard treatment for SLE. He first received Theracurmin® alone and, after the washout, started standard treatment with hydroxychloroquine. During treatment, the patient was closely observed for any worsening in his condition, which would lead to an immediate discontinuation of the protocol.

Plasma levels of FH and factors B and C3 were assessed before and throughout the treatment. Plasma levels of IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α were quantified before the first dose (D0), and on D9 (**Table 1**).

Tolerance and side effects were assessed using clinical and laboratory parameters throughout the protocol. Lupus activity was measured using SLEDAI-2 K (16). The patient's quality of life was assessed using the Paediatric Quality of Life Inventory 4.0 - PedsQL 4.0 - (17), covering four domains: health and activities; emotional aspects; social aspects; and school performance before treatment (D0), D135, and D200. During the protocol, the patient had sinusitis, mumps despite being vaccinated, and self-limiting episodes of arthritis. Our patient reported poor compliance at two time points during the treatment. These events are illustrated in **Figure 1**.

Results and discussion

SLE and FH deficiency

To confirm the diagnosis of SLE, clinical and laboratory findings were correlated with the scoring criteria from the American College of Rheumatology (ACR) (18), Systemic Lupus International Collaborating Clinics (SLICC) (19), and the EULAR/ACR classification (EULAR) (20). Although low levels of C3 are primarily caused by FH deficiency, SLE was diagnosed in this patient by all three classifications. Since the patient developed clinical signs of lupus before the age of 18, cSLE was confirmed.

The patient presented with more than 6 of the 11 points of ACR classification. The sensitivity and specificity of the 1982 ACR criteria for paediatric lupus are 96% and 100%, respectively (21). Without considering the low level of C3, the patient met two clinical and two immunological criteria of the SLICC classification. In the EULAR/ACR classification, the patient scored more than 10 points. Although the characteristic skin biopsy is not scored as a criterion, immunofluorescence performed on biopsy reinforces lupus diagnosis.

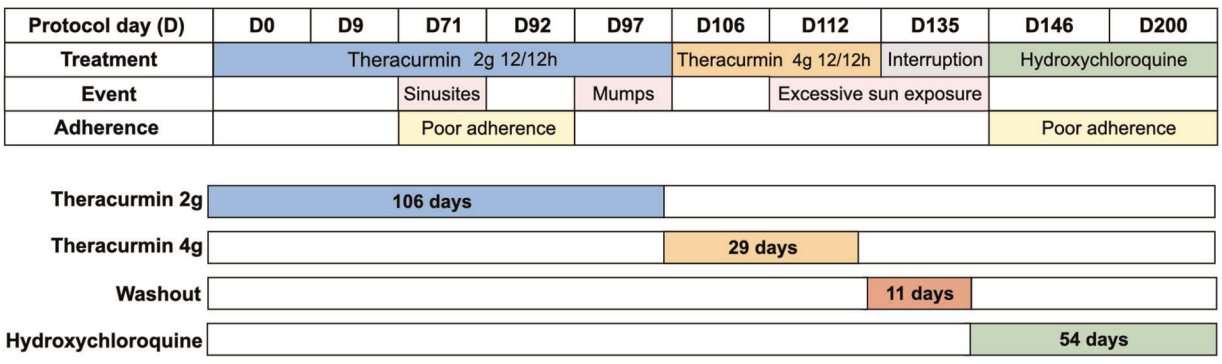

FIGURE 1
Protocol design, evaluation time, therapeutic intervention, events and report of treatment adherence.

To confirm that cSLE was absent at 3 years of age, when he was diagnosed with primary immunodeficiency, the same autoantibodies were also tested in the patient's frozen serum samples. The following auto antibodies were analysed: HEp-2 ANA, anti-DNA, ANCA, anti-JO1, anti SCL-70, RNP-SM, anti-SM, anti-Ro, anti-La, anticardiolipin IgG, and anticardiolipin IgM. All titres were negative, except for HEp-2 ANA (1:320). Autoantibodies can be present many years before the diagnosis of SLE (22), but for this patient, the retrospective assessment for lupus was negative at 3-year-old, confirming that cSLE occurred after the primary immunodeficiency.

Case reports that relate autoimmune diseases to the complement system are often related to the deficiency of components of the classical pathway and this association between immunodeficiency and autoimmune diseases has been well-documented in the literature (23). Turley et al. (2015) studied 77 complement-deficient patients and observed that 37% of those presented defects in the classical pathway had SLE-like disease (24). The most remarkable genetic association with SLE is the high frequency of deficiencies in early classical pathway components, mainly C1q (90%–93%), C1r/C1s (50%–57%), C4 (75%), and C2 (10%). These patients usually present with SLE at an early age, with severe symptoms and poor prognosis (15). However, the association between SLE and deficiencies in the components of the alternative pathway is unusual. Homozygous FH deficiency is a rare phenomenon and only a few cases have been reported (2). There are only two cases in the literature of concomitant FH deficiency and SLE (25, 26). In one case, a Caucasian daughter of non-consanguineous parents presented with subacute cutaneous lupus, with ANA and anti-DNA positivity, FH deficiency, and undetectable C3 serum levels. C2 levels were reduced, with normal serum C4 and C1q levels. Until the period when the case was published at age 59, this patient did not present with glomerulonephritis (25). In another case, a Caucasian daughter of consanguineous first-degree cousins had arthritis, fever, erythema malar, anaemia, nephritis, ANA positivity, and intense fluorescence for IgG in the nuclei of keratinocytes in the skin biopsy. The patient had undetectable serum concentrations of FH, C3, and FB; low concentrations of C2; and low levels of C1q and C4, with normal C1-INH (26). These two cases reported FH deficiency and lupus. They also had deficiencies in the initial components of the classical pathway, which could justify their association with lupus. Here, we describe a rare association of a homozygous deficiency in FH, a regulatory protein of the alternative pathway, and cSLE. To the best of our knowledge, there is no previous case of a patient who initially presented with FH deficiency at an early age, with normal components of the classical pathway, and cSLE development during adolescence. To date, we cannot speculate which pathophysiological mechanisms could explain a possible association between FH deficiency and SLE. Possibly, there are underlying genetic variants that may predispose to SLE, which we have not been able to explore until now.

Curcumin treatment evaluation

Patient plasma concentrations of curcumin were assessed at the beginning of the treatments with 2-g and 4-g doses of Theracurmin®. Blood samples were collected immediately before and at 30 min, 60 min, 90 min, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h after the administration of the first 2-g dose of Theracurmin®. The same protocol was performed with the first 4-g dose Theracurmin® (there was no washout period during treatment).

There are studies using doses as low as 500 mg up to 12 g with good tolerance and minor adverse events. The different curcumin treatment regimens and formulations available in the literature are not comparable with each other and there is no consensus on their use. We designed this specific protocol with Theracurmin® because its better absorption might be an advantage for its clinical function (27–29).

It was possible to identify through HPLC-MS/MS that the highest plasma concentration of curcumin throughout the treatment was 432 ng/ml (1,17 μM), which was reached immediately after the first dose. The plasma curcumin concentration after the very first 2-g dose Theracurmin® was consistently higher than the results obtained after chronic use, even with a 4-g dose as well as throughout the treatment. This finding of lower plasma curcumin concentrations in chronic use despite the increased dose of Theracurmin® has not been previously explained in the literature.

A previous report assessed plasma curcumin levels in healthy volunteers after a single oral 150-mg dose followed by a 210-mg dose of Theracurmin®, separated by a washout period of two weeks between dose escalation. They demonstrated an increase in plasma curcumin levels in a dose-dependent manner (10).

Oral curcumin is known to have low bioavailability owing to its low absorption by the small intestine, coupled with extensive reductive and conjugative metabolism in the liver and elimination through the gall bladder. After ingestion, curcumin is subsequently reduced in enterocytes and hepatocytes by a reductase to dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin, which can be found in free forms or as glucuronides (9). Several studies have been performed using oral curcumin powder supplements to investigate their absorption. Degradation reactions change the structure and properties of curcumin, thereby affecting its pharmacokinetic and pharmacodynamic behaviour (9).

We speculate that our finding of lower plasma curcumin levels despite increasing (doubling) the dose of Theracurmin® in a continuous treatment could be an effect of enzymatic induction and tolerance with acceleration of the drug's

metabolism over time (30–33). Both curcumin and its major reduced forms (dihydrocurcumin, tetrahydrocurcumin, and hexahydrocurcumin) can undergo glucuronidation. To clarify these questions, plasma samples were treated with glucuronidase, and the amounts of curcumin and tetrahydrocurcumin were assessed using HPLC-MS/MS for comparative analysis. This additional evaluation showed high concentrations of plasma curcumin after the first 2-g dose of Theracurmin®, whereas high levels of its metabolite, tetrahydrocurcumin, were observed after continuous use, assessed with 4-g dose of Theracurmin® (**Figure 2**).

Albuquerque et al. (2012) used 2 μM pure curcumin (Sigma-Aldrich) in the patient's fibroblast culture (8). The *in vitro* concentration of curcumin in that experiment was high, and this was not achievable in the *in vivo* treatment protocol because curcumin is unstable under physiological conditions and rapidly metabolised to other products.

Plasma levels of FH, FB and C3 were assessed before and throughout the treatment. Despite the levels of curcumin and its metabolites in the patient's plasma, the treatment did not affect the concentration of FH, FB and C3.

The plasma concentrations of IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α were determined before treatment (D0) and on D9 under regular use of Theracurmin® 2 g every 12 h (**Table 1**). Considering the cytokine response to treatment, there was a marked drop in the plasma concentration of IL-6, and a reduction of approximately 20% in IL-8 levels. However, IL-1β increased more than 50%, and slight increases in TNF-α, IL-10, and IL-12p70 levels were observed. A meta-analysis of nine randomised controlled studies demonstrated that IL-6 levels were reduced by treatment with curcumin, and this effect was more evident in more intense inflammatory states. Our results only partially agree with the literature, which describes the reduction in serum concentrations of IL-1β, IL-6, IL-8, IL-12, and TNF-α with the use of curcumin (34).

To ensure the safety of the treatment, the patient was closely monitored and lupus activity was measured using SLEDAI-2K throughout the treatment. SLEDAI-2K remained stable, as did haematologic, renal, and hepatic parameters (**Table 2**). Since

TABLE 1 Concentrations of the cytokines IL-1ß, IL-6, IL-8, IL-10, IL-12p70 and TNF-α were assessed pre-treatment at D0 and D9 in regular use of Theracurmin® 2-g every 12 h.

Cytokine	D0 (fg/ml)	D9 (fg/ml)
IL-6	297	68
IL-8	4,008	3,103
IL-10	1,002	1,183
IL-12p70	506	553
IL1-ß	1,188	1,882
TNF-α	1,091	1,377

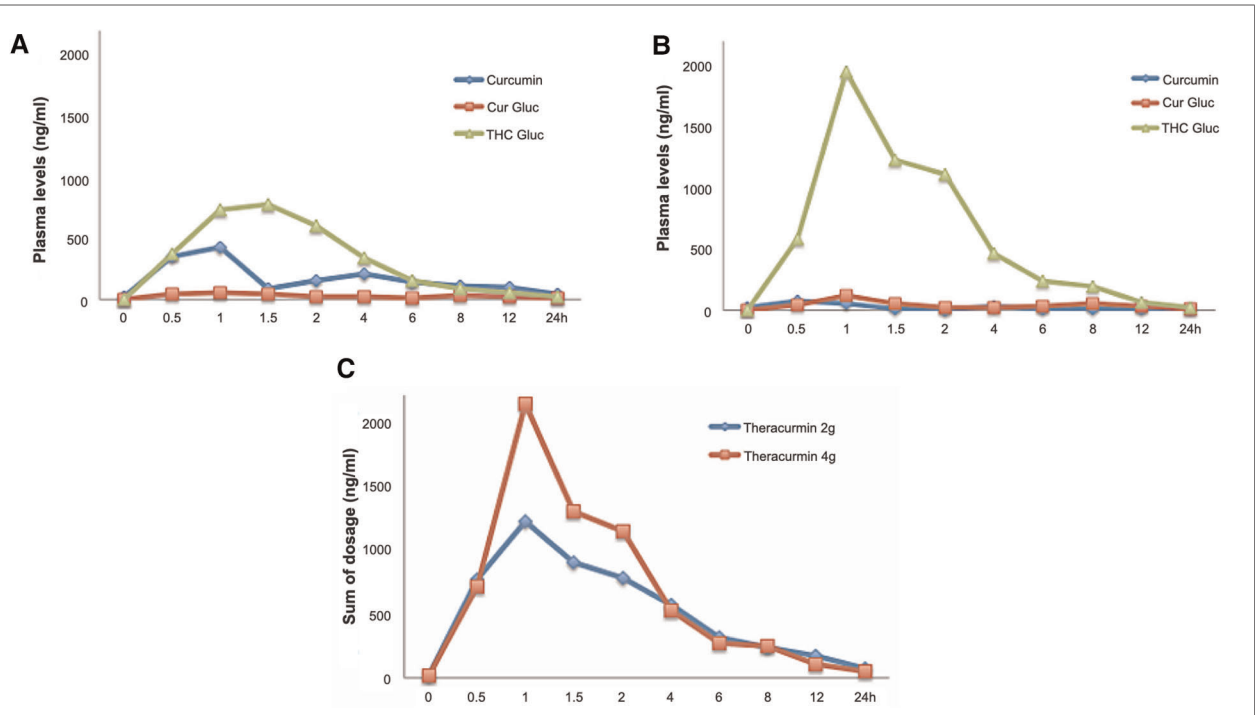

FIGURE 2
Curcumin and metabolites levels in patients's plasma. (**A**) 2-g Theracurmin®; (**B**) 4-g Theracurmin®; (**C**) Sum comparison of all curcumin fractions and metabolites with 2-g and 4-g Theracurmin®. Cur Gluc: Curcumin Glucuronidase; THC Gluc: Tetrahydrocurcumin Glucorunidase.

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TABLE 2 Laboratorial tests assessed pre-treatment at D0, D113 in regular use of Theracurmin® 4 g every 12 h, D147 after 11 days washout, and D201 in regular use of Hydroxychloroquine 400 mg.

Protocol day (D)	D1	D113	D147	D201
Serum creatinine (0.70–1.20 mg/dl)	0.79	0.88	0.85	0.8
Serum urea (13–43 mg/dl)	18	22	27	25
Urine density U (1003–1029)	1,020	1,020	1,015	1,020
Urine pH (4.50–7.80)	6	6	6	5
Urine leucocytes (0–7,000)	0	1,000	1,000	1,000
Urine red blood cells (0–3,000)	0	1,000	0	500
Urine protein/creatinine ratio (0.06–0.2 g/g)	0.1	0.06	NA	0.07
Urine albumin/creatinine ratio (<30 mg/g)	9.2	6.58	NA	5.69
Urine NGAL (0.40–72 ng/ml)	7.61	6.69	2.19	NA
C-reactive protein (<5 mg/dl)	2.2	1.87	2.77	1.08
White blood cell count (4,500–11,000/mm^3)	6,560	7,100	5,030	5,480
Neutrophils (45,5–69,5%)	47	67	50	44
Lymphocytes (20,3–47%)	32	17	27	32
Monocytes (1,6–10%)	15	11	15	13
Eosinophils (0–4,4%)	5	5	7	10
Basophils (0,2–1,2%)	1	0	1	1
Haemoglobin (13.5–17.5 g/dl)	14.6	14.3	13.2	14.2
Platelet count (150–450×103/mcL)	300	374	261	318
Aspartate transaminase (15–40 U/L)	16	15	29	17
Alanine transaminase (10–40 U/L)	18	21	29	15
Bilirubin (<1 mg/dl)	0.64	0.36	0.54	0.62
Gamma-glutamyltransferase (2–30 U/L)	22	20	18	16
Cholesterol (<150 mg/dl)	133	127	119	131
Triglycerides (<100 mg/dl)	91	107	86	62
Serum total protein (6.0 a 8.0 g/dl)	7.6	7.8	7.7	8.2
Serum albumin (3.2 a 5.0 g/dl)	3.9	3.9	4.1	4.4
Serum globulin (0.7 a 1.5 g/dl)	1.7	1.9	1.7	1.8
C1q (100–250 mg/dl)	389	NA	NA	NA
C2 (14–25 mg/dl)	14.1	NA	NA	NA
C3 (67–149 mg/dl)	<4	5	<4	<4
C4 (10–38 mg/dl)	26.7	27.8	19.8	21.4
HEp-2 ANA (non-reactive)	1:1,280	NA	NA	NA
Anti-double-stranded DNA (<1.0)	NR	NA	NA	NA
Anti-C1q (<9.0 U/ml)	32	NA	NA	NA
Anti-RNP (non-reactive—U/ml)	>200	NA	NA	NA
Anti-Sm (non-reactive—U/ml)	42.8	NA	NA	NA
Anti-Ro/SSA (non-reactive—U/ml)	>200	NA	NA	NA
Anti-La/SSB (non-reactive—U/ml)	35.9	NA	NA	NA
IgG anti-cardiolipin (<10 U GPL/ml)	21.5	NA	NA	NA
IgM anti-cardiolipin (<10 U MPL/ml)	26.1	NA	NA	NA
ANCA (non-reactive)	NR	NA	NA	NA
Anti-JO1 (non-reactive)	NR	NA	NA	NA
Anti SCL-70 (non-reactive)	NR	NA	NA	NA
Rheumatoid factor (<14 U/ml)	219.2	NA	NA	NA

Normal values are indicated in parentheses. NR: non-reactive; NA: not available; NGAL: Neutrophil gelatinase-associated lipocalin; ANCA: Antineutrophil cytoplasmic antibodies; Anti-JO1: Anti-histidyl T-RNA synthetase; Anti SCL-70: Anti-topoisomerase I; HEp-2 ANA: Antinuclear antibodies on HEp-2 cells.

the low level of C3 is secondary to FH deficiency, we did not consider C3 in the SLEDAI-2K; however, even if it were considered, it would have remained at 4 (a low activity index) throughout the protocol. We concluded that neither the introduction nor interruption of curcumin treatment interfered with lupus activity.

We conclude that the patient showed good tolerance to both doses of Theracurmin® without adverse symptoms or side effects, as reported in previous publications.

Patient perspective: PedsQL 4.0

The perception of quality of life by PedsQL 4.0 was assessed before treatment on D0, on D135 (during treatment with Theracurmin® 4 g every 12 h) and on D200 (after discontinuation of Theracurmin® and under treatment with hydroxychloroquine 400 mg). In the PedsQL 4.0, the best quality of life was related to the lowest score. In the patient's opinion, the scores were 11, 15, and 4 at the respective three time points. Parents' views on adolescents' quality of life were 17, 19, and 2 at the same time points. Considering the four domains, there was a significant improvement in quality of life, mainly in health and activities, in the third assessment under use of hydroxychloroquine.

