CHALLENGES OF COVID-19 IN DERMATOLOGY PATIENTS ON IMMUNOSUPPRESSION: RISK, OUTCOME, VACCINATION AND BEYOND

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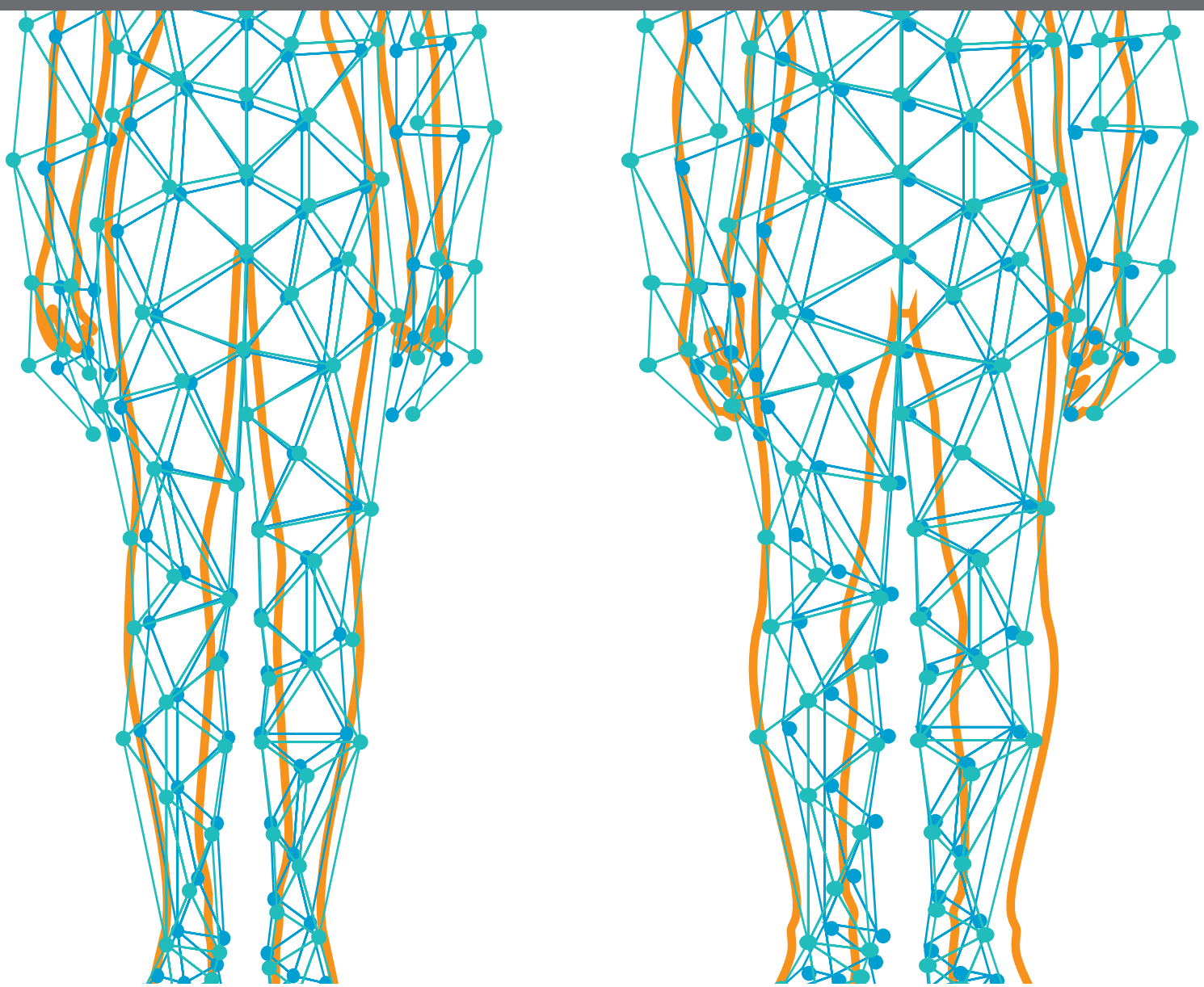

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CHALLENGES OF COVID-19 IN DERMATOLOGY PATIENTS ON IMMUNOSUPPRESSION: RISK, OUTCOME, VACCINATION AND BEYOND

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Editorial: Challenges of COVID-19 in dermatology patients on immunosuppression: Risk, outcome, vaccination, and beyond

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KEYWORDS

COVID-19, SARS-CoV-2, psoriasis, melanoma, vaccination, autoimmune bullous diseases

Editorial on the Research Topic
Challenges of COVID-19 in dermatology patients on immunosuppression: Risk, outcome, vaccination and beyond

Corticosteroids, other immunosuppressive drugs, and biological agents are key elements of the treatment of immune-mediated diseases. There is limited data available about the outcome of dermatology patients on immunosuppressants who are infected with SARS-CoV2. Meanwhile, the release of pro-inflammatory cytokines and the so-called cytokine storm of COVID-19 may trigger the onset or exacerbation of autoimmune or autoinflammatory diseases.

On the other hand, COVID 19 vaccines are considered the game-changer of the pandemic. Some issues related to SARS-CoV2 vaccination should be addressed in dermatology patients, most notably, vaccine efficacy in patients on immunosuppressants and the risk of worsening of autoimmune diseases.

One of the most intriguing questions is whether the cytokine storm and the immune system overreaction after COVID-19 infection may induce the development either of a new autoimmune disease or the relapse of an existing one. In this issue, Lotfi et al. describe a rare case of pansclerotic morphea that rapidly progressed a few weeks after infection with COVID-19 in a woman with no history of any autoimmune skin or rheumatic disease. Drenovska et al. also report a woman with preexisting chronic cutaneous lupus erythematosus controlled with topical

corticosteroids and photoprotection. She developed a flare of disease as Rowell syndrome with erythema multiforme-like lesions and high anti-Ro and anti-Ro B2 antibodies 2 weeks after a SARS-CoV-2 infection. It is important to enrich the existing literature with similar cases and add knowledge about the outcomes of COVID-19 infection for further research.

Another intriguing concept is the impact of the COVID-19 vaccine on the clinical course of autoimmune diseases. In a single-center study from Taiwan, Huang and Tsai reported 15 episodes of psoriasis worsening and morphological changes in 51 patients with psoriasis likely due to Th17 activation after vaccination. Additionally, all but one of the patients who received two doses of vaccination experienced disease exacerbation after the first shot but not the second. Under the same concept, COVID-19 vaccines may induce bullous pemphigoid, as reported in an Italian multicenter study by Maronese et al. collected clinical, histopathological and immunopathological data of 21 patients with new onset bullous pemphigoid (BP) associated with COVID-19-vaccines.The authors concluded that, in this subset of patients, there are slight differences between BP possibly triggered by COVID-19-vaccines and classical BP, such as a male predominance and a reduced humoral response to BP230.

Many theories have been proposed regarding the pathogenic mechanisms of autoimmunity following viral infection or vaccination; one of them is molecular mimicry. Kasperkiewicz et al. examined this hypothesis by testing the sera of 12 seropositive post-COVID-19 individuals and 12 seropositive healthy volunteers who received two doses of an mRNA COVID-19 vaccine for autoantibodies to the main immunobullous autoantigens. Interestingly, none of the subjects had concomitant antibody reactivity. The authors concluded that their results argue against a relationship between SARS-CoV2 infection/vaccines and AIBDs with respect to disease-triggering antibody cross-reactivity.

During the pandemic, especially before vaccination, the potential benefits and risks of the use of immunosuppressants and biologics, especially rituximab in AIBDs, were under continuous discussion. Miyamoto et al. report a case series of four pemphigus patients from Brazil who required adjustment of treatment and present the challenges of therapeutic decisions. It is considered to be extremely important to monitor B-cell recovery after anti- CD 20 therapy, in order to determine the most appropriate timing to vaccinate patients and achieve a maximized seroconversion. The authors also suggest that additional studies are necessary to evaluate COVID-19 outcomes in vaccinated AIBD patients with the aim to better understand the safety of immunosuppressive and biologic treatments after immunization.

Biologic treatment is another hot topic in the COVID-19 era. In the review article prepared by Zeng et al., the authors discuss the pearls and pitfalls of using biologic treatments in patients with psoriasis during the COVID-19 pandemic. Although the exact consequences of the treatment on the risk of COVID-19 infection and severity have not been determined yet, the authors suggested that, according to the available data, there is a low risk of severe COVID-19 infection in patients being treated with anti-TNF-α, IL17, and IL23 inhibitors. Therefore, none of the biologic treatments mentioned in this article is likely to result in serious adverse effects for patients with COVID-19. Nonetheless, it is important to carefully assess the impact of such treatments during the pandemic.

Melanoma is the most lethal form of skin cancer, and the COVID-19 pandemic may have a profound impact on the diagnosis, treatment, and follow-up of patients suffering from melanoma. As part of their comprehensive review, Li et al. discussed practical points regarding screening, diagnosis, surgical treatment, and the use of new treatment options in patients with melanoma during the COVID-19 era.

As the COVID-19 era unfolds, there is increased concern regarding the effects of using immunosuppressive agents in the development of successful immunity to SARS-CoV-2 vaccines. Benucci et al. examined this hypothesis in 110 patients with psoriatic arthritis receiving immunomodulatory therapy (anti-TNF-a, anti-IL17, methotrexate). As compared with the control group, the selected patients demonstrated a reduced humoral response. Even though the antibody response did not differ significantly between groups treated with different medications. In another study on a small group of dermatological patients, Seree-aphinan et al. observed decreased humoral immune responses after a complete course of an inactivated vaccine in participants using azathioprine, cyclosporin, mycophenolate mofetil, or prednisolone >10 mg/day compared to those receiving methotrexate <10 mg/week, prednisolone <10 mg/day, or secukinumab, ixekizumab, or omalizumab. They concluded that poor responders may benefit from vaccine platforms that trigger a greater level of immunogenicity or booster doses.

Overall, the articles in this Research Topic highlight the challenges of dermatology patients in the COVID-19 era among them worsening of autoimmune diseases by SARS-CoV2 infection/vaccine, and reduced immunogenicity of vaccines and provide us with a clearer insight into the interaction between COVID-19 and skin disorders.

Author contributions

Conceptualization: HM, AP, DM, ST, and MD. Data curation: HM, AP, and MD. Supervision and writing- review and editing: DM and MD. Writing-original draft: HM, AP, ST,

and MD. All authors contributed to the article and approved the submitted version.

Dedication

This issue is dedicated to the challenges dermatology patients have been facing during the COVID-19 pandemic.