Conclusion

We have reported a rare case of FH deficiency and cSLE. Oral curcumin supplementation for FH deficiency was well tolerated with no adverse effects. Despite the previous success of *in vitro* treatment of patient fibroblasts, *in vivo* treatment did not result in an increase in the plasma levels of FH, C3, and FB. Although the plasma concentrations of IL-6 and IL-8 declined and IL-1β increased after the treatment, no improvement or burden in the clinical and laboratory cSLE parameters were observed.

It is well established that curcumin has low bioavailability and that it can be ameliorated by new formulations. In our case, using a nanoparticle formulation (Theracurmin®), the plasma levels of curcumin rapidly decreased with continuous use, whereas the level of tetrahidrocurcumin increased. These results could be due to enzymatic induction and tolerance with acceleration of the drug's metabolism over time and might justify the absence of an effect of curcumin treatment for this patient.

For this patient, personalised translational medicine showed that previous successful *in vitro* treatment could not be assumed as a beneficial long-term treatment for FH deficiency. More efforts are needed to clarify curcumin bioavailability, absorption, reductive, and conjugative metabolism during short-term and long-term treatment.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by local institutional review board (CEP 1151183). The patient and the legal guardian provided their written informed consent to participate in this study.

Author contributions

LI, JATA, and ACLM conceptualised and designed the study. ACLM, JATA, and LESL performed the initial analyses and drafted the initial manuscript. CAS, LECA, DMV, and LI critically reviewed this manuscript. NJCD, PR, PARE, and VMR provided curcumin and metabolite dosages throughout the treatment. ACLM and DMV were responsible for the patient treatment. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by grants from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP #2010/50043-0 and FAPESP #2017/12924-3) and Conselho Nacional de Pesquisa e Desenvolvimento (CNPq 421474/2016-5 and 312654/2021-9).

Conflict of interest

The 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.

Publisher's note

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frontiers | Frontiers in Pediatrics

TYPE Case Report
PUBLISHED 14 November 2022
DOI 10.3389/fped.2022.1054025

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 26 September 2022
ACCEPTED 25 October 2022
PUBLISHED 14 November 2022

CITATION
Kwong EYL, Kuok MCI and Chan WK-Y (2022) Case Report: Multiple autoimmune syndrome (MAS)—An unusual combination. Front. Pediatr. 10:1054025. doi: 10.3389/fped.2022.1054025

Case Report: Multiple autoimmune syndrome (MAS)—An unusual combination

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This is a case report of a Chinese adolescent boy who had multiple autoimmune syndrome (MAS) of a rare combination comprising type 1 diabetes, Hashimoto thyroiditis and childhood-onset systemic lupus erythematosus (SLE). He developed SLE within one year of symptom onset, presenting with necrotising histiocytic lymphadenitis and hepatitis. We highlight the importance for physicians to be aware of the need for continued surveillance for developing new autoimmune diseases in patients with multiple autoimmune diseases. It is also essential to remain vigilant for overlap syndrome as autoimmune diseases commonly share similar subphenotypes and non-specific autoantibodies. Long-term follow-up is warranted to define the final phenotype.

KEYWORDS

multiple autoimmune syndrome (MAS), diabetes mellites (DM), autoimmune thyroid desease, systemic lupus erythematosus, kikuchi - fujimoto disease

Case history

A 12-year-old Chinese adolescent boy presented with a two-week history of polydipsia, polyuria, nocturnal enuresis and weight loss. His blood tests showed high glucose (26.7 mmol/L), beta-hydroxybutyrate (3.59 mmol/L), metabolic acidosis and presence of anti-islet cells. He was diagnosed with type 1 diabetes with ketoacidosis. He was also incidentally found to have Hashimoto thyroiditis with the presence of anti-thyroglobulin and anti-thyroid peroxidase antibodies.

One year later, he presented with a prolonged remittent and intermittent fever of more than three weeks. He had a painless swelling on the right side of his neck which progressively increased in size. He had no constitutional symptoms. He had no family history of autoimmune diseases. Upon physical examination, a chain of enlarged lymph nodes measuring 2.5 cm was noted in the right upper cervical region. The nodes were firm and non-tender without overlying skin changes. Enlarged lymph nodes were also present in the left cervical region but to a lesser extent. Shotty lymph nodes were noted in the groins bilaterally. The rest of the systemic examination was normal.

His blood tests showed microcytic anaemia (hemoglobin 9.6 g/dl) due to iron deficiency, leukopenia (3.4×10^9/L), lymphopenia (0.8×10^9/L) and normal platelet count of 202×10^9/L (**Table 1**). The reticulocyte was 0.4%. The peripheral blood smear showed hypochromia and microcytosis without abnormal blasts. The clotting

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TABLE 1 A table illustrating the laboratory values of the patient.

	Result	Reference interval
Hemoglobin (g/dl)	9.6	13.4–17.1
White blood cell ($\times10^9$/L)	3.4	3.7–9.2
Lymphocyte ($\times10^9$/L)	0.8	1.0–3.1
Platelet ($\times10^9$/L)	202	145–370
Reticulocyte (%)	0.4	0.5–2.0
C-reactive protein (mg/L)	17	<5
Erythrocyte sedimentation ratio (mm/hr)	76	<17
Lactate dehydrogenase (IU/L)	358	118–221
Ferritin (pmol/L)	1166	32–342
Triglyceride (mmol/L)	1.3	<1.7
Albumin (g/L)	32	37–47
Globulin (g/L)	47	24–37
Aspartate transaminase (IU/L)	424	<42
Alanine aminotransferase (IU/L)	307	<51
Gamma-glutamyl transferase (IU/L)	105	<42
Alkaline phosphatase (IU/L)	272	74–290
Anti-nuclear antibodies	1:640 (speckled and cytoplasmic pattern)	
Anti-double-stranded DNA (IU/ml)	69	<50
Anti-extractable nuclear antigens		
Anti-ribonucleoprotein/Smith	Present	
Anti-Smith	Not detected	
Anti-Ro	Not detected	
Anti-La	Not detected	
Anti-Scl-70	Not detected	
Anti-Jo-1	Not detected	
Anti-cardiolipin (GPL-U/ml)	15.3	<13.3
Lupus anticoagulant	Present	
Rheumatoid factor	Present	
Complement 3 (g/L)	0.99	0.9–1.61
Complement 4 (g/L)	0.11	0.13–0.38
Direct Coomb's test	Positive	
Immunoglobulin G (g/L)	20.8	5.95–13.1

profile was normal. Inflammatory markers were elevated. C-reactive protein (CRP) was 17 mg/L (reference <5 mg/L). Erythrocyte sedimentation ratio (ESR) was 76 mm/h (reference <17 mm/h). Lactate dehydrogenase (LDH) was 358 IU/L (reference interval 118–221 IU/L). Ferritin was 1,166 pmol/L (reference interval 32–342 pmol/L). Triglyceride was normal at 1.3 mmol/L (reference <1.7 mmol/L). There was a reversal of the albumin to globulin ratio. Albumin was 32 g/L (reference interval 37–47 g/L). Globulin was 47 g/L (reference range 24–37 g/L). He had normal serum bilirubin. Liver enzymes were normal initially but started to rise on day 8 of admission. They peaked on day 12 of admission with aspartate transaminase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) at 424 IU/L (reference <42 IU/L), 307 IU/L (reference <51 IU/L), 105 IU/L (reference <42 IU/L) and 272 IU/L (reference interval 74–290 IU/L) respectively, suggestive of predominantly hepatocellular pattern of liver injury. Viral markers including hepatitis A, B and C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), dengue virus, Japanese E encephalitis virus (JEV) were negative. Bacterial cultures from peripheral blood, bone marrow, urine, stool and throat yielded no growth. Serologies for atypical organisms were negative, including Salmonella typhi, Bartonella henselae, Brucella abortus and melitensis, and Toxoplasma gondii. Antinuclear antibodies (ANA) were present at 1:640 with a speckled and cytoplasmic pattern. Anti-double-stranded DNA (dsDNA) was mildly elevated at 69 IU/ml (reference ≤50 IU/ml). The screening of autoantibodies against extractable nuclear antigens (ENA) showed the presence of anti-ribonucleoprotein/Smith (RNP/Sm). Anti-Smith (Sm), anti-Ro, anti-La, anti-Scl-70 and anti-Jo-1 were not detected. There was the presence of anti-cardiolipin at 15.3 GPL-U/ml (reference <13.3 GPL-U/ml), lupus coagulant and rheumatoid factor. Anti-liver-kidney-microsomal (LKM) antibody was not detected. Serum complement 4 was mildly depressed at 0.11 g/L (reference range 0.13–0.38 g/L), while complement 3 was normal. Direct Coomb's test was positive. The immunoglobulin profile showed hypergammaglobulinaemia at 20.8 g/L (reference internal 5.95–13.1 g/L). Urine examination did not suggest proteinuria or hematuria.

His neck ultrasound revealed prominent and enlarged lymph nodes in bilateral cervical regions. The largest one measured 1.9 cm in transverse diameter, 0.8 cm in anteroposterior diameter and 2.2 cm in craniocaudal diameter in the right upper posterior triangle region (**Figure 1**). A lymph node biopsy was performed on day 8 of admission to rule out malignancy. The hematoxylin and eosin (H&E) slide showed necrosis accompanied by histiocytes and significant karyorrhectic debris (**Figure 2A**). There were crescentic histiocytes with dual expression of MPO (usually a marker for myeloid lineage) (**Figure 2B**) and PGM1 (a histiocyte marker) (**Figure 2C**) by immunohistochemistry. Neutrophils were absent. There was no evidence of malignancy. Serial sections with the Ziehl-Neelsen stain did not show acid-fast bacilli, and the Grocott stain did not show fungal organisms. The histopathological finding was suggestive of necrotising histiocytic lymphadenitis. His bone marrow aspirate and trephine biopsy did not suggest malignancy. The chest radiograph, echocardiogram and hepatobiliary ultrasound were normal.

He met three criteria of The American College of Rheumatology (ACR) 1997: hematologic disorder (leukopenia,

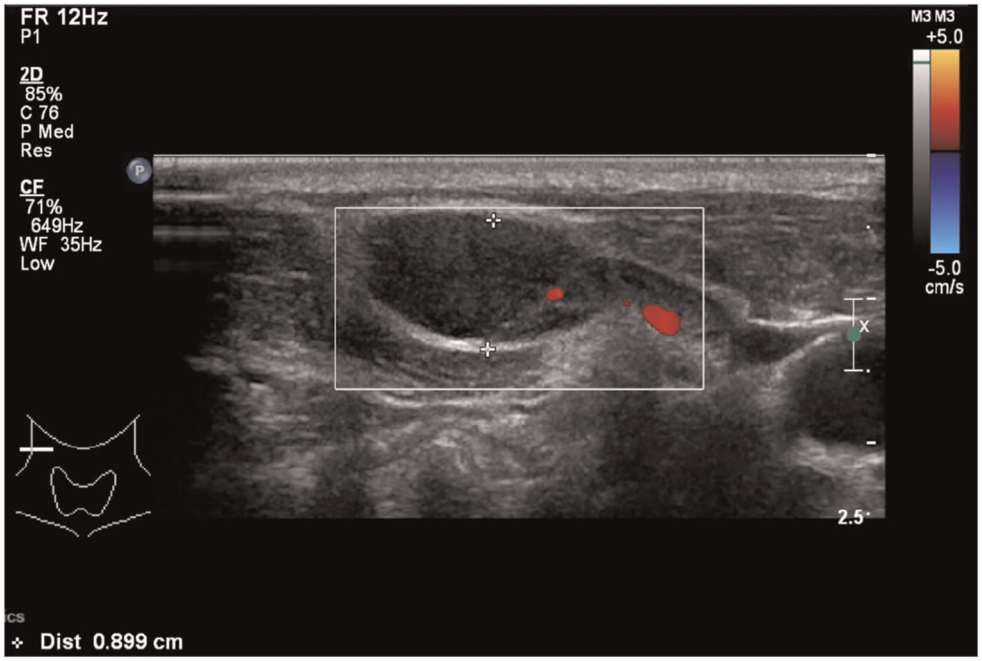

FIGURE 1
A neck ultrasound showing an enlarged lymph node which measures 1.9 cm in transverse diameter, 0.8 cm in anteroposterior diameter and 2.2 cm in crania-caudal diameter in the right upper posterior triangle region.

lymphopenia), positive ANA and immunological disorders (presence anti-dsDNA, anti-cardiolipin antibodies and lupus anticoagulant).. He fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) criteria, which was more sensitive especially in early childhood systemic lupus erythematosus (SLE), including leukopenia, presence of antinuclear antibodies (ANA), anti-double-stranded DNA (dsDNA), anti-cardiolipin, lupus anticoagulant, low complement 4 and positive direct Coomb's test. He was diagnosed with systemic lupus erythematosus (SLE), which manifested as necrotising histiocytic lymphadenitis and lupus hepatitis. He received preemptive intravenous (IV) cefotaxime without clinical or biochemical improvement after admission. He was treated with intravenous immunoglobulin (IVIG) of 2 grams on days 13 and 14 of admission. Liver parenchymal enzymes showed a downtrend, but his fever persisted. He was treated with intravenous methylprednisolone 50 mg every 24 h on day 15 of admission after the lymph node biopsy ruled out malignancy. The fever settled promptly after the commencement of methylprednisolone (**Figure 3**), and the enlarged cervical lymphadenopathy resolved in four days. ALT elevated transiently before it dropped again five days after methylprednisolone treatment (**Figure 4**). Both AST and GGT showed a downtrend. ALP remained within the reference range throughout the whole of the admission. The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) at the time of admission was 6 which suggested an active disease, and by the time of follow up, the score decreased to 2. He had been followed for a total of 22 months so far without further recurrence. He is currently on prednisolone 2 mg daily, azathioprine 75 mg daily and hydroxychloroquine 200 mg daily to control his SLE.

Discussion

Multiple autoimmune syndrome (MAS)

Autoimmune disease is a systemic immune response resulting from the loss of immunological tolerance to self-antigen. It encompasses more than 100 individual diseases. They are often diagnosed according to classification criteria. However, they share common clinical manifestations, pathophysiologic mechanisms and genetic factors. This is known as an autoimmune tautology (from Greek auto, "the same" and logos, "word/idea"). The term "kaleidoscope of autoimmunity" describes the possible change of one disease to another or the fact that more than one disease may coexist in the same individual. Around 25 per cent of patients with autoimmune diseases tend to develop another autoimmune disorder (1). When more than one autoimmune disease coexists, this is defined as polyautoimmunity. When three or more autoimmune diseases coexist, this is known as multiple autoimmune syndrome (MAS).

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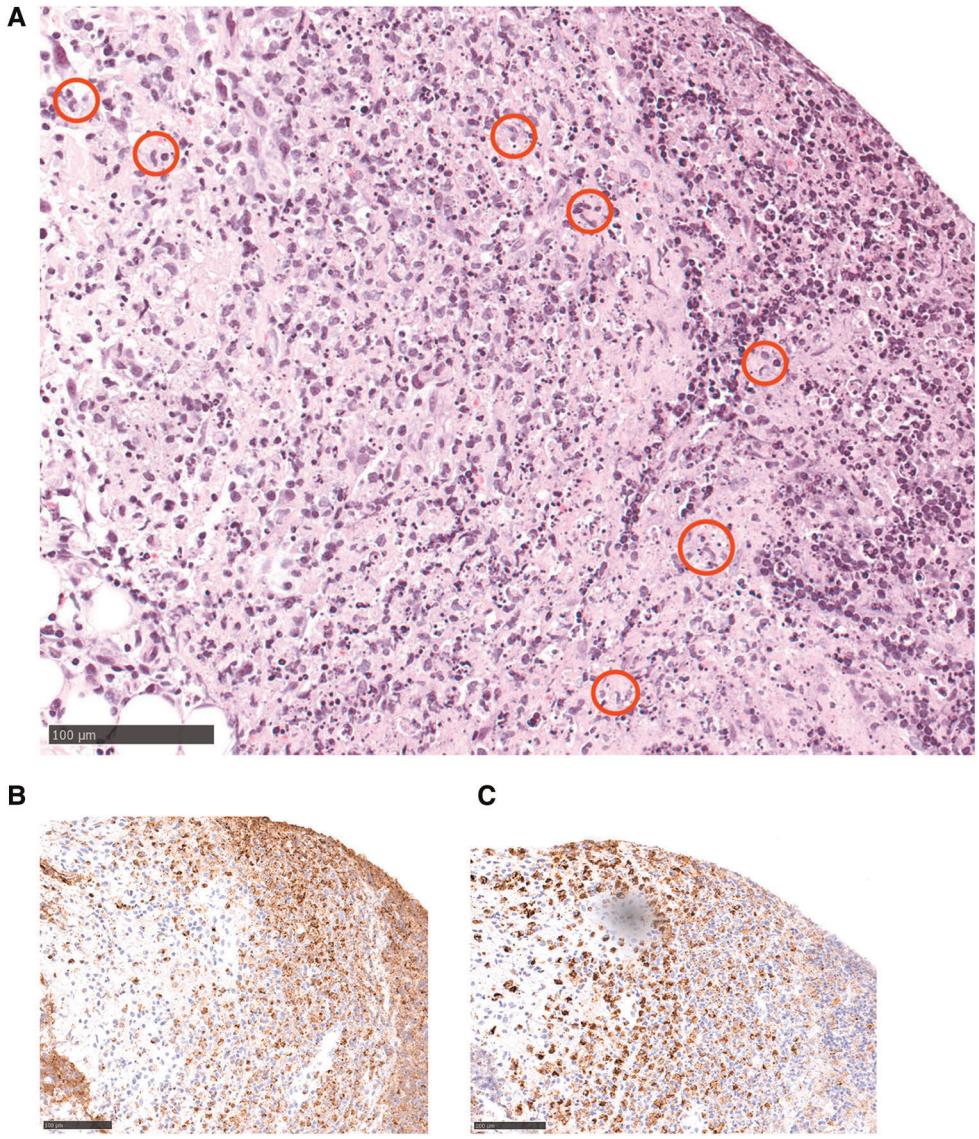

FIGURE 2
(A) A hematoxylin and eosin (H&E) slide illustrating a characteristic area of necrotising histiocytic lymphadenitis: there is necrosis accompanied by histiocytes (circled in red) and significant karyorrhectic debris. (B,C) Within the necrotic area, there are crescentic histiocytes (brown-staining cells) with dual expression of MPO (usually a marker for myeloid lineage) (B, left side of the picture) and PGM1 (A histiocyte marker) (C, right side) by immunohistochemistry.