Conflict of interest

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CASE REPORT
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Pansclerotic Morphea Following COVID-19: A Case Report and Review of Literature on Rheumatologic and Non-rheumatologic Dermatologic Immune-Mediated Disorders Induced by SARS-CoV-2

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While mucocutaneous manifestations of COVID-19 have been frequently reported and added to our knowledge every day during the pandemic, another issue is the COVID-related diseases that can present as intensified lesions of underlying diseases, a new disease, or changes in the behavior of an old lesion. Given that immune system overreaction and cytokine storm are among the most prominent events in COVID-19, the incidence of autoimmune diseases is expected to increase after COVID-19, as confirmed in several reports. To increase the body of knowledge about short- and long-term outcomes of COVID-19 for specialists, it is essential that similar cases be reported and collected for years to come. The present study investigated a case of pansclerotic morphea that rapidly progressed a few weeks after infection with COVID-19 in a 57-year-old woman with no history of any autoimmune skin or rheumatic diseases. She was prescribed outpatient COVID-19 treatment of azithromycin, vitamins D and C, and then quarantined for 2 weeks. The manifestations of the disease were exacerbated at each follow-up and sampling visit at short intervals. This kind of pansclerotic morphea is reported for the first time.

Keywords: skin disorder, morphea, generalized morphea, dermatology, pansclerotic morphea

KEY POINT

COVID-19-induced autoimmune skin diseases have already been reported. Through reporting a new case of such diseases and a review of the literature, the current article attempts to facilitate the diagnosis of new cases of COVID-induced autoimmune diseases that may occur in the coming years after the pandemic has been contained.

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INTRODUCTION

The outbreak of the new SARS-CoV-2 has rapidly spread and infected many people throughout the world since early 2020 (1). Meanwhile, the complications brought by the virus have concerned many people. Given that viruses trigger immune responses, it is predictable that viral diseases cause autoimmune diseases through the viral attack itself or the immune dysregulation due to inflammatory responses. The skin is one of the most important organs that manifest the symptoms and complications of COVID-19 through various types of lesions including exanthematous rashes, urticarial rashes, and mucosal lesions. Since many chronic skin diseases are mediated by immune responses, specialists are in dire need of knowledge about COVID-induced skin diseases. To date, a number of such lesions have been investigated and reported in published articles (2, 3).

The effect of COVID-19 on autoimmune skin diseases can appear as exacerbation of a pre-existing disease (4), changes in manifestations of the disease (5), or causing the disease for the first time. It is worth noting that some of these diseases are exacerbated because patients discontinue immunomodulatory medications, which have been discussed in detail in published guidelines (6).

This is the first case report of pansclerotic morphea (PSM) following COVID-19. In this study, a new case of pansclerotic morphea following COVID-19 infection in a 57-year-old previously healthy woman was studied. After her first symptoms of malaise and stiffness of skin and myalgia, an internal medicine referred her to the rheumatologist. Then a dermatology consult was demanded after some lab tests showing high amounts of ANA and Anti-ds DNA and CRPa. Manifestations of generalized skin stiffness were noted, especially on shins, arms, and abdomen, wherein some areas had the peau d'orange feature. Afterward, a deep biopsy of the skin for further investigations was performed which resulted in sclerodermoid changes. According to clinical examination, the final diagnosis was post-COVID PSM.

CASE REPORT

A 57-year-old woman with no underlying diseases attended our internal disease clinic on October 15, 2020, presenting with respiratory symptoms, general weakness, and myalgia. Once her PCR test for SARS-CoV-2 was reported positive, she was prescribed outpatient COVID-19 treatment of azithromycin, vitamins D and C, and quarantined for 2 weeks. A retest of that patient on October 28, 2020, was negative, so she resumed her daily functions. During recovery, symptoms of weakness and myalgia persisted, to which arthralgia and arthritis of the ankles and knees were added. Furthermore, difficulty in performing knee flexion impaired the daily functions of the patient. The examinations carried out by the internist ruled out deep vein thrombosis (DVT), hemostasis problems, and heart failure. The lab tests showed high platelet count and ESR, so the physician ordered a complete rheumatology panel. The test results revealed higher than normal ranges for Antinuclear Antibody (ANA), anti-double stranded (anti-ds) DNA, Angiotensin-Converting Enzyme (ACE), and C-reactive protein (CRP). At this stage, the patient was referred to a rheumatologist for further investigations regarding suspected collagen-vascular diseases.

The rheumatologist ordered the tests again, which revealed ACE to be higher than the normal range while ANA and anti-ds DNA were negative. Physical examination revealed taut skin and subcutaneous tissue of the left upper limb, in addition to arthritis and arthralgia, so the patient was referred to the dermatology department for a scleroderma work-up. Changes in favor of scleroderma morphea were observed in the first visit of the patient to the dermatology clinic. Physical examination revealed the skin had turned shiny and tight (**Figure 1**). When touched, the skin felt rather sclerotic and lost the ability to fold compared with normal skin. Severe sclerosis was observed in both pretibial regions. In addition to changes in the arm and lower abdomen in favor of morphea, clinically deep morphea could not be differentiated from eosinophilic fasciitis. Therefore, a deep biopsy was performed on the left pre-tibial and left arm regions which showed changes in favor of sclerodermoid changes and no sign of eosinophilic fasciitis (**Figure 2**). Re-examination 2 weeks later revealed the exacerbation of previous lesions, newly formed lesions that rapidly spread to the proximal lower limbs and distal upper limbs, and difficult and painful movement of the limb. The pathology report corresponded to scleroderma/morphea in both regions. Treatment initiated with corticosteroids and the patient underwent further examinations while the case report was being written. The timeline of events can be seen in **Figure 3**.

Given the high levels of CRP and ACE in the lab tests, a CT scan on the lungs was carried out. The CT scan showed a mass in the upper lobe of the right lung, so the patient underwent a needle biopsy, which led to the diagnosis of lung adenocarcinoma. Next, a PET-scan of the lung was performed to assess staging of the adenocarcinoma, and the patient underwent lobectomy of the right lung. Given the patient's underlying conditions, the systemic treatment for morphea was postponed and the patient received only topical medications until the results of the lung cancer assessment were ready. At this stage, the lesions of the patients had stabilized and tissue pain and tenderness reduced. Afterward, lung lobectomy surgery was performed, and the tumor was excised completely. During the follow ups, there were no signs of tumor recurrence. Considering her condition, we preferred to treat her skin condition with topical therapy with corticosteroids and emollients. Then, the patient declared an improvement in pain and stiffness of the skin.

Given the onset of these lesions and their rapid spread immediately after infection with COVID-19, the imbalance of immunomodulatory factors and the activation of the autoimmune response to the virus were considered to have triggered this rapid spread. Lung cancer was accidentally found during the follow-up. Although morphea has been reported as a paraneoplastic syndrome in various types of cancer such as lung small cell carcinoma or breast carcinoma (7–9), it has not been

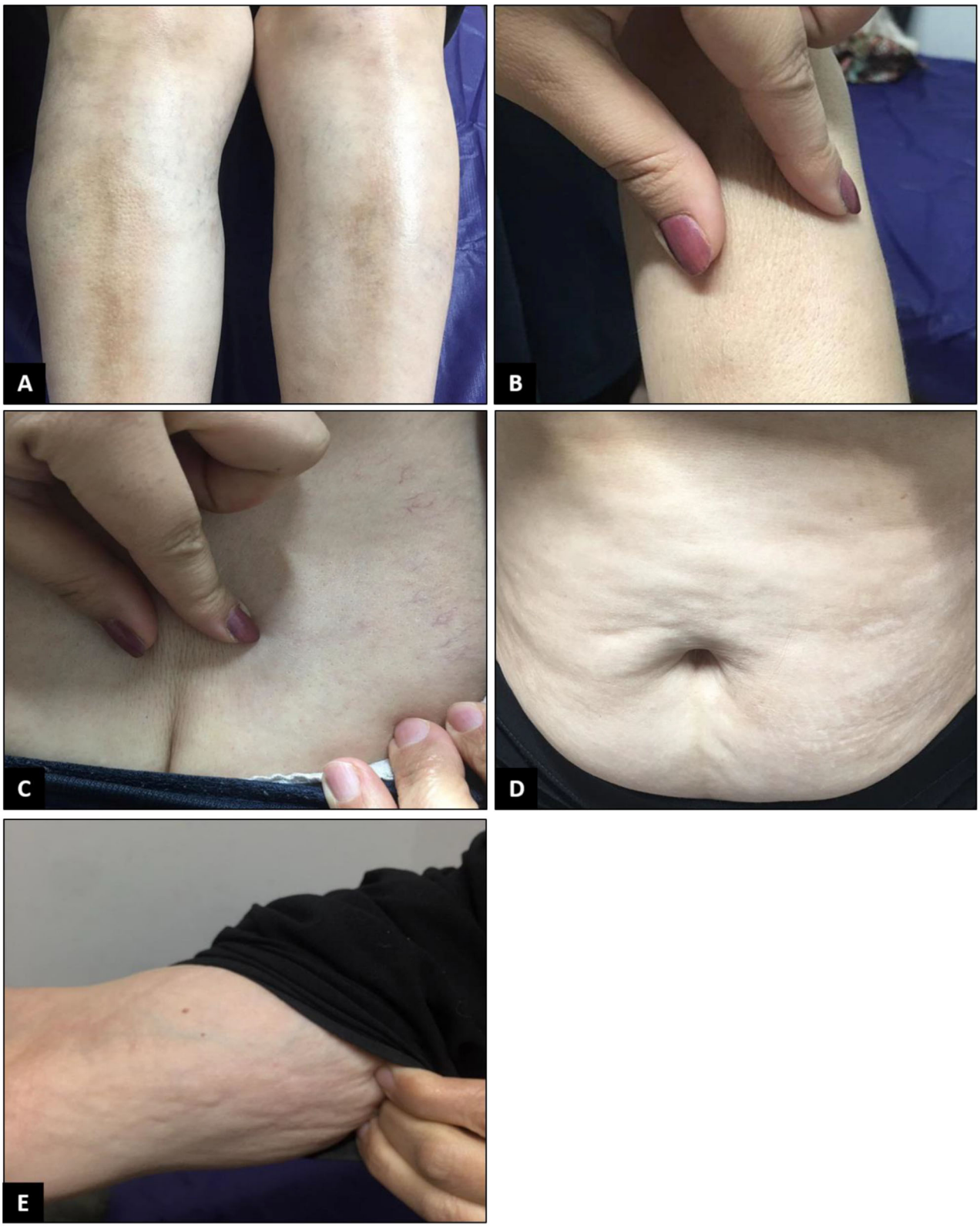

FIGURE 1 | Physical examination revealed the skin had turned shiny and tight. Severe sclerosis was detected on both pretibial regions **(A)**. When touched, the skin felt rather sclerotic and lost the ability to fold compared to normal skin **(B,C)**. Changes in the arm and lower abdomen in favor of morphea were also observed **(D,E)**.

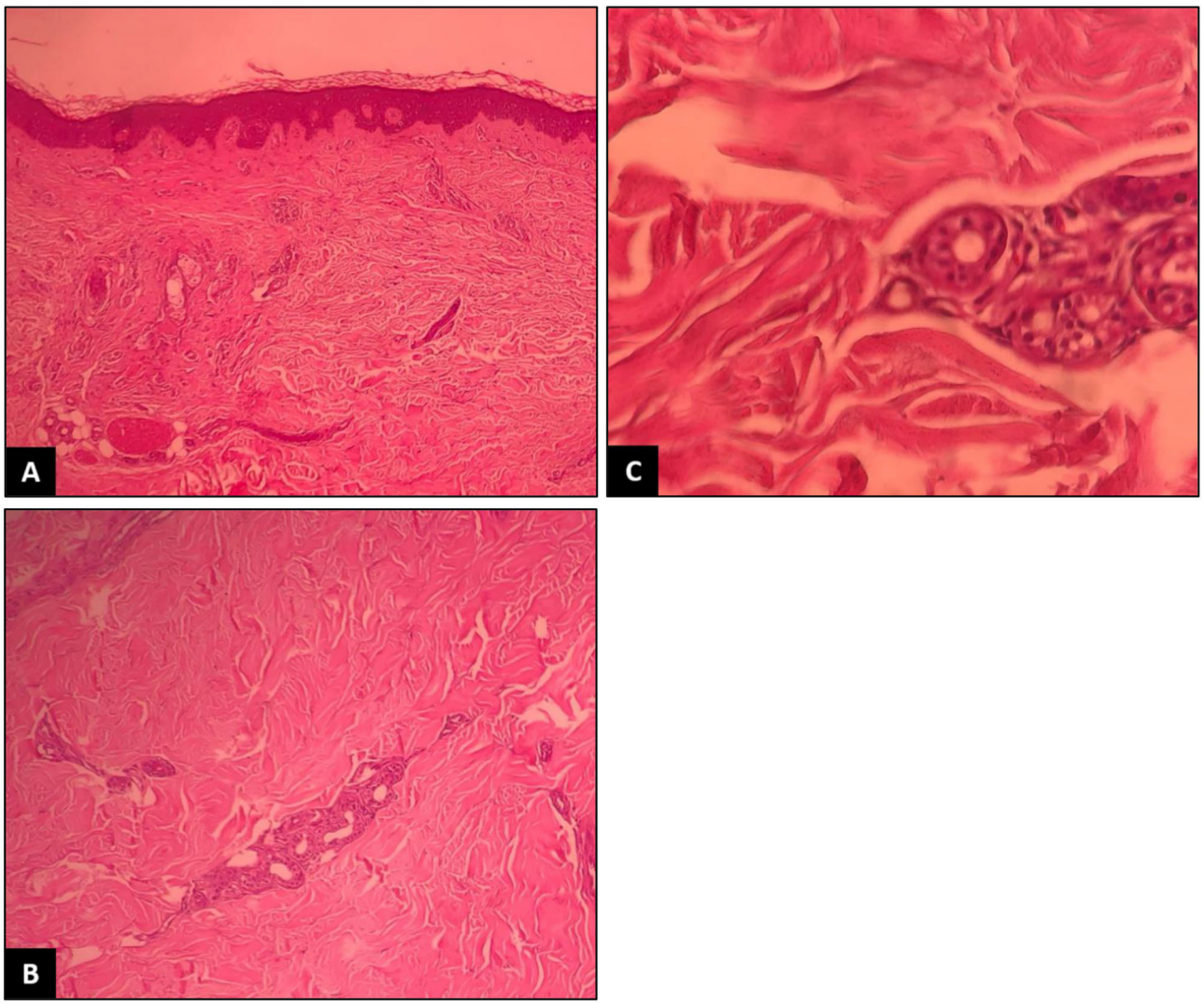

FIGURE 2 | Thickening and hyalinization of connective tissue of deep dermis, subcutaneous fat and muscular fascia, and mucin deposition **(A)**. Atrophy of adnexal structures, increased fibroblastsand dense collagens through the deep dermis **(B)**. Infiltrative changes in the eccrine glands **(C)**. No obvious eosinophilic infiltration was detected.

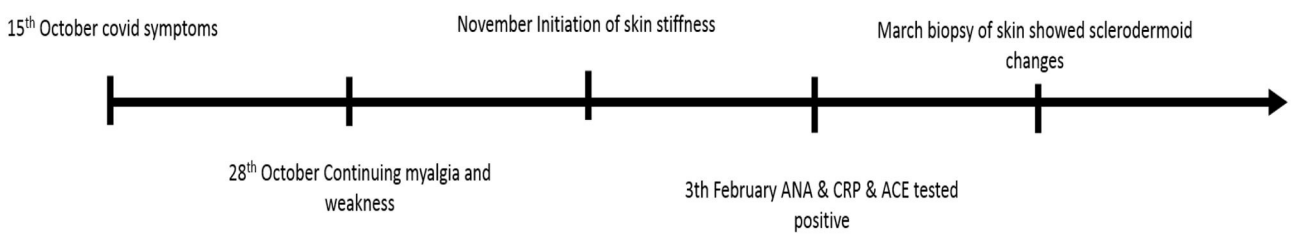

FIGURE 3 | Timeline of events.

reported as a paraneoplastic phenomenon after adenocarcinoma of the lung. Therefore, its occurrence in this patient can be more attributed to COVID-19 complications. This is the first report of this type of PSM after COVID-19 infection.

DISCUSSION AND CONCLUSION

Morphea, also known as localized scleroderma, is a chronic autoimmune disease identified by skin inflammation and

TABLE 1 | Categories of different types of morphea.

Morphea subtype		Type	Clinical manifestation
Circumscribed		Superficial	One or more round/oval lesions Histopathological changes limited to the dermis
		Deep	One or more round/oval lesions Histopathological changes involve dermis, subcutaneous tissue, fascia, or muscle
Linear		Trunk/limb	Linear lesions Probably from subcutaneous tissue without the involvement of the dermis May involve muscle or bone
		Head	Progressive hemifacial atrophy (PHA); En coup de saber (ECDS); linear lesions on the face and scalp (with possible involvement of the underlying bone)
Generalized	Coalescent plaque		$\geq$ 4 plaques in at least 2 of the 7 anatomical sites (Head and neck, right/left upper limbs, right/left lower limbs, anterior/posterior trunk) Uniform pattern: interconnected inflammatory plaques in the folds, pelvic girdle, lower abdomen, and proximal thighs. Symmetrical pattern: Peripheral symmetrical plaques around the breast, umbilicus, arm, and legs
	Pansclerotic		Peripheral involvement of large parts of the body surface (without involving the tips of the fingers and toes), including skin, subcutaneous tissue, muscle, and bone. No involvement of internal organs, which is characteristic of scleroderma
Mixed			A mixture of any of the above subtypes (for example: linear—circumscribed)

TABLE 2 | COVID-19-induced collagen-vascular diseases.

Researchers	Treatment measures	Tests	Skin lesions Timing of lesions	Patient Disease	Row
Slimani et al. (30)	**Inpatient treatment for COVID-19** ========== Single-dose hydroxychloroquine ———————— Methylprednisolone	Thrombocytopenia Lymphopenia ↑ PT ↑ D-Dimer ↑ PTT ANA Anti-dsDNA Anticardiolipin Anti-β_2 Glycoprotein Lupus Anticoagulant ↓ Complement Positive direct coombs test Proteinuria	Papular lesions	23-year-old woman	1
	No treatment for skin lesions		13 days after the diagnosis of SARS-COV-2	Systemic lupus erythematosus	
Zamani et al. (31)	**Outpatient treatment of COVID-19** ========== Hydroxychloroquine	Leukopenia Thrombocytopenia ↑ CRP ↑ LDH ↑ Troponin Anti-Ro Anti-La Anti-CCP Anti-dsDNA	Urticaria	43-year-old man	2
	Treatment for skin lesions ========== Methylprednisolone pulse ———————— Hydroxychloroquine ———————— Prednisolone ———————— Cyclophosphamide pulse		4 weeks after the diagnosis of SARS-COV-2	Systemic lupus erythematosus	

(Continued)

TABLE 2 | Continued

Researchers	Treatment measures	Tests	Skin lesions	Patient	Row
			Timing of lesions	**Disease**	
Bonometti et al. (32)	**Treatment for skin lesion** ========== Single-dose hydroxychloroquine – – – – – – – – – – – – – Methylprednisolone	Thrombocytopenia ANA Hematuria	Edema, fingertips, and lower limb cyanosis (Vasculitis of fingertips)	85-year-old woman	3
			–	Systemic lupus erythematosus	
Severino et al. (33)	**Treatment for skin lesion** ========== Topical clobetasol	–	White sclerotic lesions with red halo (lilac ring) on the trunk	62-year-old woman	4
			While recovering from SARS-COV-2	Morphea	

TABLE 3 | Other COVID-19-induced skin diseases.

Researchers	Treatment measures	Tests	Ski lesions	Patient	Row
			Timing of lesions	**Disease**	
Capalbo et al. (34)	**Diagnosis was confirmed by trichoscopy**	–	Some alopecia patches in the beard area	38-year-old man	1
			A month after infection with SARS-COV-2	Alopecia areata	
Rossi et al. (35)	**Diagnosis was confirmed by trichoscopy** **Treatment for skin lesions** ========== Triamcinolone Acetonide Topical steroids Bimatoprost Vitamin D Probiotics	–	Progressive hair loss with a patchy pattern in the vertex and parietal regions	29-year-old woman	2
			A month after infection with SARS-COV-2	Alopecia areata	
Sgubbi et al. (36)	**Outpatient treatment for COVID-19** ========== Hydroxychloroquine	-	Hair loss with a patchy pattern in the temporoparietal	54-year-old woman	3
	Diagnosis was confirmed by dermatoscopy Treatment for skin lesions ========== Topical Clobetasol		Two months after infection with SARS-COV-2	Alopecia areata	
Fivenson et al. (37)	–	–	Rapidly progressive hair loss causing loss of total body hair	56-year-old woman	4
			Two months after infection with SARS-COV-2	Alopecia areata	
Mathieu et al. (38)	**Diagnosis of psoriasis was confirmed by punch biopsy**	–	Blisters on the palms of the hands spreading to the forearms, trunk, and scalp	62-year-old woman	5
			Two weeks after the diagnosis of SARS-COV-2	Pustular psoriasis	
Dadras et al. (39)	**Inpatient treatment for COVID-19** ========== Methylprednisolone pulse	–	Extensive patch and pustular erythematous	60-year-old man	6
	Treatment for skin lesions ========== Prednisolone tapering – – – – – – – – – – – – – Acitretin		26 days after diagnosis of SARS-COV-2	Spreading pustular psoriasis	

sclerosis. Scleroderma and morphea are diagnosed with skin sclerosis and have common pathological manifestations. Both diseases present with dermal and subcutaneous sclerosis and no fibroblast proliferation. However, morphea is different from scleroderma in demographic and clinical terms. Unlike scleroderma, involvement of the internal organs is uncommon and the mortality rate is lower in morphea. Different types of morphea are shown in **Table 1** (10).