Humbert and Dupond first described multiple autoimmune syndrome (MAS) in 1988 (2). It is classified into three groups according to the prevalence of their associations. Type I includes myasthenia gravis, thymoma, polymyositis and giant cell myocarditis. Type II groups together Sjögren's syndrome, rheumatoid arthritis, primary biliary cirrhosis, scleroderma and autoimmune thyroid disorders. Type III comprises ten autoimmune diseases, including autoimmune thyroid disease, myasthenia and, or thymoma, Sjögren's syndrome, pernicious anaemia, idiopathic thrombocytopenic purpura, Addison's disease, insulin-dependent diabetes, vitiligo, autoimmune hemolytic anaemia, systemic lupus erythematosus (SLE). Subsequent studies evaluating polyautoimmunity have found associations between other autoimmune diseases which were not reported in the original report. Our patient has three autoimmune diseases, namely type 1 diabetes mellitus, Hashimoto's thyroiditis and childhood-onset SLE, which are a rare combination among MAS type III.

The cohort of 388 patients from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry showed that the prevalence of polyautoimmunity in childhood-onset SLE was 8.8% (3). Another retrospective

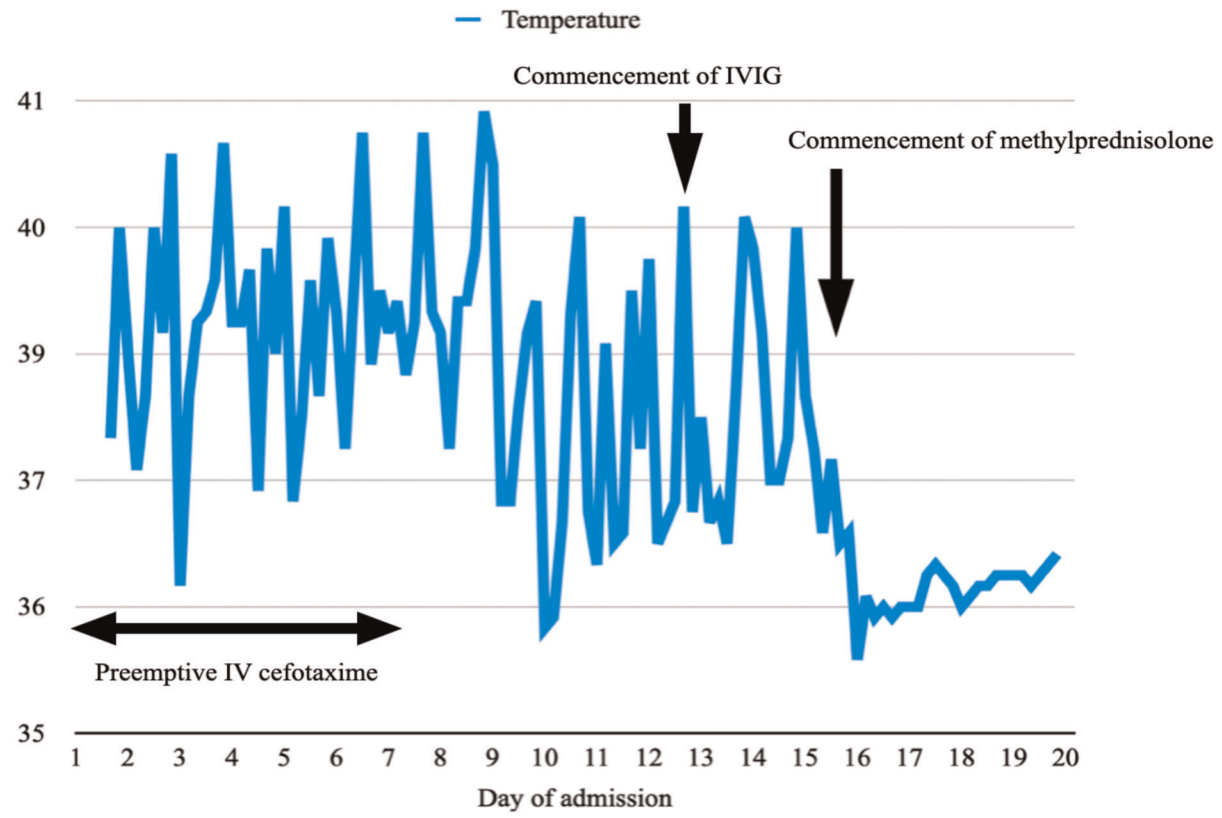

FIGURE 3
A temperature graph illustrating a remittent and intermittent fever, which persists despite a course of IV cefotaxime from day 1 to 7 of admission and IVIG on days 13 and 14. The fever settles promptly after the commencement of IV methylprednisolone on day 15 and does not recur.

review of 1,463 Brazilian pediatric patients demonstrated a similar prevalence of 9.8%. Hashimoto thyroiditis, autoimmune hepatitis and type 1 diabetes mellitus accounted for 29%, 18% and 15.9%, respectively. Other reported autoimmune diseases in lupus patients included antiphospholipid syndrome, autoimmune vitiligo, coeliac disease, Sjogren syndrome, autoimmune gastritis, primary sclerosing cholangitis and myasthenia gravis (4). Most patients were diagnosed with SLE within one year of symptom onset. Polyautoimmunity was associated with a higher hospitalisation rate and more aggressive immunotherapy use. However, it appeared to have no impact on the SLE activity and quality of life over time.

Research has identified several risk factors for developing polyautoimmunity. First, acute and chronic forms of stress facilitate the autoimmune process by increasing inflammatory markers in the blood. Stressed individuals were around three times more likely (95% Cl, 9.2 per 1000) to develop some form of autoimmunity vs. the non-stressed cohort (95% Cl, 2.99–3.25 per 1,000), as shown by the Swedish retrospective cohort study in 2018. In addition, they are more likely to develop multiple autoimmune diseases (5). The meta-analysis by Steptoe in 2017 suggested a modest increase in circulating inflammatory markers, including interleukin (IL)-1β, IL-2, IL-8, tumour necrosis factor (TNF)-α, C-reactive protein, interferon (IFN)-γ following laboratory-induced psychological stress (6) these elevated inflammatory markers exacerbated by stress may lead to multiple autoimmune diseases. Second, viruses, typically Epstein-Barr virus and cytomegalovirus, predispose the development of autoimmunity. There are two main hypotheses, namely molecular mimicry and bystander activation. In molecular mimicry, individual T cell exhibits receptors for both foreign and self-antigens. The T cell also attacks healthy body tissues when a foreign insult triggers it. This has consistently been linked to polyautoimmunity and multiple autoimmune diseases (7). Another hypothesis that explains how viruses predispose to autoimmune diseases suggests that a virus induces a systemic and non-specific activation of the immune system. This leads to an overexcitability state and autoreactive immunopathology. This is known as bystander activation (8). Third, the PTPN22 gene is responsible for regular T-cell receptor signalling pathways. Its mutation is an important factor in MAS. Familial autoimmunity is also a factor that is significantly associated with MAS. Individuals with a family history of autoimmune

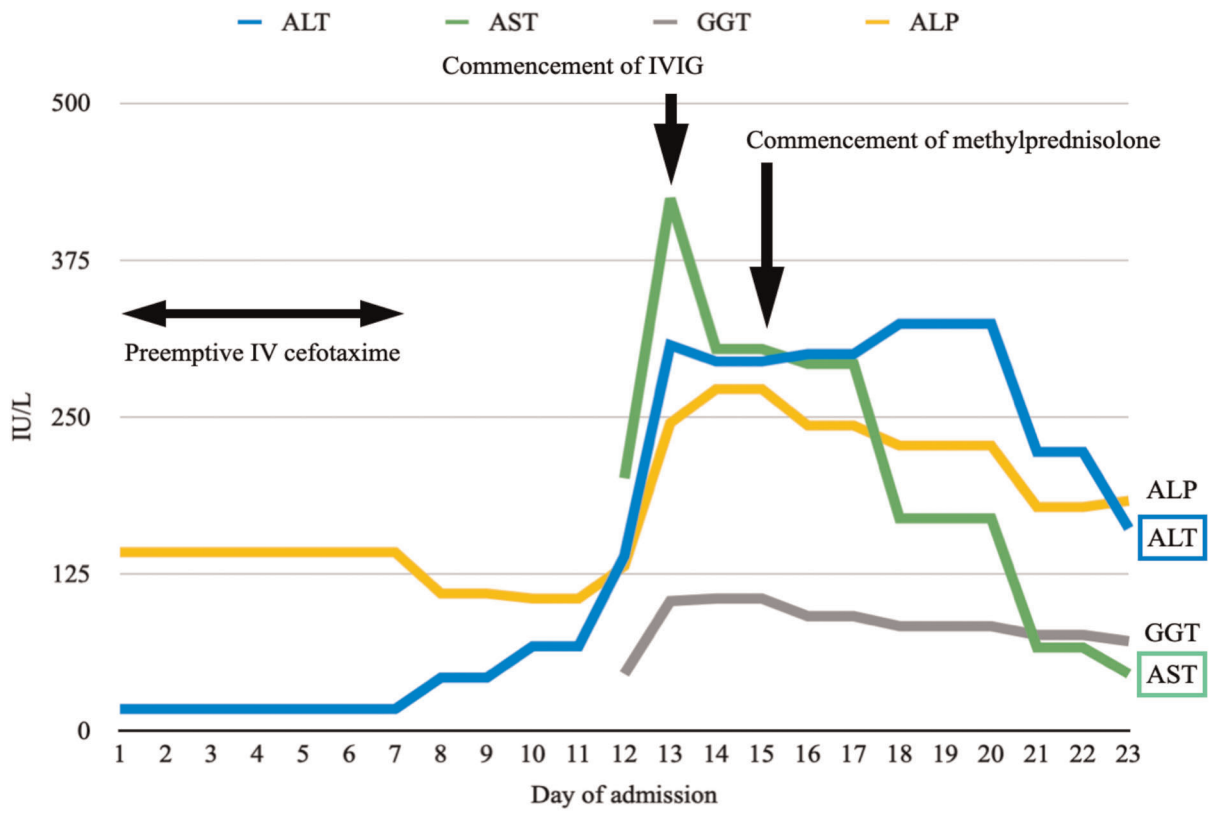

FIGURE 4
A graph illustrating the rise of predominantly ALT and AST since day 8 of admission. They show a downtrend after the commencement of IVIG on days 13 and 14 of admission. ALT elevates transiently after the commencement of methylprednisolone on day 15 before it drops again five days later. Both AST and GGT show a downtrend. ALP remains within the reference range throughout the whole of the admission.

disease, who are genetically susceptible to autoimmune diseases, stressed or infected with multiple viruses, have a significant risk of developing multiple autoimmune diseases. A whole genome sequencing may be considered in our patient.

Necrotising histiocytic lymphadenitis (Kikuchi disease) and childhood-onset SLE

Childhood-onset systemic lupus erythematosus (SLE) is a chronic autoimmune disease with heterogeneous manifestations. The incidence and prevalence are 0.3–0.9 per 100,000 children-years and 3.3–8.8 per 100,000 children, respectively (9). The median age of onset is between 11 and 12 years. About 80% of patients are female (10).

Lymphadenopathy is a common finding in SLE at some point during the course of the disease, but it is rarely the primary presenting feature. In most cases, no lymph node biopsy is performed; therefore, the histopathological diagnosis remains unknown. The only study in which a biopsy of lymphadenopathy associated with SLE was performed reported that 20% of cases displayed histological findings indistinguishable from Kikuchi disease (11).

Kikuchi-Fujimoto's disease, also known as histiocytic necrotising lymphadenitis, is a benign and self-limited disease that typically presents with cervical lymphadenopathy and fever. The disease was first described in young women from Japan by Kikuchi and Fujimoto in 1972 (12). The aetiology is not clearly known. The underlying pathogenesis is proposed to be an immune response to viruses due to its self-limiting clinical course and the lack of a neutrophilic response. A recent retrospective review of 98 children by *SN Selvanathan* et al. in 2019 showed a male predominance in children with a ratio of 1.13:1, different from that seen in adults. Laboratory findings are non-specific. Mild leukopenia occurs in 30%–70% of cases (13). Antinuclear antibodies (ANA) are positive at the time of diagnosis in 30% of cases (14). A lymph node biopsy is necessary for histopathological diagnosis. It typically shows patchy necrosis of the lymph node with surrounding foamy histiocytes.

The systemic review by Bernardo Sopeña in 2017 has identified 113 patients with Kikuchi disease associated with SLE (15). The patients ranged from 14 to 56 years old and are

commonly Asians. SLE was diagnosed before Kikuchi disease in 20 cases (18%), Kikuchi disease and SLE were simultaneously diagnosed in 58 cases (51%), and the onset of SLE occurred after that of Kikuchi disease in 35 cases (31%). The two diseases share a common clinical presentation. Lymphopenia is the most frequent hematological manifestation. While the diagnosis of Kikuchi's disease is histological, the diagnosis of SLE is based on a set of clinical and laboratory findings. In both conditions, a corticosteroid is commonly adopted as the cornerstone treatment. Other treatments have shown to be effective include hydroxychloroquine, intravenous immunoglobulin and rituximab in severe cases.

Our patient presents with pyrexia of unknown origin and predominantly cervical lymphadenopathy, which are common presentations of both Kikuchi disease and SLE. Despite the fact that he lacks the typical manifestations of SLE, including dermopathy, joint disease, neurological disorder and serositis, he fulfils one clinical criterion (leukopenia) and five immunological criteria (presence of ANA, anti-dsDNA, anti-cardiolipin, lupus anticoagulant, low complement 4 and positive direct Coomb's test) among the SLICC criteria for the diagnosis of SLE. The presence of hepatitis is more suggestive of SLE than Kikuchi disease. However, being the highly specific autoantibodies in SLE, anti-dsDNA is only mildly elevated at his initial presentation, and anti-Sm is absent. Instead, he has the presence of anti-RNP/Sm and rheumatoid factor, which are commonly present in mixed connective tissue disease and rheumatoid arthritis, respectively. Hence it is important to remain vigilant for an overlap syndrome with SLE, mixed connective tissue disease and rheumatoid arthritis.

Conclusion

This patient illustrated a rare combination of multiple autoimmune syndrome comprising type 1 diabetes, Hashimoto thyroiditis and childhood-onset systemic lupus erythematosus. Pediatrician should remain vigilant for multiple autoimmune syndrome and possible overlap syndrome as autoimmune diseases commonly share similar subphenotypes and non-specific autoantibodies.

Data availability statement

'The original contributions presented in the study are included in the article/Supplementary Materials, 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.

Author contributions

EYLK - 80%. MCIK -10%. WK-YC - 10%. All authors contributed to the article and approved the submitted version.

Conflict of interest

The 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 | Frontiers in Pediatrics

TYPE Case Report
PUBLISHED 18 November 2022
DOI 10.3389/fped.2022.1044007

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 14 September 2022
ACCEPTED 31 October 2022
PUBLISHED 18 November 2022

CITATION
Zanatta L, Biscaro F, Bresolin S, Marzaro M, Sarcognato S, Cataldo I, Marzollo A and Martelossi S (2022) Case Report: An early-onset inflammatory colitis due to a variant in *TNFAIP3* causing A20 haploinsufficiency.
Front. Pediatr. 10:1044007.
doi: 10.3389/fped.2022.1044007

Case Report: An early-onset inflammatory colitis due to a variant in *TNFAIP3* causing A20 haploinsufficiency

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Autoinflammatory diseases (AID) are a heterogeneous group of inherited conditions caused by abnormal activation of systems mediating innate immunity. Recent literature focuses on A20 Haploinsufficiency, an autoinflammatory disease with a phenotype resembling Behçet disease (BD). It is caused by *loss-of-function* mutations in *TNFAIP3* gene that result in the activation of a pro-inflammatory pathway. In this case report we describe a one-year-old baby who came to our attention for hematochezia appeared at three months of age which was considered an expression of early-onset colitis. The following appearance of cutaneous inflammation Behçet-like and the positive family history concurred with the diagnosis of an autoinflammatory disease. Extended genetic tests in the patient allowed to identify a heterozygous variant in *TNFAIP3* [NM_006290.4:c.460G > T, p.(Glu154Ter)], not previously described and not present in the GnomAD database. As a consequence the diagnosis A20 Haploinsufficiency was established and the appropriate management was started. The same *TNFAIP3* variant was also found in her father who had suffered from recurrent oral aphthosis, vitiligo and thyroiditis since childhood. In conclusion, we described a young patient with a novel heterozygous mutation in *TNFAIP3* who developed BD-like symptoms. We proposed that loss-of-function variants in *TNFAIP3* may be associated with a very early-onset intestinal BD phenotype.

KEYWORDS

colitis, haploinsuffciency, HA20, anemia, TNFAIP 3, autoinflammatory diseases (AID), autoimmune diseases (AD)

Abbreviations
AID, Autoinflammatory diseases; BD, Behçet disease; TNFAIP3, TNF Alpha Induced Protein 3.

10.3389/fped.2022.1044007

Introduction

Autoinflammatory diseases (AID) are a heterogeneous group of inherited conditions caused by abnormal activation of systems mediating innate immunity (1).

A20 Haploinsufficiency (HA20) is a recently described autoinflammatory disease with a phenotype resembling Behçet disease (1, 2). It is caused by loss-of-function mutations in the TNF *Alpha Induced Protein 3 (TNFAIP3)* gene encoding A20 that result in the activation of the pro-inflammatory pathway of nuclear factor (NF)-kB (3, 4).

Patients may present with dominantly inherited, early-onset systemic inflammation and a Behçet-like disease or a variety of autoinflammatory and autoimmune features (1, 2, 5).

In this case report, we describe a case of non-specific colitis as the first manifestation of A20 Haploinsufficiency.

Case report

A one-year-old caucasian baby girl came to our attention for severe normocytic anemia, without signs of hemodynamic failure. From 3 months of age, our patient had a history of hematochezia during exclusive maternal breastfeeding. This condition was diagnosed as allergic proctitis and a maternal diet free of milk and derivatives was started. The weaning was conducted in a dairy-free diet but a complete resolution never occurred (6, 7).

At admission to our Center, the first hypothesis was anemia due to gastrointestinal bleeding so the baby performed a colonoscopy, which revealed a macroscopic picture suggestive of colonic lymphoid nodular hyperplasia with ulcerated and bleeding mucosa (**Figures 1–3**).