The generalized morphea is identified by more than four plaques of at least 3 cm that involve two or more anatomical regions. This type of morphea is differentiated from scleroderma by the absence of Raynaud's, sclerodactyly, no facial involvement, no nail fold involvement in capillaroscopy, no visceral involvement, and no specific autoantibodies. Although systemic sclerosis has been reported as a paraneoplastic phenomenon, the association of morphea with cancer has not been demonstrated (11).

Pansclerotic morphea is a type of severe and progressive generalized morphea that deeply spreads into the subcutaneous tissue and invades the muscles, tendons, and bones. The lesions normally appear on the extensor side of the four limbs and trunk, and gradually affect the entire body surface, including the head and neck, causing joint stiffness, deformity, ulceration, and calcification. Squamous cell carcinoma has been reported on the skin lesions of this kind of morphea (12). Disabling PSM of childhood (DPMC) is a rare subtype of juvenile localized scleroderma (JLS) characterized by pansclerosis mainly affecting children under the age of 14. This aggressive disease has a poor prognosis due to the rapid progression of deep musculoskeletal atrophy resulting in cutaneous ulceration and severe joint contractures (13).

Given the stiffness and swelling of the knee in the patient, the above-discussed case was considered to be of PSM type.

There has been much concern about the effect of COVID-19 on the incidence or exacerbation of autoimmune diseases since the outbreak of SARS-CoV-2. Numerous papers have been published about the effects of COVID-19 on the exacerbation of autoimmune diseases. The experience of COVID-19 in people with underlying skin diseases, such as psoriasis, lupus, and rheumatoid arthritis, was documented over time and led to recommendations for modifying the administration of immunomodulatory medications during the pandemic. However, the new cases of these diseases following infection with SARS-CoV-2 when the initial symptoms of COVID-19 abate. Given the high burden of collagen-vascular and chronic skin diseases on the life of the patient, we decided to gather and review articles investigating the incidence of new skin diseases reported after COVID-19 to draw the attention of specialists to this important issue (**Tables 2**, **3**). COVID-induced collagen-vascular diseases are presented in **Table 2**, and other COVID-induced skin diseases in **Table 3**. It should be noted that COVID-19 vaccination might have some similar effects on immune system responses and cause autoimmune diseases, as there have been some reports to date (14, 15). Therefore, similar reviews of literature and more investigations on that topic are recommended.

It is recommended that reports of new cases of skin diseases be gathered in review articles to help specialists in this field properly diagnose, treat, and manage such diseases.

During the pandemic, the authors especially focused on various skin manifestations of COVID-19 in their research on the subject (16–29).

LIMITATION AND STRENGTH

Our study had a limitation. We did not long-term follow-up. Because of the pandemic, the authors decided to release the information to be available to researchers as soon as possible. Thus, the diagnosis of lung cancer in between may have affected the results. However, the importance of our study is that it reported a unique and new manifestation, which is the first case of a particular type of autoimmune disease following COVID-19.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Written informed consent was obtained from the patient for participation in the study and the rights of the subject were protected. To observe ethical principles, the names of the patients were not mentioned in the paper. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

AUTHOR CONTRIBUTIONS

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

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Emerging Developments in Management of Melanoma During the COVID-19 Era

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In March 2020, the designation of the COVID-19 outbreak as a worldwide pandemic marked the beginning of an unprecedented era in modern medicine. Facing the possibility of resource precincts and healthcare rationing, leading dermatological and cancer societies acted expeditiously to adapt their guidelines to these contingencies. Melanoma is a lethal and aggressive skin cancer necessitating a multidisciplinary approach to management and is associated with significant healthcare and economic cost in later stages of disease. In revisiting how the pandemic transformed guidelines from diagnosis and surveillance to surgical and systemic management of melanoma, we appraise the evidence behind these decisions and their enduring implications.

Keywords: melanoma, coronavirus, SARS-CoV-2, malignant melanoma, COVID-19

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INTRODUCTION

Cutaneous melanoma is the fifth most commonly diagnosed malignancy in the United States, and the most lethal cutaneous cancer (1, 2). The treatment of advanced and metastatic melanoma requires a multidisciplinary team of specialists and multimodal regimens, with later stages of disease associated with significant healthcare and economic burden (1, 3). Emergence of the COVID-19 pandemic broached an unprecedented need for judicious rationalization and allocation of healthcare resources worldwide (4). In response, governing bodies released new guidelines on the management of melanoma in the COVID-19 era, shaped with a greater consciousness for minimizing patient exposure to infection and reducing healthcare consumption in mind. While in some geographical areas this has abated and vaccination rates are improving, new variants pose a risk to patients and healthcare delivery methods should variants evade the effectiveness of current vaccines. Here, we review these new guidelines, the evidence behind them and the potential implications of these recommendations as well as possible remedies.

DEVELOPMENTS IN SCREENING, DIAGNOSIS, AND DISEASE SURVEILLANCE

Screening

Early detection of melanoma is imperative for survival but restrictions to outpatient services from March to June 2020 in response to the SARS-CoV-2 pandemic resulted in a significant drop in skin cancer screenings (5). With the cessation of screenings, questions have been raised about resuming these preventative practices in the post-COVID-19 era. To date modifications of screening recommendations during the COVID pandemic have stemmed from theoretical concerns not directly from data on viral exposure or outcome data (5). Thus, it is not clear that

a change in current practice is yet warranted so long as safe patient care can be provided. The American Academy of Dermatology (AAD), the leading representative dermatological society in the United States, continues to advocate for routine screenings in their guidelines and their SPOT ME Skin Cancer campaign, with recommendations for in-person screenings in compliance with local and state Center for Disease Control and Prevention (CDC) guidelines (6). Additionally, the AAD, jointly with the Skin Cancer Foundation, endorsed continuation of self-skin examinations and application of the ABCDEs of melanoma (6, 7).

Diagnosis

Given that the diagnosis of melanoma is primarily made on skin exams, delays in screening have raised concerns for ensuing delays in diagnosis (8). The long-term consequences of the COVID-19 pandemic on survival outcomes in melanoma are effectively unknown. A study conducted by the University of Pennsylvania Dermatopathology Department found no overall difference in median Breslow thickness or T staging at time of diagnosis between the pre-COVID-19 and COVID-19 era cohorts (9). However, surgical candidates had higher median thickness and higher proportions of T3 and T4 lesions at time of diagnosis than patients from the pre-COVID era (9).

Moreover, the pandemic prompted a substantial increase in the use of telemedicine services. In a survey of International Dermoscopy Society members, there was a reported 83.3% increase in teleconsultations (10). Despite an increase in utilization of these services, 57% of total respondents recounted making zero diagnoses of melanoma, raising concerns for an increase in missed cases during this time (10). On March 6, 2020, The National Comprehensive Cancer Center (NCCN) recommended that all new patients be evaluated with telehealth when possible, with a subsequent complete history and physical on the day of surgery if necessary (11). The goal, it would seem, was to reduce in-person exposure risks. A trade-off is if modification to a treatment plan is required when the patient arrives. Additionally, if telehealth is determined to be inferior for this purpose, as suggested by data, a future increase in delayed diagnoses or upstaged melanoma may occur (11). Aside from screening, diagnostic evaluations of an obvious, perhaps self-reported, lesion could be inaccurate through telemedicine. Further data collection to assess the accuracy of telemedicine compared with in-person diagnostic evaluation would be helpful in order to interpret recommendations for or against telehealth in this setting.

A potential solution for improving diagnostic accuracy is through the integration of imaging techniques with telemedicine services. Total body photography (TBP) is a commonly used non-invasive imaging technique for the photographic assisted detection of melanoma (12). Data has shown integration of TBP and dermoscopy with telemedicine services ensues a number-needed-to-biopsy (NNB) per one case of melanoma comparable to previously published reports for in-person encounters with dermatologists and physician assistants (13, 14). Additionally, prospective results found inclusion of TBP and sequential digital dermoscopy imaging to surveillance protocols aided clinicians in detecting the majority of new lesions in high-risk patients (15). Moreover, these outcomes are likely to be improved with the integration of artificial intelligence. Despite being in its nascent stages of development, diagnostic efficacy through machine learning have been comparable to that of trained clinicians, indicating these technical advances hold significant promise in enhancing the efficacy of image-based diagnostics (16).

Surveillance

For patients with a history of melanoma, clinical surveillance can be delayed for 3–6 months in patients with asymptomatic localized disease (e.g., stages 0–II) or asymptomatic resected stage III disease, in the absence of concurrent systemic therapies, according to modified NCCN guidelines (11). In the setting of asymptomatic stage IIB/IIC melanoma, follow-up imaging can be deferred for 3–6 months (11). As screening guidelines have given wide latitude regarding frequency these modifications for surveillance screening are reasonable.

Additionally, the NCCN's adjusted guidelines related to patients on active therapy as well. Here, in the setting of adjuvant therapy, restaging was suggested to be delayed for upwards of 3 months (11). A clinician actively treating such patients need to use judgement regarding this proposed modification. The previous intention of restaging amidst adjuvant treatment was to ensure that the therapy is effective. Delaying that evaluation only continues to place the patient at risks and side-effects of the therapy without knowledge of its benefit. Since intravenous immunotherapy still obligates the patient to be available in-person repetitively every few weeks delaying restaging only reduces exposure to the Radiology department—a small imperceptible change in risk status but potentially with larger consequences should disease progression occur undetected.

DEVELOPMENTS IN SURGICAL MANAGEMENT

Local Wide Excision and Sentinel Lymph Node Biopsy

Consensus to delay LWE for up to 3 months for new cases of melanoma *in situ* and stage T1 melanoma was ubiquitous across various associations, including the NCCN, American College of Mohs Surgery, British Association of Dermatologist (BAD) and British Society for Dermatological Surgery (BSDS) (11, 17, 18). The NCCN endorsed deferring LWE for up to 3 months in patients with T1 melanoma, even in the setting of positive margins, in the absence of observable residual disease (11). However, larger enduring lesions should be excised in an office setting (11).

Current evidence on the association between surgical timing from excisional biopsy to LWE and survival have been inconsistent (18). A retrospective study of patients with cutaneous melanoma found time from excisional biopsy to LWE did not result in meaningful differences in overall survival (OS) and disease free survival (DFS) between surgical groups (19). However, analyses of patients with stage I–III melanoma in the National Cancer Database (NCBD) found LWE within 60 days of

diagnosis granted a modest survival advantage while LWE ≥90 days after initial biopsy was associated with increased mortality (20, 21). Additional prospective studies are needed to ascertain the effect of surgical timing on survival outcomes given the limitations of retrospective studies.

On March 24, 2020, the European Society for Medical Oncology (ESMO) published their own guidelines on the management of melanoma in the COVID-19 era, stratifying patients into high, high to medium, and low priority treatment groups (22). LWE and sentinel LN biopsy were recommended for all patients with invasive T1b disease or higher, with T3 and T4 lesions assigned high priority and T1 and T2 lesions designated medium priority for excision (22). In the U.S., the NCCN recommended discussing sentinel LN biopsy for lesions of stage T1b or higher, with the potential for delaying LN biopsies for up to 3 months unless LWE in an operating setting is planned (11). These recommendations were formulated to reduce patient and staff exposures. Also early in the pandemic a shortage of supplies and resources was either real or perceived. As understanding of infection risks, mitigation thereof, improved delivery of supplies and vaccinations programs have been carried out and resumption of surgical services have occurred. Surgical guideline modifications may not need to be as stringent moving forward. Furthermore, delay of definitive surgery can lend to increased patient anxiety and would require careful patient counseling in this situation.

Resections and Lymphadenectomies

The NCCN advocated for deferring therapeutic lymphadenectomies for palpable LN, and offering neoadjuvant therapy, including immune-checkpoint inhibitors (ICIs) or BRAF/MEK inhibitors, instead (11). However, in the absence of available adjuvant therapies, the British Association of Plastic and Reconstructive Aesthetic Surgeons (BAPRAS) considered lymphadenectomies a viable primary treatment for achieving local control for recurrent nodal disease (23). For non-metastatic stage III melanoma, surgical resection should be performed 8–9 weeks following initiation of neoadjuvant therapy according to modified NCCN guidelines (11). Additionally, resections of metastatic stage III and IV disease should be deferred, unless the patient is critical or symptomatic, with continuation of systemic monotherapy instead (11). ESMO considered curative resections of stage III lesions, surgery for patients on neoadjuvant therapies, and management of surgical complications as high priority, but recognized delaying surgery is acceptable as it has not been shown to influence survival in many cases (22).

Radiotherapy

Patients with stage IV disease and brain metastases are high-priority for radiotherapy according to ESMO guidelines (22). In accordance, the NCCN guidelines recommended stereotactic radiosurgery as initial treatment for patients with symptomatic or steroid-dependent metastatic disease and endorses discontinuation of, or tapering steroids when initiating ICIs (11). Evidence for ICIs in patients with metastatic melanoma after stereotactic radiosurgery (SRS) have been reported in several retrospective studies but these findings have been inconsistent and additional prospective studies are still ongoing (24–27). With respect to radiotherapy of brain metastases amidst the pandemic, it is difficult to advise modification of this treatment modality as there is not an equivalent for it. Diligent screening of patient symptoms, rapid COVID testing and use of PPE is imperative in this case.

DEVELOPMENTS IN SYSTEMIC TREATMENTS

Neoadjuvant Therapies—Immune Checkpoint Inhibitors

Consideration for the possibility of resource limitations was commonly addressed across multiple guidelines, especially in the case of neoadjuvant therapies. Although the NCCN recognized that neoadjuvant therapy is not superior to combination surgery and adjuvant therapy, neoadjuvant therapy for primary management of stage III disease may be a judicious option in the setting of resource limitations (11). For neoadjuvant ICI, the NCCN and ESMO both recommended a regimen of higher dose pembrolizumab at 400 mg every 6 weeks or nivolumab at 480 mg every 4 weeks (11, 22). On April 28, 2020, the FDA approved the accelerated regimen of pembrolizumab following the results of the KEYNOTE-55 trial (28). Interim analysis found 400 mg of pembrolizumab every 6 weeks was comparable to the original regimen of 200 mg every 3 weeks (29). An accelerated regimen is advantageous as longer intervals between cycles minimizes exposures.

Regarding dual therapy, the NCCN, ESMO and BAPRAS recommended clinicians exercise caution when starting combination ICI regimens (11, 22, 23). Results of Checkmate-067 found combination nivolumab-ipilimumab therapy significantly prolonged OS than nivolumab or ipilimumab alone (60.0 vs. 36.9 vs. 19.9 months) but correspondingly produced increased rates of grade ≥3 adverse events (AE) from 20–30% to 50–60% (30).

Immune-related AE (irAE) are due to an augmented immune response secondary to ICI therapy (31). Immunosuppressants are frequently used to temporarily attenuate the immune response, but can promote an increased risk for COVID-19 infections (8, 32). Pneumonitis can be a confounding toxicity that can mimic an active SARS-CoV-2 infection with symptoms such as shortness of breath, cough and dyspnea (33). The NCCN recommended COVID-19 testing if a diagnosis of pneumonitis was suspected prior to initiation of steroids (11). While this was a reasonable recommendation, in practice patients have not always been able to expeditiously schedule testing or receive quick results depending on their locale. A potential delay in treatment of pneumonitis can have high morbidity and exemplifies an unintended negative outcome that new recommendations can promote. For routine monitoring of patients on ICIs, the ESMO, and BAPRAS both endorsed routine telemedicine visits, and labs at healthcare facilities equipped with appropriate COVID-19 precautions (22, 23).

Taking into consideration the risk and benefits, the decision for initiation of dual ICI therapy should be made on an individual basis according to the NCCN and ESMO (11, 22). The BAPRAS recommended monotherapy in the setting of metastatic disease for all but high risk patients (23). Likewise, the NCCN endorsed dual ICI therapy for stage IV disease with brain metastases, citing superior intracranial tumor response to ICIs (11). A number of phase II trials have shown improved response rates of brain metastases associated with dual immunotherapy over other agents but the phase III NIBIT-M2 trial assessing ICIs in the treatment of melanoma brain metastases is still ongoing (34, 35).

For stage IV disease, a regimen consisting of nivolumab 1 mg/kg and ipilimumab 3 mg/kg (NIVO1+IPI3) for four cycles has been established (11). An alternative regimen of nivolumab 3 mg/kg and ipilimumab 1 mg/kg (NIVO3+IPI1) may be considered if there is notable concern for irAE according to the ESMO and NCCN (11, 22). These recommendations were based on the results of CheckMate 511, which showed the alternative regimen of NIVO3+IPI1 decreased the incidence of grade 3–5 AEs (34 vs. 48%), with no meaningful difference between median progression free survival (PFS) (9.9 vs. 8.9 months) or overall response rate (45.6 vs. 50.6%) compared to the prior NIVO1+IPI3 regimen (32, 36). Applying the alternate dosing strategy will substantially reduce dual ICI risks during the pandemic.

In the setting of a SARS-CoV-2 infection, patients can resume immunotherapy once fully recovered or after 10 days from last presentation of symptoms under the BAD and BSDS guidelines (17). There is currently no clear evidence that use of ICIs worsens outcomes of COVID-19 infections (37–39). Nonetheless, there is evidence to suggest ICIs may be discontinued in patients with metastatic melanoma who achieved complete remission with PD-1 blockade (40). Follow up analysis of KEYNOTE-001 showed patients with melanoma who discontinued pembrolizumab after complete response to PD-1 blockade had comparable rates of DFS to that of all complete responders (e.g., including those who continued ICI therapy) at 24 months (89.9 vs. 90.9%) (40).

Neoadjuvant Therapies—Targeted Therapy

The ESMO considered targeted therapy high priority in patients with non-operable stage III and IV disease (22). The NCCN recommended a regimen of BRAF/MEK inhibitors for 8 weeks followed by surgery in the setting of neoadjuvant therapy (11). Specifically, the BAPRAS recommended combination encorafenib and binimetinib, given these agents are less likely to mimic the symptoms of SARS-CoV-2 infections compared to ICIs (23). The most common grade 3–4 AEs associated with dual BRAF/MEK inhibitor therapy include elevated gamma-glutamyl transferase (9%), creatine phosphokinase (7%), and hypertension (6%) (41).

Adjuvant Therapies

Adjuvant therapy can be delayed for up to 12 weeks in accordance with NCCN and ESMO guidelines (11, 22). This seemed reasonable given that trial design which established adjuvant therapy allowed for this type of delay in most cases (42, 43). Patients with high-risk stage III disease, defined as sentinel LN deposit >1 mm or stage >IIIa disease, are considered high to medium priority for adjuvant therapy according to ESMO (22). In contrast, the BAPRAS only recommended adjuvant therapy in the setting of stage IIIc, IIId, and IV disease, but not in stage IIIa or IIIb cases (23). Restricting adjuvant therapy by these guidelines appears arbitrary and undoubtedly will lead to a reversal in average OS gains. It also contradicts the aforementioned consideration of starting neoadjuvant therapy on advanced stage melanoma patients in order to briefly postpone surgery.

Depending on hospital operations and resources, ESMO advised physicians to consider starting patients on a BRAF/MEK inhibitor given the ease of oral dosing, with a potential for transition to intravenously routed immunotherapies later on (22). Currently, there are no head to head trials comparing survival outcomes of adjuvant BRAF/MEK inhibitors with adjuvant ICIs for resected stage III melanomas (44). In the COMBI-AD trial, patients treated with combination BRAF/MEK inhibitor therapy of dabrafenib plus trametinib had an estimated 58% relapse-free survival rate at 3 years, compared to 39% with placebo (45). However, high rates of fever (63%) and chills (37%), as well as other flu-like symptoms associated with dabrafenib plus trametinib may make this combination counterintuitive (45). Such symptoms amidst a viral pandemic could be confounding, leading to anxiety and increased in-person resource use. Comparably, KEYNOTE-054 showed patients with resected stage III melanoma treated with adjuvant pembrolizumab had a 64% relapse-free survival rate, compared to 44% in placebo group at 3-year median follow up (42). Given that immunotherapy is not likely to cause fevers and chills, it is especially attractive at the present tine as an adjuvant strategy having similar efficacy on cross trial comparison to combination BRAF/MEK inhibitor therapy.