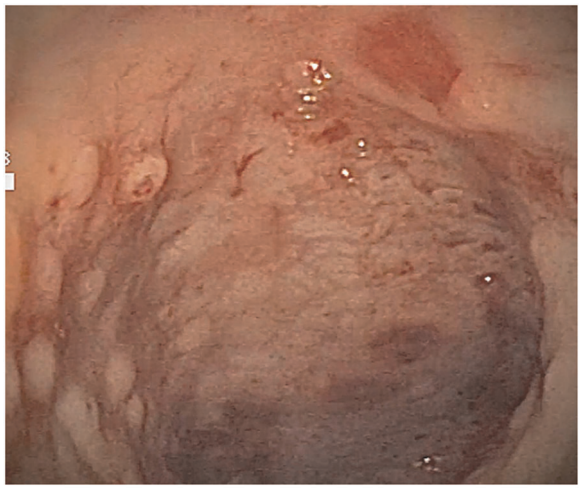

FIGURE 1
Ulcerated and bleeding colonic mucosa with petechial hemorrhages.

The histological examination revealed the presence of active colitis with no signs of chronicity and so the diagnosis of allergic colitis was excluded (**Figure 4**).

Since the genetic definition was not available, during the initial hospitalization we started only intravenous steroid therapy (methylprednisolone 2 mg/kg daily). At discharge, we continued an oral steroid therapy (betamethasone 0.2 mg/kg daily) without other immunosuppressive agents.

Moreover, in consideration of the low values of hemoglobin, she started an oral iron supplementation therapy and a gastroenterological follow-up was scheduled.

However, two weeks later, during steroid withdrawal, she came to the Emergency Room for acute panniculitis of the limbs without red flags (normal vital signs, good general condition with normal cardiovascular, thoracic and abdominal physical examination) and an anti-inflammatory therapy was prescribed.

After only 48 h the skin condition worsened and the patient became febrile and suffering. On physical examination baby girl presented ulcerative and necrotic lesions associated with painful edema of the limbs (**Figures 5–8**).

Therefore, she was hospitalized for further investigations and intravenous steroid therapy was started. Blood tests showed a rise in inflammation indexes (WBC 35,000/µl with neutrophils prevalence and CRP 28 mg/dl, serum amyloid 100 mg/L) but the exams for infectious disease and neoplastic conditions were all negative. First-level autoimmune tests (VES, complement system, immunoglobulins, TNF, lymphocyte subpopulations, ASCA and ANCA antibodies) were all normal. The biopsy of the skin lesions showed leukocyte exocytosis of the epidermis and histiocytic and

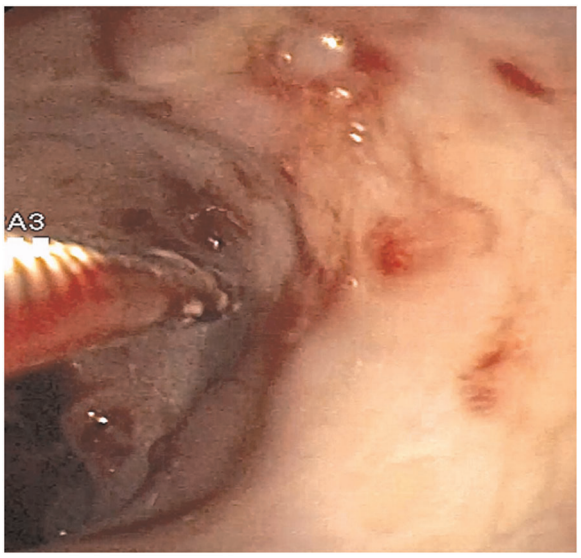

FIGURE 2
Fragile colonic mucosa with petechial hemorrhages.

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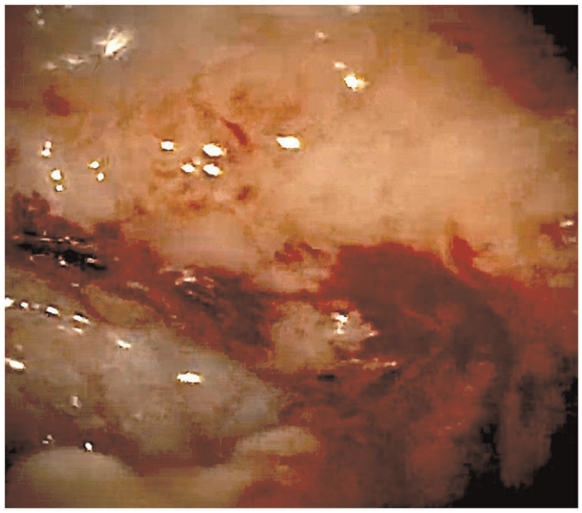

FIGURE 3
Bleeding colonic mucosa.

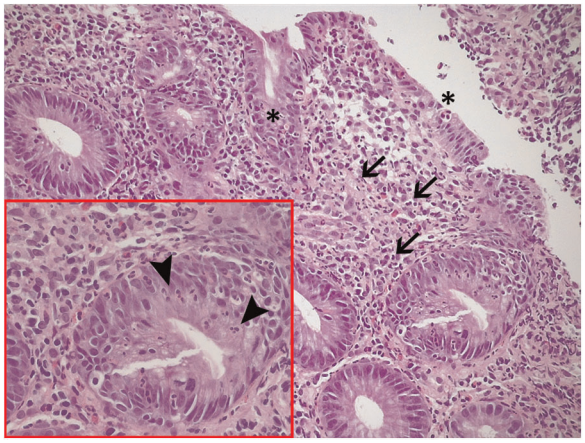

FIGURE 4
Histological examination of colonic biopsies: active colitis, with mucosal microerosions.(asterisks), a moderate inflammatory infiltrate in the lamina propria, including lymphocytes, plasmacells, and neutrophils (arrows), and an associated multifocal cryptitis, defined by the presence of intraepithelial neutrophils in colonic crypts (arrowheads in the box).

lymphocytic inflammation of the dermis. The eye examination was negative, in particular for uveitis. Fecal occult blood test (FOBT) turned out positive in three different samples and fecal calprotectin was elevated (>1,000 μg/g). IFN signature was normal and ADA-2 deficiency was excluded. Considering the laboratory exams and the early-onset gastrointestinal manifestations, the possibility of very early-onset inflammatory bowel disease (VEO-IBD) was evaluated so blood tests were performed but genetic studies were reported negative (8).

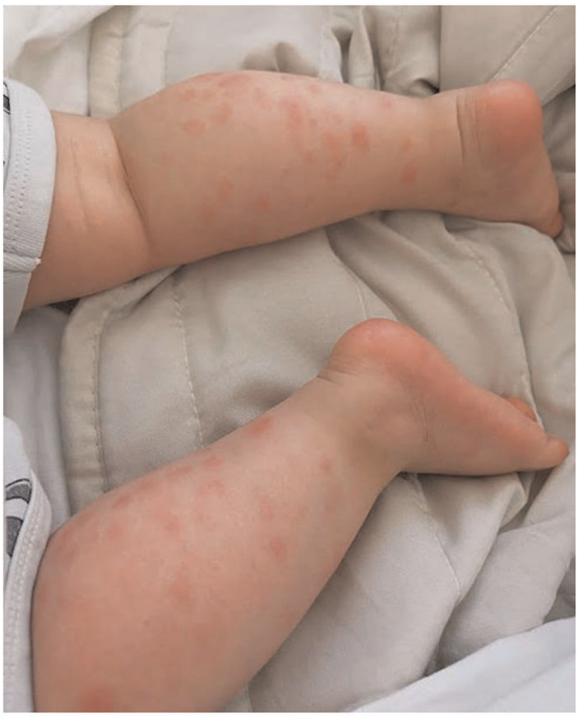

FIGURE 5
Panniculitis of the lower limbs.

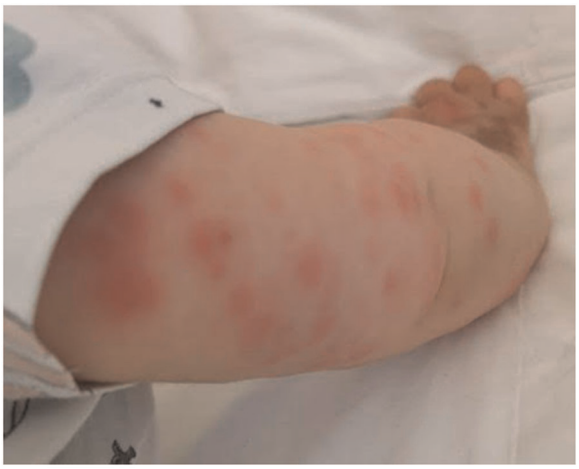

FIGURE 6
Panniculitis of the upper limbs.

The patients had a family history of autoimmune conditions that involved the paternal line: her father with recurrent oral aphthosis, vitiligo and thyroiditis, her father's brother with recurrent oral aphthosis and vitiligo, a paternal grandfather with liver disease started when he was young, brother of paternal grandfather died at 16 years old due to unknown disease and father's uncle with Crohn's disease.

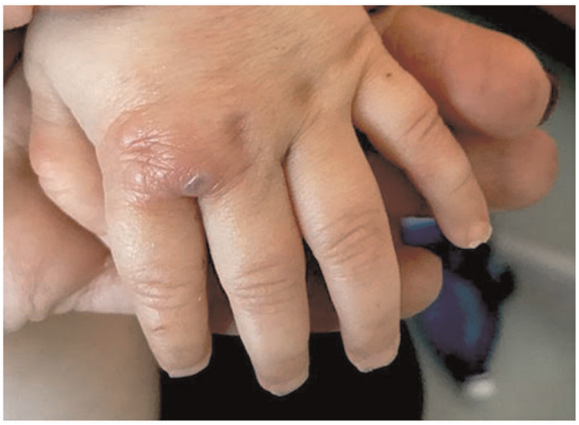

FIGURE 7
Ulcerative lesion of the hand.

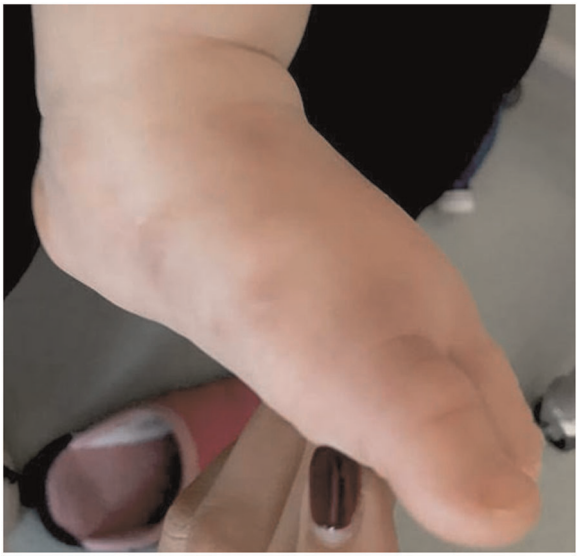

FIGURE 8
Necrotic lesion of the foot.

A custom gene panel sequencing including all genes included in the IUIS classification (9, 10) was employed to explore the genetic causes of the clinical phenotype, as previously described (11–13). We identified a heterozygous variant in *TNFAIP3*, namely NM_006290.4:c.460G > T, resulting in a premature stop codon *p*.(Glu154Ter). This variant was not previously described and is not present in the GnomAD database. Based on the characteristics of the variant, the genetic diagnosis of A20 haploinsufficiency was established. Additionally, a heterozygous known risk allele in *TNFRSF13B*, NM_012452.3:c.204dupA, p.(Leu69ThrfsTer12), was identified (14). Family segregation studies demonstrated the paternal origin of the *TNFAIP3* variant and the maternal origin of the *TNFRSF13B* allele. Family members truly screened for mutations in TNFAIP3 were the baby girl's mother and father. Later, the father's brother performed genetic test and identified the same mutations in TNFAIP3. The other family members in the paternal line presented potential clinical conditions of HA20 but could not be screened for mutations (**Figure 9**).

Initially, our patient was treated with a combination protocol, including systemic corticosteroids (betamethasone 0.1 mg/kg) and IL1 receptor antagonist (Anakinra from 2 to 6 mg/kg).

In consideration of the treatment-refractory disease with persistent gastrointestinal and skin manifestations, we shifted to an anti-TNF drug (Infliximab from 5 to 10 mg/kg, initially once a week and later every six weeks) in association with Methotrexate (7 mg once a week) (15).

Moreover, we decided to stop steroid therapy because of the important side effects (weight gain, changes in mood and behaviour, diabetes.).

After an initial resolution of clinical manifestations, two months later our patient presented a new relapse with unpainful skin lesions and widespread arthralgia. As a consequence, we decided to shift to Adalimumab (20 mg/kg every two weeks) in association with Methotrexate with good clinical response and rapid laboratory outcomes.

Skin and gastrointestinal manifestations resolved and blood tests known as inflammatory markers were negative, detecting a complete resolution of the inflammatory condition.

Discussion

HA20 is an autoinflammatory disease due to a loss of function of A20 protein, whose role is to down-regulate the pro-inflammatory pathway of NF-kB (3, 4). It is inherited as an autosomal dominant trait, with early-onset and with very heterogeneous expressivity even within the same family (1, 2, 5). This condition is often called Behçet-like, with which it shares some features: recurrent painful oral and/or genital ulcers, musculoskeletal pains such as polyarthritis and/or arthralgia, gastrointestinal involvement with abdominal pain or mucosal bleeding, cutaneous lesions, episodic fever and recurrent infections (1, 5, 15). This variability also affects therapy: treatment regimens should be based on disease severity but it is difficult because of the lack of standardized protocol (15, 16).

In our case, the disease appeared at 3 months of age with indeterminate early onset colitis and later skin manifestations started. Probably the father, the paternal uncle and the other members of the family in the paternal line present the same condition, but with later and milder manifestations.

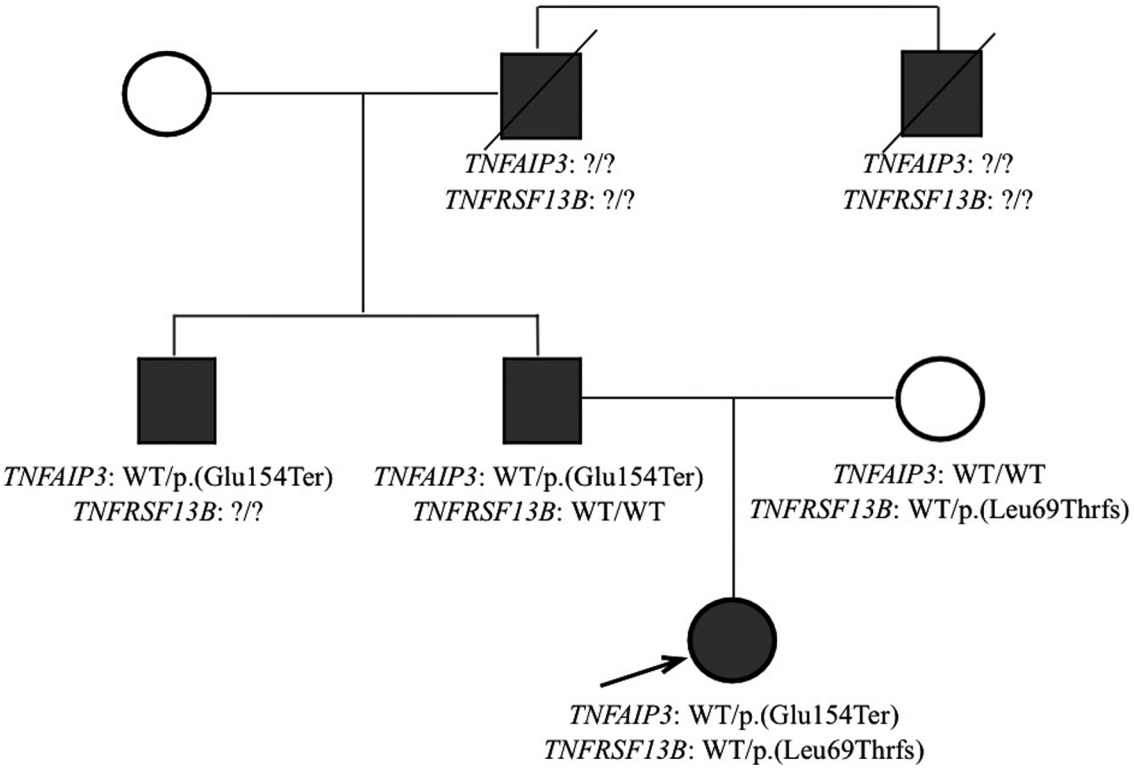

FIGURE 9
Family tree.

The variability of phenotypes in patients with HA20 is striking with a substantial difference also in the same family (16). In the family described here, the index patient presented with an infantile onset severe intestinal, joint and skin involvement, while the other affected family members presented later in life, with less severe clinical manifestations. We speculate that the coexistence of the maternally inherited risk allele in *TNFRSF13B* might have contributed to disrupting a potential compensatory mechanism in adaptive immunity. Indeed, digenic inheritance has been described in patients with proteasome-associated autoinflammatory syndromes (PRAAS) and relatively common genetic variants can act as disease modifiers (17).

In literature our patient's clinical presentation, characterized by colitis and cutaneous manifestations, was already mentioned. Nevertheless, such important symptoms and the very early onset are two rare aspects, not described in other works.

According to the literature, patients with A20 Haploinsufficiency require treatment but at the moment a standardized therapeutic approach does not exist and every patient needs an individual treatment regimen (16). Some patients receive immunosuppressive drugs, others anti-cytokine agents and patients with severe disease go into haematopoietic stem cell transplant.

Based on studies, because of the very early-age of onset, the primary treatment is anti-interleukin 1 (Anakinra) but the remission was partial. Then we attempted to use TNF-antagonist (Infliximab) and Methotrexate with a temporary response. Finally, we shifted to Adalimumab and Methotrexate with rapid and good outcomes (15, 16). As far as concern therapeutic strategy, an interesting work reported that a type I interferon (IFN) signature or elevation of IFN-stimulated genes (ISGs) predicts a positive response to JAK-inhibition. In our case, this could not be applied because the interferon signature of the patient was normal (18).

Conclusion

In conclusion, we presented a HA20 patient with gastrointestinal BD-like symptoms and identified a novel heterozygous variant (c.460G > T, p.Glu154Ter) in *TNFAIP3*.