CONCLUSIONS

The COVID-19 pandemic swept in a period of uncertainty and forced clinicians to rethink the existing paradigms in treatment of melanoma to minimize both healthcare consumption and exposure. The unforeseen nature of the pandemic required societies to act quickly and swiftly to enact provisional guidelines and served as a catalyst for adapting new applications such as telemedicine into routine practice. A general impetus has been to limit patient exposure, reduce durable supply use and allow for redeployment of medical resources in a priority manner. How this will affect patient care will be the subject of review for years to come. The data generated during the pandemic to date is likely not robust enough to merit recommending long-term practice changes. Yet, despite the provisional nature of these guidelines, the COVID-19 pandemic highlighted many opportunities for optimization in our healthcare system. For instance telehealth may become more wide-spread and potentially could include software technology to assist in improving diagnostic accuracy. Neoadjuvant therapy, if appropriate, can defer surgery and operating room risks and resources, potentially until a pandemic has subsided or

resources and PPI restocked. Systemic therapies have been scrutinized and compared to assess efficacy and side-effects. Clinical judgement on selecting these and the appropriate dose and schedule is still important. Despite best efforts some recommendations can be controversial in producing unintended consequences. As shown one recommending body may conflict with another. Hopefully ongoing efforts will provide input on cancer patient outcomes on and off therapy during this pandemic (46). Until further evidence based data is available clinicians will be challenged to modify cancer care safely for their patients' welfare.

AUTHOR CONTRIBUTIONS

AL: provided the conception and was a major contributor in writing the manuscript. MV: drafted and revised the manuscript critically for important intellectual content. DR: was a major contributor in writing the manuscript and revised it critically for intellectual content. AL, MV, and DR: provided final approval of the version of the manuscript to be published and agree to account for all aspects of work in ensuring accuracy and integrity. All authors contributed to the article and approved the submitted version.

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REVIEW
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Biologics for Psoriasis During the COVID-19 Pandemic

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Coronavirus disease 2019 (COVID-19), a new form of acute infectious respiratory syndrome first reported in 2019, has rapidly spread worldwide and has been recognized as a pandemic by the WHO. It raised widespread concern about the treatment of psoriasis in this COVID-19 pandemic era, especially on the biologics use for patients with psoriasis. This review will summarize key information that is currently known about the relationship between psoriasis, biological treatments, and COVID-19, and vaccination-related issues. We also provide references for dermatologists and patients when they need to make clinical decisions. Currently, there is no consensus on whether biological agents increase the risk of coronavirus infection; however, current research shows that biological agents have no adverse effects on the prognosis of patients with COVID-19 with psoriasis. In short, it is not recommended to stop biological treatment in patients with psoriasis to prevent the infection risk, and for those patients who tested positive for SARS-CoV-2, the decision to pause biologic therapy should be considered on a case-by-case basis, and individual risk and benefit should be taken into account. Vaccine immunization against SARS-CoV-2 is strictly recommendable in patients with psoriasis without discontinuation of their biologics but evaluating the risk-benefit ratio of maintaining biologics before vaccination is mandatory at the moment.

Keywords: COVID-19, psoriasis, biologics, TNF, IL23, IL17, vaccination, SARS-CoV2

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread across the globe rapidly since its outbreak (1, 2). Similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), the SARS-CoV-2 can cause excessive and aberrant non-effective host immune responses that are associated with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (3, 4). Ren et al. (5) identified five hyperinflammatory cell subtypes that might be the major sources driving the inflammatory storm in lung injury, including a subtype of macrophage (Macro_c2-CCL3L1), three subtypes of monocytes (Mono_c1-CD14-CCL3, Mono_c2-CD14-HLA-DPB1, and Mono_c3-CD14-VCAN), and neutrophils. These hyper-inflammatory subtypes highly express specific cytokines, for example, Macro_c2-CCL3L1, specifically expresses CCL8, CXCL10/11, and interleukin (IL)-6; Mono_c1-CD14-CCL3 uniquely expresses high levels of IL-1β, CCL20, CXCL2, CXCL3, CCL3, CCL4, HBEGF, and tumor

necrosis factor (TNF); and neutrophils express cytokines including TNFSF13B, CXCL8, FTH1, and CXCL16. This is consistent with the research results of Blanco-Melo et al. (6).

Psoriasis is an immune-mediated inflammatory skin disease with erythema, papules, and scales as the main clinical manifestations, in which both genetic and environmental factors participate. A self-sustaining cycle of inflammation plays an important role in psoriasis pathogenesis, mediated mainly by T cells and cytokines such as TNF-α, IL-23, and IL-17 (7). With these cytokines as targets, biological agents have become a major innovation in the treatment of psoriasis in the past 20 years and drastically changed our ability to treat psoriasis and psoriatic arthritis. Until now, there are biologics in four different classes (anti-TNF-α, anti-IL-17, antiIL-12/IL-23p40, and anti-IL-23p19) have been approved for the treatment of moderate-to-severe psoriasis (8).

Biologics are considered to have high infection risks, and some studies found that the overall infection rate is higher than that of placebo (9, 10). However, it is inappropriate to speculate the susceptibility of SARS-CoV2 according to these previous studies because these studies did not analyze the risk of virus infection separately. More importantly, a published study suggested that the SARS, which has similar pathogenesis with SARS-CoV-2, may have a different immune response compared with other respiratory viruses (11). In the pandemic era, explaining the relationship between biologics and coronavirus infection is imperative. Our review will summarize key information that is currently known about the impact of biologics on the risk of SARS-CoV-2 infection and severe COVID-19 outcomes.

BIOLOGICAL AGENTS FOR PSORIASIS AND COVID-19 INFECTION

Anti-TNF-α

Tumor necrosis factor α (TNF-α) is an inflammatory cytokine produced by macrophages/monocytes during acute inflammation. It plays an important role in host defense against intracellular bacterial infections, such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*, and it is indispensable in epithelial granuloma formation (12–15). Currently, four anti-TNF-α agents are in use for psoriasis: adalimumab, certolizumab pegol, etanercept, and infliximab (16). A fifth anti-TNF-α agent, golimumab, is currently approved for the treatment of psoriatic arthritis but not psoriasis (8).

The role of TNF-α in virus defense is complex, and different viruses seem to have different immune effects. An early *in vitro* study showed that H5N1 virus infection was capable of leading to highly excessive TNF-α secretion by macrophages, quantitatively similar to that seen after stimulation with lipopolysaccharide (17). This means that if TNF-α participates in the inflammatory cascade, which results in lung injury in virus infection, then TNF-α inhibition could have the potential to dramatically reduce this lung damage. This has been certificated in an animal trial, in which mice with lung disease caused by respiratory syncytial virus or influenza virus have a dramatic reduction of overall illness severity without interfering with viral clearance after anti-TNF antibody treatment (18). For SARS-CoV-2, higher serum levels of TNF-α have been observed in many patients with severe COVID-19 compared with individuals with mild disease (19, 20). Based on these findings, after the outbreak of the COVID-19, the use of TNF-α inhibition to treat this disease was proposed (21). However, the role of TNF-α in the inflammatory response is still unclear, and key questions are whether and when anti-TNF-α therapy should be given. Therefore, more research and clinical trials are needed to confirm the effectiveness of TNF-α blocking treatment in COVID-19.

The increased risk of opportunistic infections by anti-TNF-α therapies has been reported in patients with inflammatory bowel disease (22). However, there are no relevant research results on the risk of infection of SARS-CoV-2 for patients with psoriasis with anti-TNF-α therapy. Some current case reports show that patients with psoriasis receiving TNF-α inhibition therapy can recover from the infection, even without any clinical symptoms. Conti et al. (23) described a case series of four patients with psoriasis treated with biologics who had a risk contact with COVID-19. In the series, a 67-year-old woman receiving adalimumab since September 2019 was quarantined because of contact with three of her family members suffering from mild COVID-19. This patient with psoriasis did not develop any signs or symptoms of COVID-19 while continuing adalimumab therapy during her quarantine. Another case reported by Valenti et al. (24) presented a 57-year-old male patient with psoriasis and psoriatic arthritis treated with adalimumab since June 2018. He was confirmed with Sars-CoV-2 infection and hospitalized, and he soon recovered from his COVID-19. The resumed adalimumab treatment after discharge did not cause a relapse of COVID-19-related symptoms. It seems that anti-TNF-α use does not lead to a serious outcome for patients with COVID-19. However, ARDS has been reported in patients with psoriasis under anti-TNF-α therapy (etanercept), in which the patient was affected by multiple comorbidities including obesity, hypertension, diabetes, and chronic renal failure (25). The relation between anti-TNF-α and ARDS is still not clear. Investigations with higher evidence, such as cohort study, and systematic reviews are needed to clarify it.

Anti-IL17A/IL17R

There are several anti-IL-17 agents approved for psoriasis treatment, including secukinumab, ixekizumab, and brodalumab. Both secukinumab and ixekizumab specifically target IL-17A, and brodalumab targets the IL-17 receptor A unit (IL-17RA), inhibiting IL-17A, IL-17F, and two other members of the IL-17 cytokine family (IL-17C and IL-17E or IL-25) (26). Bimekizumab, targeting both IL-17A and IL-17F, is in phase 3 clinical trial for psoriasis (27). The IL-17 family includes six IL-17-family ligands [IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F], and five receptors (IL-17RA, IL-17RB/IL-25R, IL-17RC, IL-17RD/SEF, and IL-17RE) (28). IL-17A (hereafter referred to as IL-17) is the most intensively studied, and it is produced by multiple immune cells including T cells, macrophages, dendritic cells (DCs), natural killer cells, natural killer T cells, lymphoid tissue inducer cells, and γδ-T cells (29).

IL-17 plays a vital role in protecting the host from infection, and this is particularly evident at the skin and mucosal sites, such as the lung, gut, and oral cavity. It performs immune defense functions mainly *via* stimulation of granulopoiesis and neutrophil trafficking and promotes the expression of various anti-microbial genes. However, IL-17 is not always beneficial in protecting the host from infection. In certain infectious settings, it can mediate pathogenic inflammatory responses and contribute to inflammatory injury secondary to infection (28). Its predominant role seems to be dependent on where the cytokine is expressed (the gut, lung, or skin) and what the precipitating trigger is. These two factors appear to influence whether the prevailing effect of its expression is protective or whether it leads to a detrimental hyper-inflammatory state (30).

Similar to TNF-α, the mean serum levels of IL-17 in the patients with COVID-19 were significantly higher than those observed in the control group. And systemic IL-17 level was observed to have a positive and significant correlation with TGF-β, which is seen as a predictive factor of disease severity in patients with COVID-19 (31–33). The synergistic effects with IL-6 to prevent apoptosis of infected cells and promote the virus persistence and stimulating downstream cytokine release may be a possible molecular mechanism in immune injury by virus (30, 34). These effects suggest that IL-17 may be related to cytokine storm and disease severity, and IL-17 inhibitors could be presented as promising targets for the prevention of aberrant inflammation and acute respiratory distress in COVID-19. Of note, there is a clinical trial on the safety and efficacy of ixekizumab treatment for patients with COVID-19 in progress in China (35).

Galluzzo et al. (36) conducted a 136-week, real-life study of 151 patients with moderate-to-severe plaque psoriasis being treated with secukinumab, and they found that there were no cases of confirmed infection with SARS-CoV-2 among 119 patients who continued to receive treatment with secukinumab. Only one patient had been placed in quarantine due to contact with a COVID-19 positive patient, and he completed the isolation period without infection. Balestri et al. (37) reported a patient with psoriasis infected with COVID-19 completely asymptomatic during ixekizumab induction treatment, and he recovered from COVID-19 without any antiviral therapy 1 month later. Mugheddu et al. (38) reported two patients with psoriasis infected with SARS-CoV-2 while on long-term secukinumab administration. They rapidly recovered from the infection between the two scheduled doses of secukinumab. For those who are elderly and affected by hypertension, which is both risk factors found to be associated, respectively, with overall case-fatality rate and severity of COVID-19, there seems still is a favorable outcome with secukinumab (39).

Current knowledge and clinical practice have shown that IL-17 inhibition will not interfere capacity of patients to develop excellent responses to SARS-CoV2. Therefore, it can be safely continued in patients with psoriasis exposed to COVID-19, with a favorable course and rapid recovery even in more critical patients.

There is no evidence that IL-17 inhibition can increase the risk of SARS-CoV-2 infection or lead to a severe outcome. However, Foti et al. (40) reported a contrary case in which a 57-year-old man with psoriatic arthritis who was treated with methotrexate and secukinumab reported COVID-19 symptoms and was tested for SARS-CoV-2 positive. This patient developed rapid worsening of clinical symptoms and resulted in ARDS. Unlike the previous findings, low IL-6 values were found at all stages of the disease in this patient, and the authors think other cytokines and mechanisms may have a role in this critical patient with COVID-19 who progressed to multiple organ dysfunction. In this case, the effect of methotrexate also should be taken into consideration. Methotrexate has been reported to significantly decrease IL-6 and TNF-α in T cells (41). This may lead to an insufficient immune response for virus defense. A meta-estimate on the risk of respiratory tract infections (RTIs) and symptoms in patients with psoriasis treated with IL-17 inhibitor biologics found an increased risk of RTIs compared with placebo (odds ratio, 1.56; 95% CI:1.04–2.33) (42). These findings indicate that it is necessary to evaluate the impact of IL-17 inhibitors on RTIs in the pandemic more meticulously. And clinicians should use their clinical judgment to help patients make clinical decisions about whether to discontinue biological agents.

Anti-IL23

IL-23 is a heterodimer composed of a p40 subunit also found in IL-12 and a p19 subunit exclusive to IL-23 (43). IL-23 is involved in promoting chronic tissue inflammation during infection, granuloma formation, and autoimmunity by maintaining the amplification of Th17 and cytotoxic T-cell type 17 (Tc17) responses. The IL-23/Th17 immune axis has been identified as a major immune pathway in psoriasis pathogenesis, in which IL-23 plays a predominant driver (44). There are currently four agents that target IL-23 in clinical use for psoriasis: ustekinumab, which blocks the common p40 subunit of IL-12 and IL-23, and guselkumab, risankizumab, and tildrakizumab, which target the p19 subunit of IL-23. A fourth anti-IL-23p19 biologic, mirikizumab, is currently in phase 3 clinical studies (8).

Different from TNF-α and IL-17, which respond to coronavirus and viral pneumonia, IL-23 does not seem to contribute to these complications, neither to have a major impact on anti-viral immunity (23). The safety of IL-23 inhibitors during the COVID-19 epidemic has also been reported. A multicenter study conducted during the first 4 months of the pandemic in Central Italy showed excellent tolerance and safety of risankizumab. In the study, only one patient (1.8%) experienced upper RTI, three patients (5.3%) had contact with SARS-CoV-2-infected subjects, and no one experienced SARS-CoV-2 infection among 57 patients (45). These results indicated that the use of IL-23 inhibitors will not increase the rate of SARS-CoV-2 infection. A series of clinical case reports also indicate that IL-23 inhibitors will not allow patients to experience a more serious disease process or outcome. Patients who suffered COVID-19 during their anti-IL-23 treatment achieved full recovery from COVID-19 and remained asymptomatic or developed mild symptoms, even some at risk of severe COVID-19 development (46–48). As a driver for IL-23/Th17 immune axis, IL-23 plays a role by increasing IL-17 in psoriasis pathogenesis. Theoretically, it has little impact on interferon-γ or mucosal immune, which is

important for virus defense. So, this may contribute to the low SARS-CoV-2 infection risk, and its attenuation effects on IL-17 may result in a milder manifestation of COVID-19.

THE RELATIONSHIP BETWEEN PSORIASIS AND COVID-19

The Risk of COVID-19 Infection and Outcome in Psoriasis on Biologics Therapy

As early as when the COVID-19 epidemic broke out, research on the safety of biological agents during the special period began to appear. The results of an observational study of 107 patients with psoriasis treated with biologics conducted in Wuhan showed that none of the 107 patients with psoriasis were diagnosed with COVID-19, including 55 (51.4%) patients who were either residents or had traveled to Wuhan after November 2019. Four patients (3.7%) had a history of close contact with patients infected with COVID-19, but none of these patients developed any COVID-19 symptoms (49).

As the epidemic spreads globally, more reports have emerged describing the susceptibility to COVID-19 and the severe clinical course of the disease. The results of several cohort studies from Italy conducted by Gisondi et al. (50) show that, compared with the general population, the use of biological agents for patients with psoriasis does not increase the infection rate, hospitalization rate, and mortality of COVID-19. They found the COVID-19 incidence rate (IR) was 9.7 (95% CI 3.9–20.1) per 10,000 person-months in a 1,830-patient cohort and 11.5 (95% CI 11.4–11.7) per 10,000 person-months in the general regional population. The IR of hospitalization for COVID-19-related pneumonia and COVID-19-related death was 6.5 (95% CI 2.0–15.6) and 0 (95% CI 0–10.4) per 10,000 person-months in their cohort, lower than the general population with 9.6 (95% CI 9.4–9.7) and 1.16 (95% CI 1.10–1.21) per 10,000 person-months. Here, we speculate that there may be two factors contributing to these results. First, long-term use of anti-inflammatory agents (including biologics) for patients with psoriasis may reduce the release of inflammatory cytokines and alleviate the inflammatory damage; moreover, patients with psoriasis may tend to have stricter personal protective measures and social isolation for fear of infection. Similar observations are also shown in their other two papers (51, 52). Another observational study from Italy also observed that the incidence of COVID-19 observed in the cohort of patients with psoriasis (0.2%) is similar to that seen in the general population (0.31%), and the course of the disease was mild in most patients (53) and similar observational conclusions have been confirmed in other studies (54–57).

When compared with patients with psoriasis without biological agents, there comes to a consistent conclusion. Mahil et al. (58) analyzed the factors for adverse outcomes in 374 patients with psoriasis infected with COVID-19, and they found biologic use was associated with a lower risk of COVID-19-related hospitalization than with the use of non-biologic systemic therapies. A multicenter study in Istanbul recorded demographics and disease characteristics of 1,322 patients with psoriasis with a semi-structured questionnaire. The results of the study showed that 23 patients have been diagnosed or suspected of COVID-19, and the rate of distribution of biological treatment in COVID-19(–) and COVID (+) groups showed no statistically significant difference. Hospitalization from COVID-19 between patients using biologics ($n = 9$) and those not using them ($n = 14$) also did not have a statistically significant difference. These data further indicate that biologics do not have any adverse impact on COVID-19 infection or outcome in patients with psoriasis. The current research results seem to be encouraging; however, clinicians should be cautious when giving treatment recommendations based on this because these studies have some limitations on the whole, such as lack of standardization for the control group, insufficient sample size, and confounding factors that are no get controlled. Therefore, rigorously designed randomized controlled trials with larger samples are needed to further confirm these conclusions.

The Impact of Psoriasis Itself on COVID-19 Infection

Most of the current research focuses on the impact of psoriasis treatment or comorbidities on the COVID-19, and there are few studies on the impact of psoriasis itself on the disease. Research shows psoriasis is one of the most common dermatological diseases in patients with COVID-19 who have had dermatological diseases for the last 3 years. Tan et al. (59) also had a similar finding. They studied 133,589 patients diagnosed and 48,418 patients hospitalized with COVID-19 with prevalent autoimmune diseases, and they found that the most prevalent autoimmune conditions among patients with COVID-19 were psoriasis (3.5–32.5%), rheumatoid arthritis (3.9–18.9%), and vasculitis (3.3–17.6%). These can pose a possibility that patients with psoriasis may be more vulnerable to the COVID-19. But the difference in the morbidity of prevalent autoimmune diseases should be taken into account when explaining the data. However, some subsequent studies showed different results. Yiu et al. (60) performed a cross-sectional study to investigate the risk of COVID-19 infection in psoriasis. They found among 1,427 patients with psoriasis, there were only 12 patients diagnosed with COVID-19, and no statistically significant elevated risk for infection with COVID-19 was found (unadjusted odds ratio, OR 0.60 [95% CI 0.33, 1.08], complete case adjusted OR 0.98 [95%CI 0.46, 2.08], and MI adjusted OR 0.50 [95% CI 0.28, 0.92]). A retrospective cohort study conducted by Raiker et al. (61) suggested that patients with Pso-COVID and PsoA-COVID were not at higher risk for severe COVID complications. The history of immunosuppressant use in both cohorts also revealed no higher risk in COVID complications. Compared with patients with non-Pso-COVID, patients with Pso-COVID had a similar risk of hospitalization (0.90 [0.78–1.03]), sepsis (0.78 [0.54–1.14]), mortality (0.82 [0.57–1.19]), and severe COVID (0.77 [0.58–1.03]), even had statistically significant lower risk of ARDS (0.51 [0.30–0.90]), and mechanical ventilation (0.65 [0.45–0.95]). As currently available evidence is relatively scarce and has certain limitations, further research in larger cohorts with representative denominators is needed to confirm this finding and to observe the longer-term impacts.

The Impact of COVID-19 Infection on Psoriasis

The host cell entry of SARS-CoV-2 depends on the angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2). ARS-CoV-2 enters the host cell by its spike protein interacting with the receptor ACE2 present on the host cell surface. TMPRSS2 plays a vital role in cleaving the SARS-CoV-2 spike protein, thereby enabling the virus to enter the host cell by endocytosis (62, 63). Since the outbreak of COVID-19, numbers of case reports and clinical series have described a complex spectrum of skin manifestations associated with the infection (64). Sun et al. (65) found that the co-expression of ACE2 and TMPRSS2 was particularly found in the granulosum of skin, so they proposed the hypothesis that skin is a potential host of SARS-CoV-2 and there is a potential risk of SARS-CoV-2 transmission *via* wounded skin in those with skin manifestations of the disease. Controlled studies on patients with psoriasis have shown a significantly increased expression of ACE2 ($p = 0.009$) in lesion skin compared with healthy controlled skin, but no significant difference was observed for TMPRSS2 ($p = 0.19$) (63, 66). These findings suggest that whether the skin lesions of patients with psoriasis are the target of SARS-CoV-2 infection still needs further investigation.