Based on our observation, HA20 should be considered in patients with infantile and very early-onset mucosal or cutaneous inflammation, especially with positive family history and genetic screening for *TNFAIP3* could be evaluated for patients with BD-like symptoms.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the individual (s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

FB: conceived the idea for this case report, coordinated the research group and critically reviewed the manuscript. LZ drafted the initial manuscript, reviewed and revised the manuscript and reviewed the literature. AM and SB contributed to the acquisition and interpretation of the data, drafted the manuscript and critically reviewed the manuscript. SM coordinated and supervised data collection, and critically reviewed the manuscript. MM contributed to the acquisition of the macroscopic images of the colonoscopy, SS and IC provided the histological examination of colonic biopsies. All authors contributed to the article and approved the submitted version.

Conflict of interest

The 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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TYPE Case Report
PUBLISHED 30 November 2022
DOI 10.3389/fped.2022.976751

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 23 June 2022
ACCEPTED 04 October 2022
PUBLISHED 30 November 2022

CITATION
Mauro A, Casini F, Congedo EC, L'assainato S, Pinto F, Ansuini V, Mascolo R, Pedroli A and Bernardo L (2022) Recurrent pericarditis in a patient with Bardet–Biedl syndrome: A case report.
Front. Pediatr. 10:976751.
doi: 10.3389/fped.2022.976751

Recurrent pericarditis in a patient with Bardet–Biedl syndrome: A case report

Angela Mauro[1]*, Francesca Casini[2], Emanuele Chittano Congedo[2], Sara L'assainato[2], Francesca Pinto[3], Valentina Ansuini[1], Ruggiero Mascolo[4], Alice Pedroli[4] and Luca Bernardo[3]

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Bardet–Biedl syndrome is a rare autosomal recessive disorder characterized by rod-cone dystrophy, renal dysfunction, obesity, learning difficulties, hypogonadism, polydactyl, and many other minor features that can affect the cardiovascular, locomotive, neurological, and endocrine systems. We report the case of a 16-year-old boy affected by Bardet–Biedl syndrome who presented with recurrent pericarditis with an optimal response to treatment with Anakinra. To our knowledge, this is the first description of an association between Bardet–Biedl syndrome and recurrent pericarditis.

KEYWORDS

Bardet–Biedl syndrome, recurrent pericarditis, anakinra, autoinflammatory disease, children

Introduction

Bardet–Biedl syndrome (BBS) is a rare autosomal recessive genetic disorder that belongs to the group of ciliopathies. According to the modified diagnostic criteria by Beales et al. (**Table 1**) (1), at least four primary features, or three primary features and two secondary features, are required to make a diagnosis. The syndrome can be suspected as early as during pregnancy, by the presence of polydactyly and structural renal abnormalities during prenatal imaging (2). The suspicion can be confirmed by genetic analysis. As for cardiovascular anomalies, aortic stenosis, situs inversus, left ventricular hypertrophy, patent ductus arteriosus, and unspecified cardiomyopathy may be found (3). Associations between BBS and recurrent pericarditis (RP) have not been described in the literature thus far. Herein, we discuss the case of a 16-year-old child affected by BBS with RP treated with anakinra.

Case presentation

A. is a Tunisian 16-year-old boy with BBS characterized by retinitis pigmentosa, polydactyly of the left foot, kidney cysts, and learning difficulties. His parents were

TABLE 1 Diagnostic criteria for Bardet–Biedl syndrome (BBS).

Primary features	Secondary features
Retinal dystrophy	Nephrogenic diabetes insipidus
Polydactyly	Developmental delay
Renal structural abnormalities	Speech defects/delay
Hypogonadism in males	Mild spasticity (mainly lower limbs)
Obesity	Imbalance/poor coordination/ataxia
Learning difficulties	Diabetes mellitus
	High arched palate/missing teeth/dental crowding/ short roots
	Brachydactyly/syndactyly
	Astigmatism/cataracts/strabismus
	Hepatic fibrosis
	Left ventricular hypertrophy/congenital heart disease.

not consanguineous, and, in his family, there are no other cases of BBS. He presented with the first episode of pericarditis at the age of 12 years, which was successfully treated with only colchicine (1 mg/day) at another hospital in Tunisia. An echocardiography was performed that showed a pericardial effusion of 4–5 mm. During this episode, a pericardiocentesis was not carried out. He continued colchine for 3 months. Later, in Italy, he presented with three further recurrences of pericarditis, at intervals of 1 year, treated with colchine (0.5 mg/day) and ibuprofen (600 mg/day) three times a day, which was progressively decreased to 200 mg/day twice a day. During the last episode, due to the presence of a large pericardial effusion, he underwent a pericardiocentesis with the evacuation of 900 ml of serum-hematic liquid. The culture and cytological examinations of the pericardial fluid were negative. He was treated with colchicine (1 mg/day) and ibuprofen (1,800 mg/day), which were progressively reduced to 600 mg/day. The patient came to our attention at the age of 16 years for retrosternal pain. On his first visit, his blood pressure was 130/90 mmHg with negative cardio-thoracic and abdominal physical examinations. Blood tests were carried out [complete blood count, erythrocyte sedimentation rate (ESR), PCR, troponin, liver and kidney function, electrolytes], which were in the normal ranges. An echocardiogram showed the presence of a minimal effusion of the free pericardium wall (5 mm) with the presence of fibrin. He was treated with colchicine (1 mg/day), indomethacin (150 mg/day, gradually tapered to 75 mg/day), and prednisone (5 mg/day). After 2 months, he returned to our department with chest pain, which worsened with movement. On physical examination, the patient was in fairly good general condition, his blood pressure was 150/90 mmHg, and his heart rate was 110 beats/minute. The cardio-thoracic and abdominal physical examination results were negative. Blood tests were carried out and showed an increase in inflammation index [C-reactive protein (CRP) 170 mg/L, ESR 80 mm/h) and white blood cell count 10,750/mm^3, and neutrophils 7,920/mm^3. Anti-nucleus antibodies, ENA antibodies, anti-phospholipid antibodies, fecal calprotectin, viral serologies, and Mantoux tests were all negative. Both chest x-ray and electrocardiogram were negative, and an echocardiogram revealed the presence of pericardial effusion (20 mm). Since the pericarditis was cortico-dependent and colchicine resistant, he started therapy with Anakinra (100 mg/day). The patient quickly showed an improvement in clinical, laboratory, and instrumental conditions. For this reason, prednisone, indomethacin, and colchicine were progressively tapered and finally discontinued. The patient had no other relapses. At his last visit, the patient appeared in good general condition; he had no dyspnea or thoracic pain. He underwent blood tests, electrocardiogram, and echocardiography, all with results in range. In fact, he continues to take Anakinra at a dose of 100 mg/day.

Discussion

BBS is a rare autosomal recessive multisystem ciliopathy. The incidence of BBS is 1 in 150,000–160,000 in Europe and North America (2) but seems to be higher in Kuwait and the Faroe Islands, where it can reach 1:17,000 and 1:3,700, respectively (4).

BBS is caused by a dysfunction of the gene coding for proteins that are implicated in the function of the primary cilia and in important signaling pathways (5).

Genetic confirmation of the diagnosis can be obtained by sequencing BBS genes. However, access to such sequencing is usually restricted due to genetic heterogeneity and excessive cost, especially in low-income countries. In fact, 21 causing genes (BBS1–BBS21) have been identified and, in particular, BBS1 and BBS10 are the most frequently involved.

In the literature, cardiac involvement in BBS is usually linked to congenital heart disease but acquired heart diseases, such as pericarditis, are extremely rare. Moreover, to date a correlation between BBS and rheumatological or autoinflammatory diseases has not been described.

Our patient presented four primary features that were in accordance with the classification by Beales et al., and a history of RP.

According to the European Society of Cardiology, pericarditis can be defined as a clinical and acute inflammatory pericardial syndrome and involves at least two of the following criteria: pericardial rubs (30% in the pediatric population); chest pain (90%–95% in the pediatric population); ECG changes (40%–50% in the pediatric population); pericardial effusion (70%–80% in the pediatric population); pericardial inflammation at imaging, and elevated inflammatory markers.

Acute pericarditis can reappear and can lead to RP, described as a recurrence of acute pericarditis after a first episode with a symptom-free interval of at least 4–6 weeks (6). In children, about 70% of cases of RP are regarded as idiopathic and are usually a diagnosis of exclusion (7). Other possible causes of RP are infections (adenovirus, enterovirus, influenza A, cytomegalovirus, human herpesvirus-6, parvovirus, Epstein–Barr virus), connective tissue diseases, vasculitis, sarcoidosis, inflammatory bowel diseases, autoinflammatory diseases such as Familiar Mediterranean Fever, TNF receptor-associated periodic syndrome, or post-cardiac injury (7).

The exact pathogenesis of RP is still unclear and potentially multifactorial. The main hypothesis is that RP is caused by an interaction between genetic predisposition, environmental factors, and the immune system. Triggers of recurrence are still unknown. Some studies have assessed a loss of immune tolerance toward pericardial antigens in the initial episodes, which can cause other relapses, suggesting a central role in adaptive immunity and autoimmunity (8, 9).

Contextually, Tsyklauri et al. suggested that patients with BBS have a higher prevalence of autoimmune disorders as a result of transport complex BBSome dysfunction, which also regulates the development and homeostasis of B cells leading to an increased number of immature cells and few mature B cells. In addition, as the BBsome is involved in leptin signaling, which regulates the immune system and prevents overreacted immune responses, its deficiency leads to a dysfunction of immunity (10–12).

In our patient, viral serologies, autoantibodies, and Mantoux test were all negative. He underwent clinical (chest pain), inflammatory (elevated CRP), and echocardiographic (pericardial effusion) tests, which produced evidence of the presence of pericarditis. The episodes were all separated by at least 2 months, with a complete resolution of clinical and instrumental cardiac findings with anakinra, suggesting that unidentified autoinflammatory-mediated mechanisms can play a role in RP.

Tombetti et al. reported that phenotypes of RP with a remarkable response to anti-interleukin 1β (anti-IL1β) therapies, such as anakinra, could have the same pathogenesis as other autoinflammatory diseases. IL1β represents a fundamental marker of the immune pathways, such as the last step of the activation of inflammasome (7).

The excellent response to treatment with anakinra in our patient reinforces the hypothesis that many pediatric cases of RP could have an underlying unknown autoinflammatory mechanism.

Moreover, anti-IL1β could be an effective alternative treatment for those patients with RP with frequent relapses with other therapies, such as colchicine or steroids.

However, we did not perform genetic screening for anti-inflammatory diseases.

To our knowledge, this is the first case of BBS associated with RP. This relationship is particularly interesting as it indicates a new possible feature associated with BBS.

Therefore, physicians should be aware of a pericardial involvement in patients with BBS. Further studies are needed to confirm this relationship and the mechanisms behind this phenomenon, especially in children.

Conclusion

We presented a case of RP in a child with BBS, who optimally responded to anakinra, suggesting a probable autoinflammatory origin of RP.

Is RP a new manifestation of BBS or a form of autoinflammatory pericarditis associated with it?

Data availability statement

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

Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conceptualization: AM, FC, SL, ECC, FP, VA, RM, and AP. Data curation: AM, FC, SL, ECC, FP, VA, RM, and AP. Methodology and project administration: AM, FC, SL, and ECC. Supervision: LB. Original draft: AM, FC, SL, and ECC. Review and editing: AM, FC, SL, ECC, FP, VA, RM, AP, and LB. All authors contributed to the article and approved the submitted version.

Acknowledgments

We would like to thank all the staff who contributed to this case.

Conflict of interest

The 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.

Publisher's note

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frontiers | Frontiers in Pediatrics

TYPE Case Report
PUBLISHED 06 December 2022
DOI 10.3389/fped.2022.1014536

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 08 August 2022
ACCEPTED 17 November 2022
PUBLISHED 06 December 2022

CITATION
Frkovic M, Kujundzic M, Cavka M and Jelusic M (2022) Successful use of adalimumab as a conservative treatment for bilateral knee lipoma arborescens in patient with psoriatic juvenile idiopathic arthritis – case report and review of literature.
Front. Pediatr. 10:1014536.
doi: 10.3389/fped.2022.1014536

Successful use of adalimumab as a conservative treatment for bilateral knee lipoma arborescens in patient with psoriatic juvenile idiopathic arthritis – case report and review of literature

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Lipoma arborescens (LA) is a chronic, slowly progressive intra-articular mass associated with the proliferation of synovial villi. It can affect one or several joints and has been commonly described in adults with degenerative joint disease. Most patients have been diagnosed with MRI and/or biopsy findings and are usually treated with partial or total synovectomy. Case reports of LA in children, particularly with juvenile idiopathic arthritis (JIA) are scarce. We present a 16-year-old girl with a prolonged course of psoriatic JIA (initial bilateral knee affection and subsequent involvement of wrists and elbows combined with psoriatic scalp lesions) and LA of both knees. Psoriatic JIA has been diagnosed at the age of 13, with immediate start of methotrexate (MTX) therapy. Several weeks later, magnetic resonance imaging (MRI) of the right knee, performed with the aim of the most swollen joint additional evaluation, revealed synovial changes consistent with LA; arthroscopic biopsy confirmed the diagnosis. After two years of MTX treatment, despite the successful maintenance of minimal JIA activity except for repetitive bilateral knee swelling, control MRI revealed bilateral knee lesions identical to those described two years earlier in the right knee. Following the step-up approach in JIA treatment, the TNF inhibitor adalimumab was added in therapy. Finally, six months later, clinical reduction of both knees swelling was noticed with almost complete LA regression in the right, and partial regression in the left knee, confirmed by final MRI control. A conservative approach, including TNF inhibitors, instead of usually performing synovectomy, seems like a reasonable option in cases of LA with underlying JIA.

KEYWORDS

juvenile idiopathic arthritis, lipoma, magnetic resonance imaging, TNF inhibitor, adalimumab, synovectomy

10.3389/fped.2022.1014536

Introduction

Lipoma arborescens (LA) is a rare, intra-articular lesion characterized by subsynovial villous proliferation of mature adipocytes (1–15). Despite its obscure etiology, it is considered a nonspecific reactive response to chronic synovial irritation (1–6, 8, 10, 15). LA is usually unilateral, with the suprapatellar pouch of the knee as the most common site of involvement (1–7, 9–11). It may also affect other joints, as well as extra-articular sites such as periarticular bursae and tendon sheaths (1, 2, 4–6, 9, 10). Slowly progressive painless swelling of the affected joint/s and episodes of joint effusion is the typical presentation (1, 2, 4, 5, 8, 9, 11, 13). MRI is the gold standard for evaluation of LA, but the definite diagnosis is usually confirmed by histological examination (1–3, 5–9, 11, 12, 14). Synovectomy is the treatment of choice and recurrences are uncommon (2, 3, 5–9, 14, 15).

Although the pathogenesis of JIA, as the most common rheumatic disease of the childhood, is closely associated with chronic synovitis, there are only several reports of LA in JIA patients (13–16). Despite the rare occurrence, LA should be considered a differential diagnosis of persistent joint/s swelling in children, adolescents, and adults in general, and in a subpopulation of consistently treated JIA patients (1, 2, 5–8, 11, 14, 17).

In this paper we present a 16-year-old patient with a prolonged course of psoriatic JIA and bilateral knee LA. We also consider contemporary perspectives on the LA diagnostic algorithm, differential diagnosis and disease outcome with particular emphasis on anti-inflammatory treatment options.

Case presentation

A 16-year-old girl was referred to our pediatric department for the first time at the age of 13, with a 10-year history of bilateral knee swelling combined with progressive motion range reduction but without morning stiffness or mechanical symptoms, such as locking, catching, and giving way and subacute development of symmetrical elbow and wrist swelling with prolonged morning stiffness along with multiple erythematous-squamous scalp lesions for the past few months (**Figure 1**).

The first physical examination demonstrated significant, diffuse, painless swelling of both knees (more prominent right) with reduced flexion up to 30 degrees, and less extensive, painless, symmetrical elbow and wrist swelling without limited range of motion. Several erythematous-squamous lesions, 1 cm to 3 cm in diameter, were detected on the scalp with no hair loss.

Laboratory findings were unremarkable other than low-positive ANA titer. x-ray and US evaluation of the clinically affected joints showed para-articular osteopenia with irregularly shaped epiphyseal ossification centers and synovial

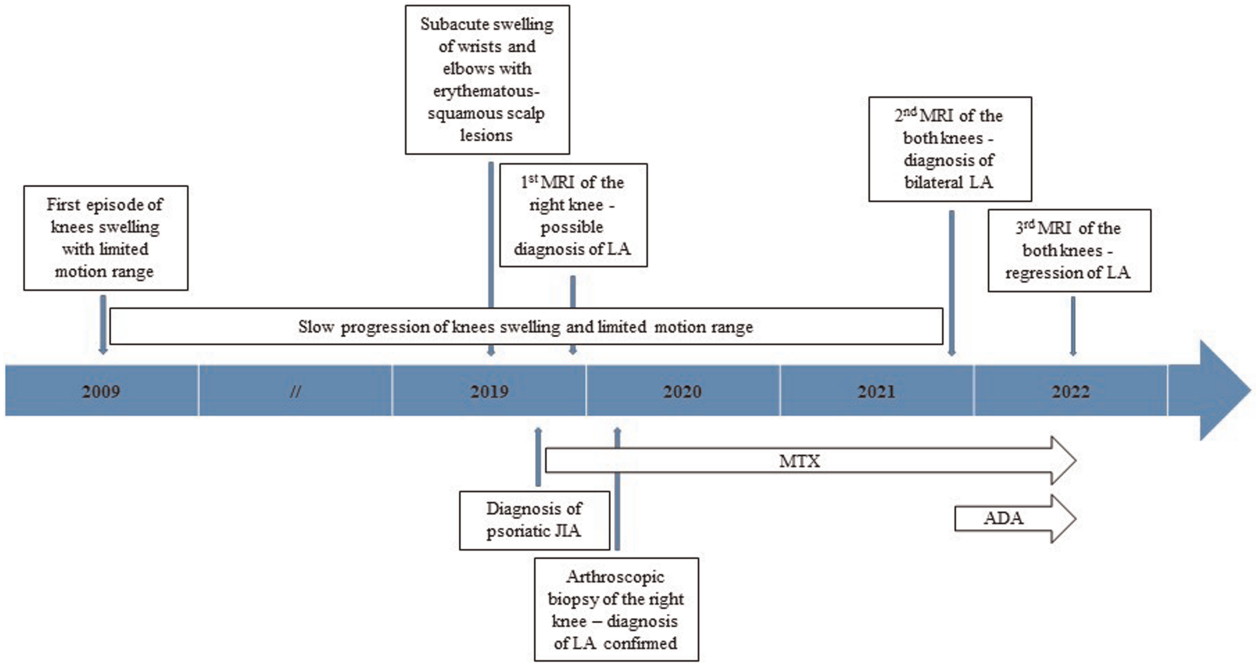

FIGURE 1
Diagram of disease progression, diagnostic evaluation, and therapeutic interventions.

10.3389/fped.2022.1014536

hypertrophy with joint effusion, respectively. Diagnostic needle aspiration of the right knee was performed, and 15-ml yellowish, jelly-like material with cytological signs of chronic inflammation was obtained.

According to the results of the diagnostic evaluation, a diagnosis of psoriatic JIA has been established.

Beside the knee intra-articular steroid injection, treatment included subcutaneous methotrexate (MTX) 15 mg/m^2 (20 mg) weekly and intensive physiotherapy. A complete clinical resolution of all affected joints followed the therapy introduction within several weeks, except for the persistent swelling of the knees. Diagnostic evaluation was completed with the contrast enhancement MRI of the more prominent swollen right knee. It depicted extended intra-articular synovial proliferation with fat inclusions, multiple marginal bony erosion of the proximal tibia, both femoral condyles and patella along with altered morphology of both menisci (**Figure 2A**). A diagnosis of chronic synovitis with LA was

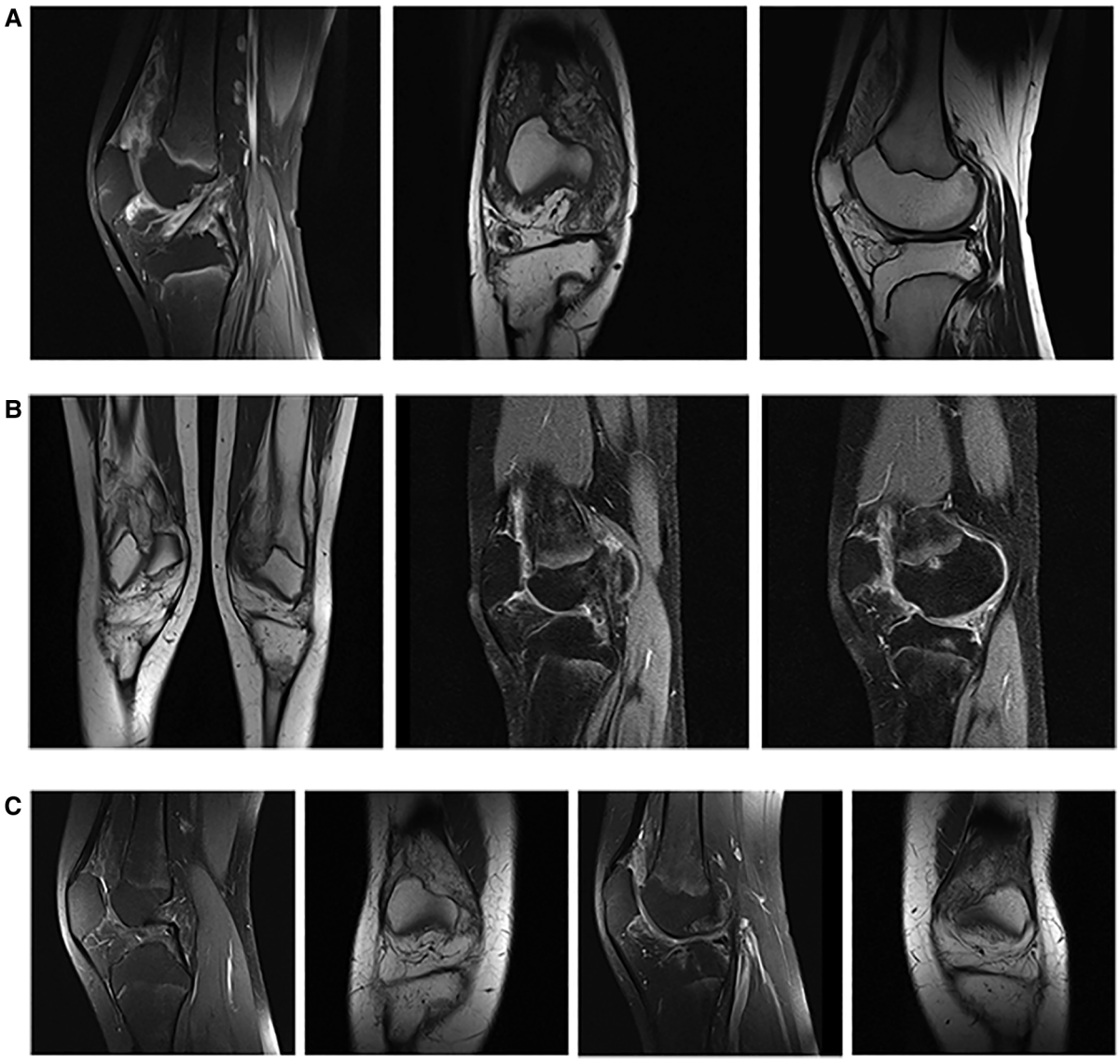

FIGURE 2
Imaging examinations. (**A**) Initial MRI scanning of the right knee [MRI Proton Density with Fat Saturation (PDFS), sagittal plane; MRI T1 weighted image, coronal plane; MRI T1 weighted image, sagittal plane] showed the extended intra-articular synovial proliferation with fat inclusions combined with multiple marginal bony erosion of the proximal tibia, both femoral condyles and patella along with altered morphology of both menisci. (**B**) Control MRI of both knees (MRI T1 weighted image, coronal plane; MRI Proton Density with Fat Saturation (PDFS), sagittal plane, right; MRI Proton Density with Fat Saturation (PDFS), sagittal plane, left) performed after 2 years of MTX therapy with almost the same, bilateral lesions as one on the initial MRI of the right knee. (**C**) Second MRI control of both knees [MRI Proton Density with Fat Saturation (PDFS), sagittal/coronal plane, right/left] with almost complete regression of the synovial proliferation in the right, and partial regression in the left knee after 6 months of TNF inhibitor therapy.

considered. Histological analysis of the specimens obtained by arthroscopic biopsy revealed hypertrophic synovium covered with 2–3 lines of synovial cells and stromal lobules of mature adipocytes with focal inflammatory infiltration—finding consistent with LA and underlying chronic synovitis.

Considering the young age of our patient and the diagnosis of psoriatic JIA, as a chronic, inflammatory underlying disease, conservative and expectative approach concerning the LA was preferred. The patient received the prescribed therapy regularly but was lost from the regular follow-up for the next year and the half. Fortunately, minimal disease activity of psoriatic JIA was successfully maintained during the specified period, without signs of arthritis of the affected joints, except the fluctuating bilateral knee swelling with reduced flexion up to 20 degrees. Control MRI of both knees at the age of 15 revealed almost the same, bilateral lesions similar to one described on the initial MRI of the right knee (**Figure 2B**).

Following the step-up approach of JIA treatment, TNF inhibitor—adalimumab was finally introduced. Within the next 6 months, bilateral knee swelling, and reduced flexion improved with almost complete LA regression in the right, and partial regression in the left knee, confirmed by final MRI control (**Figure 2C**). At the last visit the patient is satisfied with the general improvement of her condition, able to regularly conduct her daily activities with restrictions in terms of avoiding physical overloads.

Discussion

Although the etiology and pathogenesis of LA has not yet been well defined, according to most authors, it is primarily related to chronic synovial irritation, particularly in cases of osteoarthritis or previous trauma as the triggering factors (1–7, 15). During the last decade a growing number of reports advert the inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis or psoriasis, autoimmune uveitis and different types of JIA, as possible underlying conditions related to the development of LA (2, 4–6, 10, 14, 15). Simultaneously, most authors are doubtful about the success of anti-inflammatory therapy related to LA in patients with inflammatory diseases, and frequently recommend synovectomy as a standardly used, definitive treatment (12–15).

LA has rather low incidence, and up till now around only 200 cases have been reported in adults and children (3). The incidence of LA among children and adolescents, particularly with inflammatory diseases, is extremely low (10, 11). A couple of dozen childhood cases have been reported to date; however, all authors have described only one or two patients for each study (7–18). Among these, there are only a few explicit cases of commonly unsuccessful conservative therapy of LA in children with JIA (11–16) (**Table 1**). Cil et al. and Bouayed et al. reported two similar cases of 13-year-old girls with bilateral knee LA initially diagnosed with oligoarticular JIA and unsuccessfully treated with an unspecified dose of MTX for 8 years and with MTX 25 mg weekly for year and a half, respectively (11, 12). Zeybek et al. presented a case of partially successful MTX treatment in a 17-year-old girl with a 5-year history of JIA and bilateral knee LA. The girl was finally scheduled for arthroscopic synovectomy (13). Xue et al. reported a 16-year-old girl with a 4-year history of juvenile spondyloarthritis and bilateral knee LA diagnosed during the treatment with TNF inhibitor etanercept 25 mg weekly, subsequently coupled with MTX 10 mg weekly (14). Batu et al. described an 11-year-old boy with a 4-year history of psoriatic arthritis initially treated with an unspecified dose of MTX weekly and coupled with also unspecified dose of etanercept weekly a year later due to the disease flare. Bilateral

TABLE 1 Summary of lipoma arborescens reported cases in children with juvenile idiopathic arthritis.

Author (year)	Age, sex	Diagnostic procedures	Comorbidities	Localization of LA	Initial (conservative) therapy	Surgical therapy	Outcome
Cil A et al. (2005)	13, F	MRI, biopsy	JIA	Knees	MTX, NSAID	Arthroscopic synovectomy	Complete resolution
Bouayed K et al. (2017)	13, F	MRI, arthroscopic biopsy	JIA	Knees	NSAID, MTX	–	Partial relief from symptoms
Zeybek GE et al. (2019)	17, F	MRI	JIA	Knees	sulfasalazine, intra-articular glucocorticoid, MTX	Arthroscopic synovectomy in perspective	Partial relief from symptoms
Xue J et al. (2013)	16, F	MRI, arthroscopic biopsy	JIA—jSpA	Knees	sulfasalazine, MTX, etanercept	Arthroscopic synovectomy	Complete resolution
Batu ED et al. (2020)	11, M	MRI	Psoriatic JIA	Knees	NSAID, MTX, etanercept, intra-articular glucocorticoid	Arthroscopic synovectomy	Complete resolution
Dail CS et al. (2020)	16, M	MRI, biopsy	JIA	Right knee and elbow	naproxen, MTX	Partial synovectomy of the right knee	Partial relief from symptoms

MRI, magnetic resonance imaging; JIA, juvenile idiopathic arthritis; jSpA, juvenile spondyloarthritis; LA, lipoma arborescens; NSAID, nonsteroidal anti-inflammatory drugs; MTX, methotrexate.

knee LA was discovered after subacute knees swelling during the therapy course (15).

MRI in JIA is recommended during the diagnostic work-up and/or, over the disease course, in case of any doubt about an alternative diagnosis (1, 2, 5, 6, 9, 10, 12, 14). In the case of LA, MRI findings usually allow accurate identification as well as evaluation of size and grade. LA typically presents as frond-like areas of proliferation that have signal characteristics isointense with subcutaneous fat. The hypertrophied subsynovial fatty tissue does not enhance while the overlying synovium often shows diffuse enhancement after intravenous contrast administration (1, 4, 5, 14–17). Besides the typical characteristics of LA, the adipocytes may incompletely replace the synovial tissue, so atypical MRI findings with dominant synovial proliferation or irregular mixture of synovial and fatty tissue may also be observed (1, 14). Because of the possible atypical LA presentation and other differential diagnoses, histopathological examination of the specimen obtained by needle or arthroscopic biopsy is usually recommended as a confirmative diagnostic procedure (2, 6, 14, 17). In all above-mentioned cases of unsuccessful conservative therapy of the underlying JIA, LA was confirmed by the combination of MRI and histopathological analysis. In majority of reports of LA in children, including those with unsuccessful anti-inflammatory therapy, symptoms were resolved after arthroscopic synovectomy (**Table 1**).

Our patient was almost simultaneously diagnosed with psoriatic JIA and initially right knee LA, suspected by MRI and confirmed by arthroscopic biopsy, with immediate start of MTX 20 weekly as a standard therapy of psoriatic JIA. Two years later, MRI performed due to the persistent bilateral knee swelling, revealed symmetrical LA. Additional therapy with the TNF inhibitor adalimumab, 40 mg weekly during the next 6-month period resulted in clinical and MRI regression of both knees swelling and LA lesions, respectively.

Since this was the first case of LA in the 40-year history of our department (among 80–100 newly diagnosed cases of JIA per year), and due to unspecific description of initial MRI, we used the conventional diagnostic approach and confirmed the diagnosis of LA by arthroscopic biopsy. Some recent papers propose only MRI evaluation in cases of typical LA imaging, to avoid the biopsy as an invasive diagnostic procedure (1, 2, 5, 8, 11, 14).

We based our treatment approach on the commonly accepted opinion on the secondary development of the LA on the possible basis of the underlying inflammatory diseases (in our case psoriatic JIA) which are otherwise successfully treated with anti-inflammatory drugs, including TNF inhibitors. Additionally, Fraser et al. demonstrated that LA tissue itself might release TNF, which contributes to joint inflammation and therefore could theoretically be also susceptible to the action of TNF inhibitors (19).

Except our case, the only similar report of successful anti-inflammatory therapy in an adolescent with LA and underlying JIA was presented by Dail et al. They described a 16-year-old boy with LA of the right knee and right elbow combined with elevated levels of inflammatory markers, suggesting underlying inflammatory synovitis, in particular JIA. MTX was prescribed with satisfying therapy effects within several weeks. The same success was repeated after restarting the same therapy due to the loss to follow-up for a one year (16) (**Table 1**).

As opposite prospective, based on the review of literature included in their report, Xue et al. concluded that LA cannot be improved by anti-inflammatory therapy and recommended the arthroscopic synovectomy as the exclusive management of LA (14). Reports of Xue et al. and Batu et al. even indicated the possibility of developing LA during TNF inhibitor therapy (etanercept) of JIA (14, 15).

In our opinion, all options of consistent anti-inflammatory therapy with correct doses of prescribed medications (including "intensive protocols" and "switching/cycling" of biologics), primarily directed toward the treatment of underlying inflammatory disease, should be considered before definitive decision on LA surgical procedures. Slow progression of this benign lesion leaves plenty of time for tailoring different conservative options (1).

Conclusion

Here, we present the first case of successful use of the TNF inhibitor adalimumab for treating bilateral knee LA in a patient with psoriatic JIA. Although rare, particularly in pediatric and adolescent patients, LA must be considered in the differential diagnosis of chronic joint swelling. In cases of JIA as a possible underlying condition of LA in children, all anti-inflammatory treatment options, including TNF inhibitor therapy, should be considered before synovectomy, as a procedure generally reserved for types of primary or extended secondary lesions.

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. Written informed consent to participate in this study was provided by the participants'

legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

MF and MK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in drafting the article or revising it critically for important intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The 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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TYPE Case Report
PUBLISHED 13 December 2022
DOI 10.3389/fped.2022.1012582

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 05 August 2022
ACCEPTED 17 November 2022
PUBLISHED 13 December 2022

CITATION
Meneghel A, Martini G, Balzarin M, Zabadneh N, Fastiggi M, Tirelli F and Zulian F (2022) Case report: Exploring under the tip of the iceberg: A case series of "self-limiting" multisystem inflammatory syndrome in children.
Front. Pediatr. 10:1012582.
doi: 10.3389/fped.2022.1012582

Case report: Exploring under the tip of the iceberg: A case series of "self-limiting" multisystem inflammatory syndrome in children

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Multisystem inflammatory syndrome in children (MIS-C) is a serious condition triggered by SARS-COV-2 infection, characterized by persistent fever, multiorgan dysfunction, and increased inflammatory markers. It requires hospitalization and prompt treatment, with nearly 60% of the cases needing intensive care and 2% fatality rate. A wide spectrum of clinical characteristics and therapeutic approaches has been reported in MIS-C. We describe a series of four patients with MIS-C, defined according to the current case definitions, with a self-limiting course and no need for immunomodulatory treatment ("self-limiting MIS-C"). Few data about self-limiting MIS-C are available to date and no information on medium- and long-term outcome of this subset of patients has been reported. Although limited in size, our experience provides new insights into the MIS-C syndrome, highlighting an underestimated aspect of the disease that may have significant therapeutic implications.

KEYWORDS

multisystem inflammatory syndrome in children (MIS-C), COVID-19, self-limiting disease, case report, SARS-COV-2

Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a potentially life-threatening condition triggered by SARS-COV-2 infection (1). Since its first description (2, 3), huge effort has been made worldwide to better understand the

Abbreviations
ACR, American College of Rheumatology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BP, blood pressure; CMV, cytomegalovirus; CRP, C-reactive protein; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; EKG, electrocardiogram; HR, heart rate; IvIg, intravenous immunoglobulin; KD, Kawasaki disease; L, lymphocyte; MIS-C, multisystem inflammatory syndrome in children; N, neutrophils; NT-BNP, N-terminal brain natriuretic peptide; PCT, procalcitonin; PLT, platelets; PVB19, parvovirus-B19; TpnI, troponin I; US, ultrasound; WBC, white blood cells; n.v., normal value.

pathogenesis and the clinical features of this novel entity to optimize therapeutic approaches in view of a favorable short- and long-term outcome. Different MIS-C case definitions have been provided so far (4–6), partly overlapping with each other, defining the picture of a severe condition, often requiring intensive care and close monitoring, mostly characterized by persistent fever with multiorgan involvement and increased inflammatory markers in the context of a proven previous exposure to SARS-COV-2 (RT-PCR, antigen test, or positive serology) with the exclusion of other possible infectious causes. Since COVID-19 can be asymptomatic or mild infection in children (7), the finding of a positive serological test for SARS-COV-2 is a confirmatory criterion in a suspected clinical setting for MIS-C.

Despite this general wide range of clinical manifestations, outcomes have been reported with nearly 60% of cases requiring intensive care (8, 9) and 2% fatality rate (8).

Because of the overlapping features with Kawasaki disease (KD) (1–3), MIS-C patients have been treated mainly with intravenous immunoglobulin (IvIg) and corticosteroids. This combination therapy has shown to be effective (10) although recent studies did not demonstrate superior evidence of combination therapy as compared to monotherapy (11). More recently, the American College of Rheumatology (ACR) provided revised recommendations about immunomodulatory treatment in MIS-C patients, in which a panel of experts agreed that "*in mild cases, after evaluation by specialists with expertise in MIS-C, some patients may be managed with only close monitoring without immunomodulatory treatment*" (12). Furthermore, some authors recently reported their experience with a multistep therapeutic strategy, according to different severities in clinical presentation of MIS-C patients, that demonstrated a favorable impact on MIS-C course, preventing intensive care unit (ICU) admission (9).

In the context of the wide variety of clinical features and course of MIS-C, we describe a series of four patients, diagnosed according to the most recent criteria (5, 6) with a self-limiting course characterized by spontaneous recovery and no need for immunomodulatory treatment ("self-limiting MIS-C").

Case series

Case 1: An 8-year-old healthy girl presented with prolonged fever (8 days) associated with abdominal pain and erythematous skin rash involving the face, the neck, and the upper trunk. She had a history of COVID-19 family exposure 6 weeks earlier. She was not vaccinated for SARS-COV-2. Physical examination revealed the girl to be suffering with elective abdominal pain on the right lower abdomen, mild tachycardia, and hypotension [heart rate (HR) 126 bpm and blood pressure (BP) 98/59 mmHg]. Blood test showed the following: platelets (PLT) 129,000/mm^3; C-reactive protein (CRP) 127 mg/L; procalcitonin (PCT) 6.7 µg/L; D-dimer 847 µg/L; fibrinogen 4.82 g/L; and normal electrolytes, hepatic and renal function tests, pancreatic enzymes, troponin I (TpnI), and B-type natriuretic peptide (BNP). Viral serologies were negative for Epstein–Barr virus (EBV), adenovirus, cytomegalovirus (CMV), herpes virus, and parvovirus-b19 (PVB19), and positive for SARS-COV-2 IgG s-RBD (92.72 kAU/L). Blood and stool cultures were negative; fecal calprotectin was normal. Electrocardiogram (EKG) and echocardiography were normal. Abdominal ultrasound (US) showed marked and extended thickening of the last ileal loop's wall, with heterogenicity of the adjacent adipose tissue and multiple lymphadenomegalies. Intravenous ceftriaxone was administered empirically for 5 days. She showed complete resolution of abdominal pain and skin rash on day 2 after admission and fever on day 5. Repeat abdominal US confirmed decrease of the ileal wall thickening and resolution of the other findings. She was discharged on day 8. At 1-month follow-up visit, she was asymptomatic and abdominal US showed complete resolution of terminal ileitis. At 6-month follow-up visit, she was persistently asymptomatic.

Case 2: A 5-year-old healthy boy not yet vaccinated for SARS-COV-2 presented with a 6-day history of fever associated with abdominal pain, diarrhea, and bilateral conjunctivitis. He had COVID-19 infection 4 weeks earlier. On physical examination, bulbar bilateral conjunctivitis, mild systolic heart murmur, mild tachycardia, and hypotension were present (BP 108/64 mmHg and HR 110 bpm). Blood tests showed the following: PLT 179,000/mm^3; CRP 64.2 mg/L; PCT 1.73 µg/L; fibrinogen 5.24 mg/L; D-dimer 239 µg/L; BNP 129 ng/L [normal value (n.v.) < 100]; TpnI 38 ng/L (n.v. < 16); and normal electrolytes, hepatic, and renal function tests. Serology and PCR for adenovirus, parvovirus, CMV, and EBV was negative. Viral serological test found positivity for SARS-COV-2 IgG s-RBD (86.2 kAU/L). EKG showed nonspecific changes in ventricular repolarization. Echocardiography and chest x-ray were normal. Blood and stool cultures were negative. Oral amoxicillin/clavulanic acid was started. One day after admission, fever disappeared, and the gastrointestinal symptoms improved. Blood tests confirmed reduction in inflammatory markers and normalization of BNP and Tpnl. He was discharged on day 3. After 1 week, he was asymptomatic with normal EKG and echocardiography. At 1-month and 6-month follow-up visits, he was asymptomatic and blood tests were normal.

Case 3: 6 weeks after COVID-19 infection, a 12-year-old previously healthy boy, not vaccinated for SARS-COV-2 virus, presented with fever for 6 days associated with diffuse skin rash, diffuse abdominal pain, and diarrhea. Physical examination showed elective pain on the right lower abdomen and polymorphous erythematous skin rash on trunk, upper and lower limbs; and mild increased heart rate with normal

blood pressure (BP 115/75 mmHg and HR 122 bpm). Blood tests showed the following: white blood cells (WBC) 14,010/mm^3 [neutrophils (N) 12,130/mm^2, lymphocyte (L) 1,110/mm^3], D-dimer 337 µg/L, fibrinogen 9.72 g/L, normal BNP and TpnI, CRP 122.6 mg/L, erythrocyte sedimentation rate (ESR) 42 mm/h, and PCT 1.74 µg/L. Chest *x*-ray, EKG, and echocardiography were normal. Abdominal US showed marked thickening of the last ileal loop with multiple reactive lymphadenomegalies. No therapy was started. One day after admission, fever disappeared with complete resolution of mucocutaneous and gastrointestinal involvement on day 2. Repeated blood test showed: CRP 23.84 mg/L, ESR 25 mm/h; BNP 84 mg/L. He was discharged on day 3. At 1 month and 6-months follow-up visit he was asymptomatic; blood tests, EKG and echocardiography were normal.

Case 4: An 8-year-old healthy girl presented with 3-day lasting fever associated with persistent pain on the right side of the abdomen. She was not vaccinated for SARS-COV-2 and she got COVID-19 infection 4 weeks earlier. Blood tests showed the following: WBC 10,500/mm^3 (N 8,400/mm^3), PLT 214,000/mm^3, CRP 65 mg/L, ESR 73 mm/h, D-dimer 472 µg/L, fibrinogen 5.09 g/L, TpnI normal, N-terminal brain natriuretic peptide (NT-BNP) 745 ng/L, alanine aminotransferase (ALT) 56 U/L, and aspartate aminotransferase (AST) 49 U/L. SARS-COV-2 IgG s-RBD resulted positive (63.97 kAU/L). Stool and blood cultures were negative. Abdominal US showed moderate thickening of the last ileal loop's wall, with hyperechogenicity of the adipose tissue and multiple reactive lymphadenomegalies. EKG and echocardiography were normal. No therapy was started. On day 1 after admission, fever disappeared with improvement of abdominal pain, which completely resolved on day 3. She was discharged on day 7. At 1-month and 6-month follow-up visits, she was asymptomatic and blood tests were normal.

Discussion

In 2 years (April 2020–2022), we observed 54 cases of classical MIS-C and 4 patients (7.5%) with clinical features of MIS-C but with a "self-limiting" course (**Table 1**). These patients had a mean age of 8.25 years (range 5–12) and presented with fever (mean 5.75 days duration before diagnosis) associated with mucocutaneous involvement (75%), gastrointestinal complaints (100%), and cardiovascular involvement (50%). None of the patients needed hemodynamic support or pediatric intensive care admission. All documented a previous COVID-19 exposure, with positive SARS-COV-2 antibody testing (IgG s-RBD) in three cases. In one case, serological test for SARS-COV-2 was not done because of a previous documented infection 4 weeks earlier. All patients displayed a rapid resolution: three of them had spontaneous regression of fever within 24 h since admission, and cutaneous, cardiovascular, and gastrointestinal complaints subsided in some days for all. Along with the clinical findings, inflammatory and cardiac markers showed spontaneous decrease too. The absence of severe cardiovascular involvement, the favorable clinical course, and the overall good condition of the children allowed a conservative management with just clinical observation, brief hospitalization, and no need for immunomodulatory treatment.

There are few data about similar experience in the literature. Ouldali et al. in their comparative study on immunomodulatory treatment for MIS-C reported, in the supplemental contents, five patients with spontaneous resolution of fever with no need for immunomodulators (10). All patients presented with fever, with an average duration of 4.4 days, and mucocutaneous and cardiovascular involvement. Three patients presented with gastrointestinal and respiratory complaints and two with central nervous system (CNS) involvement. Indeed, two patients needed pediatric intensive care unit (PICU) referral. Considering laboratory parameters, the average values of inflammatory markers (CRP, PCT, ferritin), D-dimer, and cardiac enzymes (TpnI, BNP, NT-BNP) were higher in this cohort than in our series. Although the authors reported resolution of fever after 9.2 days on average, they did not provide any other information about the following course and outcome.

In other studies, the declared percentages of MIS-C patients spontaneously recovering with only supportive care ranged between 6% and 22% (11–13). Davies et al. reported that 12/78 (15%) patients who recovered spontaneously from MIS-C without immunomodulatory therapy. 42% of them received invasive ventilation and 58% required inotropes. The authors did not find any statistically significant difference in the short-term outcome between those treated and untreated. No data about the long-term outcome in this subgroup of patients were reported.

Finally, McArdle et al., in the BATS study, stated that 39/614 MIS-C cases (6.3%) did not receive any immunomodulatory treatment and only 15% needed organ support in the intensive care setting. They found that the average level of inflammatory markers decreased more rapidly in the group of treated patients than in those not treated. However, no information about the long-term outcome was given.

Although our experience is limited in size, we showed that after 6 months, patients with self-limiting MIS-C did not experience any significant sequelae despite no specific treatment. The observation that some patients can recover spontaneously from MIS-C is probably not surprising if we consider that self-limited cohorts of KD have been also reported (14). On the other hand, the fact that MIS-C may have a self-limiting course raises important considerations about diagnosis and management of this subgroup of patients. Firstly, it is possible that self-limiting MIS-C is underestimated because milder forms may not require

TABLE 1 Characteristics and outcome of patients with self-limiting MIS-C.

	Clinical presentation	Laboratory results	Imaging findings	COVID-19 history	SARS-COV-2 IgG (n.v. < 1)	PICU	Therapy	Hospitalization (days)	Total days of fever	Outcome 6 month
Patient 1 8 years old Female No comorbidities	8 days fever; abdominal pain; erythematous skin rash	PLT 129,000/mm^3, CRP 127 mg/L, PCT 6.7 µg/L, D-dimer 847 µg/L, fibrinogen 4.82 g/L	Normal EKG and echocardiogram. terminal ileitis on abdominal US	Intrafamily exposure 6 weeks earlier	92.72 kAU/L	None	Ceftriaxone IV	8	13	CR
Patient 2 5 years old Male No comorbidities	6 days fever; abdominal pain; non-bloody diarrhea; bilateral conjunctivits	PLT 179,000/mm^3, CRP 64.2 mg/L, PCT 1.73 µg/L, fibrinogen 5.24 mg/L, D-dimer 239 µg/L, BNP 129 ng/L, troponin I 38 ng/L	EKG: nonspecific changes in ventricular repolarization; normal echocardiogram	COVID-19 infection 4 weeks earlier	86.2 kAU/L	None	Amoxicillin/acid clavulanic p.o.	3	7	CR
Patient 3 12 years old Male No comorbidities	6 days fever; erythematous skin rash; bilateral conjunctivitis; abdominal pain; diarrhea	WBC 14,010/mm^3, N 12,130/mm^3, L 1,110/mm^3, CRP 122.6 mg/L, PCT 1.74 µg/L; fibrinogen 9.72 g/L, d-dimer 337 µg/L	Normal EKG and echocardiogram. terminal ileitis on abdominal US	COVID-19 infection 4 weeks earlier	Not done	None	None	7	7	CR
Patient 4 8 years old Female No comorbidities	3 days fever; abdominal pain	WBC 10,500/mm^3, N 8,400/mm^3, PLT 214,000/mm^3, CRP 65 mg/L, fibrinogen 5.09 g/L, D-dimer 472 µg/L, ALT 56 U/L, AST 49 U/L, NT-BNP 745 ng/L	EKG and echocardiogram normal; terminal ileitis on abdominal US	COVID-19 infection 4 weeks earlier	63.97 kAU/L	None	None	7	4	CR

PICU, pediatric intensive care unit; PLT, platelets; CRP, C-reactive protein; PCT, procalcitonin; BNP, brain natriuretic peptide; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cells; N, neutrophils; L, lymphocytes; EKG, electrocardiogram; US, ultrasound; CR, complete remission; IV, intravenous; p.o., per os; n.v., normal value.

10.3389/fped.2022.1012582

hospitalization and, due to the overlapping features with other febrile conditions of infancy, may not be properly recognized. Therefore, we need more information about the long-term outcome of this subset of patients to verify whether a missed treatment in a self-limiting disease may increase the risk of sequelae, as shown in self-limiting KD (15).

The ACR recently suggested that mild cases of MIS-C, after evaluation by experts in MIS-C, can require only close clinical monitoring without immunomodulatory treatment (12). In our series, the absence of laboratory and instrumental findings of cardiac involvement was the key point for a conservative approach, although in other cohorts in which a self-limited course has been reported, cardiovascular dysfunction was described (10–13).

Although we have seen a decline in MIS-C cases in the latest COVID-19 waves, we do not have available data to define if this reflects the impact of vaccinations or of the variants of the virus itself.

Finally, considering the variable course of the disease and the spread of SARS-COV-2 vaccination in the pediatric population, we do need more selective criteria to guide treatment decision in MIS-C patients. This may allow avoiding aggressive immunomodulatory treatments when unnecessary.

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. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

AM conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. AM, GM, MF, FT, MB, NZ, and FZ took care of the patients, collected data, carried out the initial analysis, and reviewed and revised the manuscript. FZ supervised data collection and critically reviewed the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The 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.

Publisher's note

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frontiers | Frontiers in Pediatrics

TYPE Case Report
PUBLISHED 04 January 2023
DOI 10.3389/fped.2022.1015617

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Rheumatology, a section of the journal Frontiers in Pediatrics

RECEIVED 09 August 2022
ACCEPTED 13 October 2022
PUBLISHED 04 January 2023

CITATION
La Torre F, Calabrese G, Signorile K, Bizzoco F, Mastrorilli C, Strippoli A, Amato D, Carella F, Vairo U, Giordano P, Milella L and Cardinale F (2023) Efficacy of sildenafil and high-dose anakinra in an MIS-C patient with pulmonary vasculitis: A case report.
Front. Pediatr. 10:1015617.
doi: 10.3389/fped.2022.1015617

Efficacy of sildenafil and high-dose anakinra in an MIS-C patient with pulmonary vasculitis: A case report

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Multisystem inflammatory syndrome in children (MIS-C) is a newly identified clinical entity still not very well known in terms of epidemiology, pathogenesis, and long-term outcome. Pulmonary involvement with acute respiratory failure is an unusual life-threatening complication of MIS-C, often a reason for admission to the pediatric intensive care unit (PICU) and the use of mechanical ventilation. We present a case of a 7-year-old male patient, previously healthy, hospitalized for MIS-C, treated with intravenous immunoglobulins (IVIG), high dose methylprednisolone, and anakinra. After 2 days of the aforementioned therapy, the patient presented with hypoxia ($SatO_2$: 85% in ambient air room) and breathing difficulties. A chest computed tomography (CT) scan showed the presence of multiple bilateral basal parenchymal thickening and small basal pleural effusion and an arterial blood gas analysis revealed severe hypoxia (PaO_2/FiO_2 ratio, 170 mmHg). Because of a worsening of respiratory distress, the patient was transferred to the PICU, where invasive mechanical ventilation and a continuous infusion of anakinra (12 mg/kg/day) were started. An echocardiogram was performed, which showed an increase in pulmonary pressure (40 mmHg) with normal heart ejection fraction (55%), and the hypothesis of pulmonary vasculitis involving the pulmonary arterioles was made. Therefore, therapy with sildenafil (0.15 mg/kg/day) was promptly set up, with an immediate improvement of the clinical picture of respiratory failure, reduction of pulmonary pressure (23 mmHg), and subsequent extubation at 36 h with a regular clinical course until discharge. As far as we know, our case represents the first report of pulmonary vasculitis in an MIS-C patient. The use of sildenafil and high-dose continuous anakinra may represent a rescue therapy in cases of MIS-C with pulmonary vasculitis or with difficulty in extubation, allowing a short-term hospitalization in intensive care and improving the long-term outcome in these patients.

KEYWORDS

anakinra, children, COVID-19, MIS-C, multisystem inflammatory syndrome in children, pulmonary hypertension, pulmonary vasculitis, sildenafil

Introduction

Since the first phase of the COVID-19 outbreak, a new childhood multi-inflammatory syndrome temporally linked with SARS-CoV-2 infection has been reported worldwide. It has some similarities with Kawasaki disease (KD) and toxic shock syndrome (TSS) (1, 2). This condition has been named pediatric inflammatory multisystem syndrome temporally associated to SARS-CoV-2 infection (PIMS-TS) or multisystem inflammatory syndrome associated with coronavirus disease 2019 (MIS-C) (3–7). It typically displays 2–6 weeks after SARS-Cov-2 infection and has some overlapping features with KD, with a range of clinical presentations including mucocutaneous, respiratory, gastrointestinal, neurological, and cardiac symptoms. Like KD, no pathognomonic clinical findings or diagnostic tests exist. Unlike KD, however, MIS-C has been reported to predominantly affect adolescents and children aged older than 5 years and to be associated more frequently with cardiovascular (mainly myocarditis), and gastrointestinal involvement (1, 5, 6, 8, 9). The current definition of MIS-C, established by the World Health Organization in May 2020, refers to an individual aged 0–19 years, presenting with a fever for 3 days or longer, plus at least two of the following symptoms: rash; conjunctivitis; mucocutaneous inflammation; hypotension or shock; cardiac involvement; coagulopathy; and acute gastrointestinal symptoms. Laboratory evidence of increased inflammatory markers, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or procalcitonin *plus* positive evidence of recent COVID-19 infection (by oronasal swab-PCR, serology, or antigen test) or likely recent contact, are required (10). While the underlying pathophysiology of MIS-C is currently under investigation, both the innate and adaptive immune response are thought to be strongly upregulated (11–13). One of the most intriguing theories hypothesizes that the SARS-CoV-2 spike protein can act as a "superantigen," activating both T- and B-cells, leading to the hyperinflammatory state and a subsequent cytokine storm, similar to toxic shock syndrome (TSS) induced by the staphylococcal endotoxin B (14). Furthermore, it has been observed that patients affected by MIS-C develop vasculitis with endothelial damage, as shown by high levels of MCP-1 and VEGF-A, followed by an increase in pANCA (15). Among non-specific symptoms, severe complications including cardiovascular shock and multi-organ failure appear in most severe cases of MIS-C (16–18). Vasculitis and microthrombosis, particularly at the pulmonary level, were observed by necroscopy in some patients (19), but a case report of pulmonary vasculitis has never been documented. On the other hand, MIS-C shares some clinical features with other pediatric inflammatory multisystemic syndromes, such as KD, TSS, and macrophage activation syndrome (MAS), typically associated with endothelial damage and systemic vasculitis (20–22). Current practices and published guidelines for the treatment of MIS-C support the use of intravenous immunoglobulin (IVIG) and high-dose corticosteroids as the cornerstone of therapy (3, 4, 20, 23–28), in addition to antithrombotic prophylaxis. Treatment algorithms generally recommend biologic agents as second-line medication options after initial treatment with IVIG and steroids (22, 27, 29). Anakinra is a recombinant human interleukin-1 receptor antagonist that has been previously shown to be effective with limited side effects in patients with KD (29). Many studies have shown a similar efficacy of anakinra in severe cases of MIS-C, especially in patients with a clinical course complicated by severe myocarditis, shock, and a poor response to IVIG and steroid treatment (30–33). In two large cohorts, anakinra was successfully used in 24 of 186 and 8 of 183 patients, demonstrating an overt efficacy in cases of MIS-C with severe cardiac involvement (9, 34). We present a case of MIS-C complicated by pulmonary vasculitis successfully treated with sildenafil and high doses of anakinra.

Case report

A previously healthy 7-year-old male patient was admitted to our Pediatric Department, complaining of unremitting fever above 39 °C for 5 days, fatigue, headache, and acute abdominal pain, unresponsive to non-steroidal anti-inflammatory drugs , and antibiotic treatment with amoxicillin-clavulanate. At admission on physical examination, he presented with bilateral non-exudative conjunctivitis, skin rash on the trunk and upper limbs, and neck rigidity with some sign of meningism. He had had a pauci-symptomatic SARS-CoV-2 infection approximately 4 weeks before, characterized by 2 days of fever, asthenia, and headache. The infection had been ascertained by a positive oronasal swab for SARS-CoV-2. Laboratory findings showed marked elevation of CRP (275 mg/L) and ESR (66 mm/1th h), but also of ferritin (556 mg/L) and brain natriuretic peptide (pro-BNP; 3408 pg/ml). Marked lymphopenia (440/mmc) and hypoalbuminemia (23 g/L) were also found at admission. A molecular swab for SARS-CoV-2 was negative. The work-up excluded Epstein Barr virus, cytomegalovirus, parvovirus B19, adenovirus, and HIV infection. The echocardiography performed when he presented to the pediatric emergency unit showed signs of endocarditis (mild aortic and mitral regurgitation) with normal contractility of the myocardium and normal pulmonary pressure (26 mmHg). The abdominal ultrasound showed a thin layer of fluid among the intestinal loops and the chest x-ray showed a homogeneous parenchymal thickening in the left paracardiac basal area with small left basal pleural effusion. In view of his medical history, clinical examination, and blood and instrumental tests, a diagnosis of MIS-C related to COVID-19 infection was made.

10.3389/fped.2022.1015617

According to guidelines, IVIG at a dose of 2 g/kg associated with a high dose of metilprednisolone at a dose of 30 mg/kg were started (Table 1). Subcutaneous thromboprophylaxis with low-molecular weight heparin (LMWH) at a dose of 100 UI/kg was also initiated (Table 1). After the third bolus of high-dose corticosteroids, his fever and neurological symptoms persisted, together with a persistent elevation of CRP (135 mg/L). Therefore, intravenous anakinra (a 2 mg/kg/dose every 6 h) was started while intravenous methylprednisolone (1 mg/kg b.i.d.) was continued (Tables 1 and 2), showing a rapid response, with the disappearance of the fever and skin rash and the reduction of CRP (60 mg/L) and pro-BNP (546 pg/ml). After 2 days, he suddenly presented with progressive dyspnea, increased labored breathing, and hypoxia ($SatO_2$: 85% in ambient air room), without any other associated symptoms. The delivery of O_2 by humidified high-flow nasal cannula (HFNC) was started with a FiO_2 50%. A chest CT scan was performed, showing multiple basal parenchymal thickening with small basal pleural effusion (Figure 1). An arterial blood gas analysis showed severe hypoxia (PaO_2, 56 mmHg; PaO_2/FiO_2 ratio, 170 mmHg). The blood tests showed new slowly increasing inflammatory markers (CRP 113 mg/L, ESR 68 mm/1th h). Because of the increased work of breathing and persistent altered gas exchange, the patient was transferred to the pediatric intensive care unit (PICU), and then put on invasive mechanical ventilation. Administration of anti-IL-1 was modified and a continuous infusion of high-dose anakinra (12 mg/kg/day) was started (Tables 1 and 2). Echocardiography revealed increased pulmonary pressure (40 mmHg) with normal heart ejection fraction (55%). These results confirmed the hypothesis of ongoing pulmonary vasculitis involving pulmonary arterioles. Therefore, intravenous sildenafil at a dose of 0.15 mg/kg/day was started (35, 36) (Table 1), with a progressive reduction of pulmonary pressure (23 mmHg) and resolution of the clinical picture of respiratory failure. After 36 h from the start of the treatment, the patient's clinical condition as well as laboratory parameters remarkably improved, and he was extubated and again transferred to our department. The treatment was well tolerated and after 3 days the CRP fell in the normal range, sildenafil was stopped, and the biologic treatment was escalated, taking off one dose of anakinra every 3 days, up to discontinuation (Table 1). At discharge,

TABLE 1 Summary of the immunomodulatory and thromboprophylaxis therapy administered to our patient affected by MIS-C complicated with pulmonary vasculitis.

Day of admission	IVIG	Methylprednisolone (intravenous)	Prednisone (oral)	Anakinra (intravenous)	Sildenafil (intravenous)	LMWH (subcutaneous)	Aspirin (oral)	PICU
1	2 g/kg[a]	30 mg/kg[b]				100 UI/kg		
2		30 mg/kg[b]				100 UI/kg		
3		30 mg/kg[b]				100 UI/kg		
4		1 mg/kg BID		2 mg/kg QID		100 UI/kg		
5		1 mg/kg BID		2 mg/kg QID		100 UI/kg		Yes
6		1 mg/kg BID		12 mg/kg[c]	0.05 mg/kg TID	100 UI/kg		Yes
7		1 mg/kg BID		12 mg/kg[c]	0.05 mg/kg TID	100 UI/kg		Yes
8		1 mg/kg BID		12 mg/kg[c]	0.05 mg/kg TID	100 UI/kg		
9		1 mg/kg BID		2 mg/kg QID	0.05 mg/kg BID	100 UI/kg		
10		1 mg/kg BID		2 mg/kg QID	0.05 mg/kg/day	100 UI/kg		
11		1 mg/kg/day		2 mg/kg TID		100 UI/kg		
12		1 mg/kg/day		2 mg/kg TID		100 UI/kg		
13			1 mg/kg/day	2 mg/kg BID		100 UI/kg		
14			0.75 mg/kg/day	2 mg/kg BID		100 UI/kg		
15			0.75 mg/kg/day	2 mg/kg BID		100 UI/kg		
16			0.5 mg/kg/day	2 mg/kg/day		100 UI/kg		
17			0.5 mg/kg/day	2 mg/kg/day		100 UI/kg		
Discharge			0.25 mg/kg/day for other 2 days and then stop				5 mg/kg until 8 weeks from onset	

BID, Bis in die; TID, Ter in die; QID, Quarter in die.

[a](max80 g) to be administered over at least 12 h. In patients with heart failure immunoglobulins should be administered over at least 16 h. or, alternatively, the total dose should be split into two infusions 12 h apart.

[b]in 3 h (max 1 gr).

[c]Continuous infusion.

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TABLE 2 Different modalities of Anakinra administration in MIS-C patients.

Intravenous		Subcutaneous
Pulse	**Continuous infusion**	
• Indication: in case of persistent disease activity 48 h after first-line treatment • In case of MAS. or shock with cardiac failure in adjunction to corticosteroids and IVIG • Dilute the vial of anakinra (100 mg) in 100 ml of 0.9% NaCL • Use bags (not plastic, PVC or glass containers) • Mix gently by inversion • Administer the diluted anakinra solution intravenously, *via* an infusion pump, in one hour, immediately after preparation, so as to administer 2 mg/kg (max 100 mg) per dose • Discard the remaining contents • It's possible to repeat the same preparation, every 6 h (4 times/day)	• Indication: in case of persistent disease activity 48 h after first-line treatment • In case of MAS or shock with cardiac failure in adjunction to corticosteroids and IVIG • Dilute the vial of anakinra (100 mg) in 100 ml of 0.9% NaCL • Use bags (not plastic, PVC or glass containers) • Mix gently by inversion • Administer the diluted anakinra solution intravenously, via an infusion pump, over 6 h, immediately after preparation, at dose of 2–3 mg/kg per dose (max 100 mg); discard the remaining contents • Repeat the same preparation, every 6 h, as a continuous infusion (4 times/day) • Maximum daily dose 12 mg/kg or 400 mg	• Indication: in case of persistent disease activity 48 h after first-line treatment • Administer anakinra with the pre-filled vial subcutaneously on the belly, thigh or arm area • At dose of 4–6 mg/kg/day (max 100 mg x dose)

This tble shows how to administer Anakinra in MIS-C patients. In view of acute hyperinflammatory disease, we advise intravenous use as a pulse or continuous infusion depending on the severity of the disease and organ involvement.

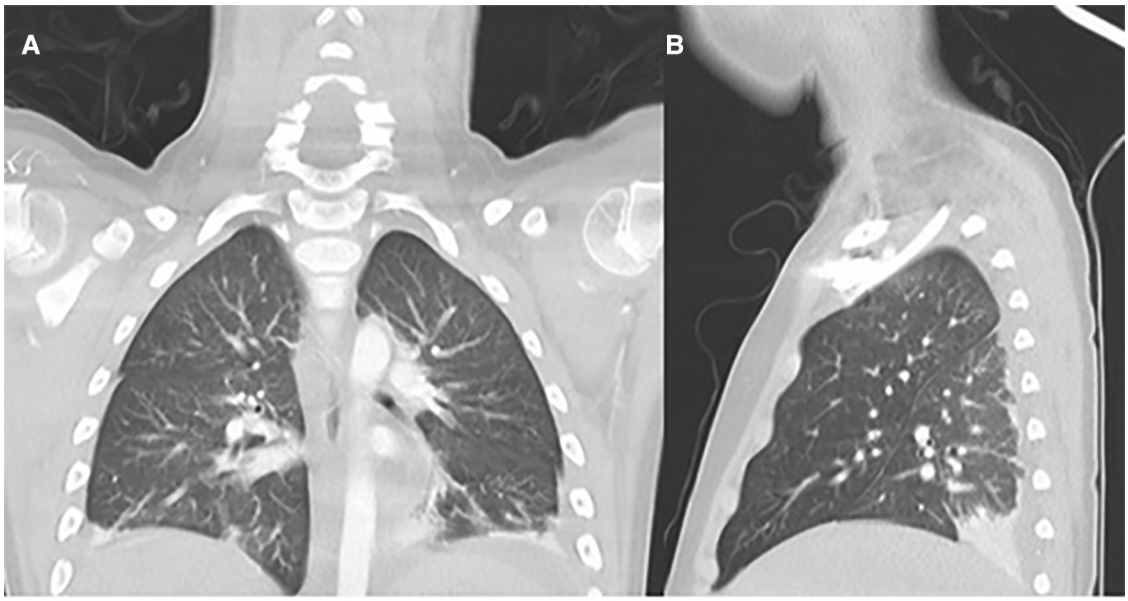

FIGURE 1
Chest computed tomography revealed multiple basal parenchymal thickening with small basal pleural effusion without signs of pulmonary embolism: (A) antero-posterior view; (B) latero-lateral view.

echocardiography revealed signs of previous cardiac involvement with persistent mild mitral regurgitation and total regression of aortic regurgitation, and chest x-ray showed a resolution of parenchymal thickening and pleural effusion. The treatment with LMWH was shifted to oral cardioaspirin at a dose of 5 mg/kg/day (max 100 mg/day) (**Table 1**). After 2 months of follow-up, the clinical examination was normal, and the blood test and cardiologic assessment with echocardiography also normalized; therefore, the cardioaspirin therapy was stopped.

Discussion

MIS-C is a post-infectious hyperinflammatory syndrome caused by a dysregulated immune response to SARS-CoV-2 infection with severe morbidity and mortality (15, 19–22). Diffuse vascular-endothelial damage is likely to play a major role in cases with severe cardiac and neurological involvement (15, 19–22). The strong association between COVID-19 and coagulopathy suggests that multiple molecular pathways are involved and dysregulated through

the disease progression, contributing to the development of thrombosis; this is true also for MIS-C (37). Endothelial dysfunction and barrier disruption lead to immune cell infiltration, and proinflammatory cytokine production, as well as thrombosis (38). MIS-C seems to have specific effects on the coagulation profile leading to hypercoagulability and a thrombogenic state; in particular, complement activation has been hypothesized as a favoring factor in thrombosis development (39). Recent studies in children have pointed to an increase in endothelial dysfunction markers in MIS-C, with a rise in soluble C5b-9 (which represents the activated product of the terminal complement cascade) and altered red blood cell morphology (39, 40). In patients with MIS-C, high levels of fibrinogen and D-dimers increase the likelihood of a thrombotic state (37). As far as we know, our case represents the first report of pulmonary arterial hypertension (PAH) likely due to pulmonary vasculitis in a pediatric patient with MIS-C. We examined several explanations for the PAH in our young patient. First, we considered a pulmonary embolism, which was ruled out by the CT scan. In addition, the echocardiographic assessment was negative for underlying heart conditions or cardiac failure. Therefore, we considered the diagnosis of pulmonary vasculitis as the only possibility of the sudden dyspnea associated with an increase of PAH after the exclusion of cardiac and other pulmonary causes, as occurring in some cases of KD with pulmonary involvement (36). Therefore, we administered sildenafil, a type 5 phosphodiesterase inhibitor, known to induce vasodilation, particularly in the pulmonary arterial district, and to inhibit endothelial proliferation. This therapy has already been shown to be effective in treating children with PAH in different conditions (35). We believe that in our case the association of sildenafil with high doses of anakinra was decisive in preventing the progression of the disease. In this regard, according to different international societies of pediatrics and rheumatology, anakinra would be considered in MIS-C patients refractory to first-line medications (IVIG and corticosteroids), or in cases complicated by MAS or shock (3, 4, 23, 27, 33). However, the effective control of the hyperinflammatory condition can depend on a window of opportunity that the step-up approach does not always allow respect. We believe that in our case, the delay of diagnosis (admission to the hospital on the 5th day of fever) along with the decision of starting the therapy with IVIG and high-dose steroids alone, without anakinra, may have played a role in the suboptimal control of symptoms, paving the way to the development of pulmonary vasculitis requiring admission to the PICU. This decision was based on recommendations from guidelines to start anakinra in MIS-C in patients without cardiac failure or MAS only in case of uncontrolled disease at 48 h after first-line treatments (3, 4, 23, 27). However, neurological involvement with meningoencephalitis and pulmonary involvement with acute respiratory failure are determining elements for admission to the PICU (8, 9, 18). In our report, the worsening of the cardio-respiratory compromise was decisive for PICU admission and prompted us to introduce a second-line treatment with high-dose intravenous anakinra and sildenafil. In our opinion, the presence of neurological involvement with overt meningism signs should be considered as criteria for starting a more aggressive treatment with anakinra, using this drug as a first-line approach. In our case, such therapy on the second day of hospitalization, after the failure of the first day of IVIG and infusion of high-dose corticosteroids, could have been started. This would have made it possible to anticipate the use of anakinra by 48 h, probably within the window of opportunity to avoid the need for intensive care and the possible complications of the hyperinflammatory picture. However, sildenafil and high doses of intravenous anakinra treatments allowed the patient to have a short-term hospitalization in the PICU and a total normalization of the neurological, cardiological, and pulmonary picture and normal long-term outcome.

Conclusion

As far as we know, our case represents the first report in pediatric literature of pulmonary vasculitis in MIS-C patients. One limitation of our report is that no pulmonary biopsy was performed to confirm our hypothesis of pulmonary vasculitis as a cause of severe respiratory distress and altered gas exchange requiring invasive mechanical ventilation. On the other hand, the rapid improvement registered in our patient with sildenafil and high doses of anakinra made the biopsy unethical to perform. We believe that the use of sildenafil and high-dose intravenous anakinra may represent an effective rescue therapy in severe cases of MIS-C with likely pulmonary vascular involvement, allowing a more rapid discharge from PICU and possibly improving the long-term outcome in these patients.

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 the Institutional Review Board of Bari, Italy. 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

FLT, PG, and FC provided the concept for the study and were major contributors to the manuscript revision. GC, AS, DA, FC, UV, and LM were involved in the patient care and collected the data regarding the patient's history and clinical course, as well as the trends in vital parameters. FLT, KS, FB, and CM collected clinical data, reviewed the literature, and drafted the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by Springer Healthcare Italia srl. for open access publication fees

Acknowledgments

The authors thank all medical and nursing staff of the Pediatric Department and of the Pediatric Intensive Care Unit of the Giovanni XXIII Pediatric Hospital of Bari for their help.

Conflict of interest

The 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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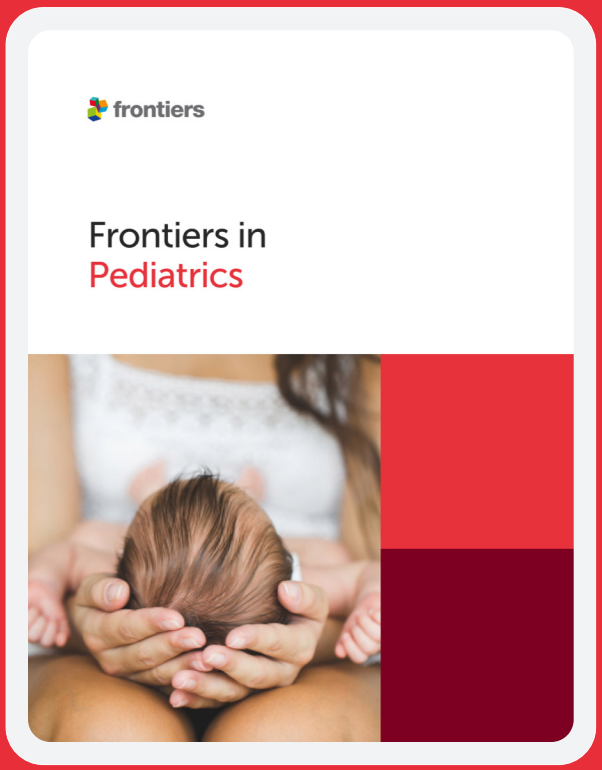

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