Psoriasis is a chronic inflammatory disease that can be aggravated by drug, stress, and viral infection, especially rhinovirus and coronavirus (67–70). In the era of the pandemic, Kutlu and Metin et al. (71) presented for the first time a case of psoriasis potentially triggered by COVID-19 infection and hydroxychloroquine. They reported a 71-year-old woman who had a history of psoriasis but without skin lesions when admitted to the pandemic clinic with the diagnosis of COVID-19. The patient had a recurrence of psoriasis on the 4th day of COVID-19 treatment with oseltamivir and hydroxychloroquine. Similarly, the exacerbation of pustular psoriasis and psoriatic arthritis also could be observed in COVID-19 who were treated with hydroxychloroquine (72–74). These suggested that the exacerbation of psoriasis was due to the use of hydroxychloroquine, but do not rule out the possibility that the COVID-19 virus might play a role in the process. Subsequent case reports provided some evidence for the vision. A 38-year-old man who confirmed COVID-19 infection was presented had an acute guttate flare of chronic psoriasis during his quarantine without any treatment (75). Zhou et al. (76) conducted an observational study on 18 patients with psoriatic arthritis and found an increased disease activity in psoriatic arthritis (DAPSA) score and statistically significant increases of swollen and tender joint count following COVID-19 infection.

A possible mechanism for psoriatic flares following COVID-19 infections is the induction of a hyperinflammatory state. It has been shown that binding of the coronavirus spike protein to the ACE2 receptor would result in ACE2 downregulation and then lead to excessive production of ACE. So, some researchers speculate that COVID-19 infection may aggravate the psoriatic condition and accompany a higher incidence of cardiovascular events in psoriasis as ACE has been proposed in the process of inflammation (77).

Based on these findings, it is important to pay attention to psoriasis when patients with COVID-19 receive treatment with hydroxychloroquine, and it is recommended to discontinue the use of hydroxychloroquine in patients with COVID-19 who develop psoriasis or experience a recurrence of psoriatic skin lesions (72). In addition, fish oil supplementation can be considered in the treatment regimen of psoriasis subjects in case of COVID-19 infection, as it can inhibit ACE activity and decrease symptoms in psoriasis subjects (78).

RECOMMENDATIONS FOR THE USE OF BIOLOGICS DURING THE PANDEMIC OF COVID-19

According to the recommendations of major global dermatological associations, patients who had not reported clinical symptoms or close contact with a confirmed or probable COVID-19 case in the last 14 days can continue biologic therapy. It is advisable to discontinue or postpone biological treatment in patients with confirmed SARS-CoV-2 infections until COVID-19 is fully cured. For those patients who are qualified for biological treatment but have not yet started, it is advisable to carefully assess the balance of benefits and risks of treatment for each patient. In populations with a high risk for severe COVID-19, a postponement of biological treatment or other therapeutic options should be considered (79–81). The National Psoriasis Foundation COVID-19 Task Force has reiterated a similar point in the guidance for the management of psoriatic disease during the pandemic. It is recommended that patients who are not infected with SARS-CoV-2 continue their biologics for psoriasis in most cases. Shared decision-making between clinician and patient is recommended to guide discussions about the use of systemic therapies during the pandemic (82).

SARS-COV-2 VACCINATION IN PATIENTS WITH PSORIASIS UNDER BIOLOGIC THERAPY

Since the outset of the COVID-19 pandemic, COVID-19 vaccines were being developed around the world. The COVID-19 vaccines currently allowed for emergency use worldwide are mainly mRNA vaccines, adenovirus vector vaccines, and whole-virion inactivated vaccines (83).

Clinical trials showed a high efficacy rate of these vaccines in protection against COVID-19 and no major safety concerns (84–88). However, there are currently no data on the efficacy and safety of COVID-19 vaccines in patients with psoriasis treated with biologic drugs as patients on immunosuppressive therapy were excluded from clinical trials. Some major international scientific societies, for example, National Psoriasis Foundation, recommend the use of the SARS-CoV-2 vaccine even in patients undergoing biological therapy without the necessity to discontinue the therapy (89, 90). Some patients with psoriasis are still reluctant to get vaccinated out of concern about its safety and efficacy, as there have been reported that patients with psoriasis may have flare-ups after vaccination, and concomitant

immunosuppression may impair the immune response to vaccination (91–93).

Damiani et al. (94) and Pacifico et al. (95) have preliminarily confirmed the safety and efficacy of the vaccines in their case series report. Patients with psoriasis under biologics and apremilast underwent Pfizer mRNABNT162b2 and AZD1222 (AstraZeneca-Oxford vaccine), and they did not experience any psoriasis flare or cutaneous manifestations. All patients developed IgG anti-S1-Receptor Binding Domain (RBD) of SARS-CoV-2 without discontinuation or modification of their therapy. A survey on the antibody responses to single-dose mRNA vaccines in patients receiving immunomodulatory drugs suggested that 15% of patients failed to detect antibody response to single-dose BNT162b2 or AZD1222 vaccines; 41% had no detectable anti-S1 IgG. Compared to biologics, non-biologic immunomodulators, such as methotrexate, had a lower level of antibody response. This contrasts with data from healthy populations, which show close to 100% (96), and then Geisen et al. (97) evaluated antibody responses following the second dose of mRNA vaccines in a cohort study of 42 controls and 26 patients with immunomodulatory drugs. The result showed that anti-SARS-CoV-2 antibodies could be detected in all participants. But lower anti-S IgG levels also could be detected in patients receiving immunomodulators. Side effects were comparable in both groups. No severe adverse effects were observed, and no patients experienced a disease flare.

These show that immunosuppressed patients may have an impaired immune response to SARS-CoV-2 mRNA vaccines, but the safety is proven. When it comes to a specific biological agent, the current evidence is limited. The impact of anti-TNF-α agents on vaccine response is controversial (98, 99). The meta-analysis performed by Subesinghe et al. (100) showed that anti-TNF-α therapy did not impair influenza vaccine responses. For anti-IL17 agents, the current literature shows that they do not seem to affect the humoral immune response to non-live vaccines. In a randomized, open-label, parallel-group study Gomez et al. (101) found, compared with the control group, the subjects who received 160 mg ixekizumab subcutaneously 2 weeks before vaccination and 80 mg ixekizumab on the day of vaccination had a comparable level of immune response to the tetanus vaccine and the Streptococcus pneumoniae vaccine. Similarly, a cohort study aimed to compare the basal antibody titers against the three influenza vaccines between psoriatic arthritis and ankylosing spondylitis who were receiving treatment with secukinumab and healthy volunteers were included. This research has reached a consistent conclusion that secukinumab did not influence the response to the influenza vaccine [relative risk, RR: 1.09 (95% CI 0.58–2.07) for h1N1, RR: 1.53 (95% CI 0.15–15.0) for h3N2, and RR: 0.72 (95% CI 0.32–1.83 for B strain)] (102).

CONCLUSION AND DISCUSSION

With the COVID-19 spreading worldwide rapidly, the biological treatment of psoriasis has become a topic of great concern. At present, there is a lack of evidence for one or a class of biological agents on the impact of SARS-CoV-2 infection. Most of the existing evidence is based on clinical case reports. Therefore, it is difficult to evaluate which biological agent has better safety for COVID-19. However, from the current unclassified research, the biological treatment of psoriasis does not seem to have a significant impact on the COVID-19. Regardless of whether biological agents have been used, patients with psoriasis were not at higher risk for severe COVID complications. However, COVID-19 infection and use of hydroxychloroquine seem to be related to the recurrence or exacerbation of psoriasis, in addition, patients with psoriasis may be at a higher incidence of cardiovascular events in case of COVID-19 infection.

This emphasizes the importance of patients with psoriasis to prevent SARS-CoV-2 infections. Vaccination still is an effective measure to prevent the spread of infection, and patients with psoriasis are advised to be vaccinated without discontinuing their biological treatment. If the situation permits, it is best to vaccinate before starting biological treatment, because the current evidence suggests that the use of immunosuppressive agents may reduce the vaccine immune response to a certain extent. Related dermatological associations and clinical guidelines also recommend that undiagnosed patients should continue their biological therapy. For high-risk patients (older age, with comorbidities, or metabolic disorders such as diabetes and obesity), discontinue decision should be made on the evaluation of the balance of benefits and risks, and the risk of disease relapse and retreatment failure also should be taken into consideration. There are few relevant studies on psoriasis during the pandemic, and the current evidence has certain limitations. Therefore, it is necessary to be cautious when making clinical decisions. More prospective studies with higher levels of evidence are needed to support clinical decision-making.

AUTHOR CONTRIBUTIONS

ZS, HZ, SW, and LC contributed to conception and design of the study. HZ drafted the manuscript. SW, LC, and ZS contributed to the critical revision of the manuscript. HZ, SW, LC, and ZS contributed to the literature retrieval. All authors approved the submitted version.

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Inactivated COVID-19 Vaccine Induces a Low Humoral Immune Response in a Subset of Dermatological Patients Receiving Immunosuppressants

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Inactivated Sinovac-CoronaVac vaccine (Sinovac Life Sciences, Beijing) for coronavirus disease 2019 (COVID-19) has been used in many countries. However, its immunogenicity profile in immunosuppressed dermatological patients is lacking. This prospective observational case-control study compared the humoral immune response between adult dermatological patients receiving systemic immunosuppressive therapies ($n = 14$) and those who did not ($n = 18$); excluding patients with HIV infection, cancer, non-dermatological autoimmune conditions, previous COVID-19 infection, and positive anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG prior to vaccination. The subjects were advised to withhold methotrexate for 1 week after each vaccine dose while continuing other therapies unadjusted. Anti-SARS-CoV-2 IgG antibody, surrogate neutralizing antibody (sNAb), and seroconversion rates (calculated from the percentages of participants in the group with positive sNAb) were used to assess immunogenicity. We found that participants using azathioprine, cyclosporin, mycophenolate mofetil, or prednisolone $\geq$ 10 mg/day had a lower level of serum anti-SARS-CoV-2 IgG antibody and sNAb than those received methotrexate $\leq$ 10 mg/week, prednisolone $<$ 10 mg/day, or biologics (i.e., secukinumab, ixekizumab, omalizumab). Patients who received methotrexate $\leq$ 10 mg/week, prednisolone $<$ 10 mg/day or the biologics had a similar immunogenicity profile to those without immunosuppressive therapies. Despite the lack of statistical significance, a reduction of humoral immune response was observed among the study participants who used $\geq$2 immunosuppressants or pemphigus patients. Our findings suggest that a subset of patients with immune-mediated skin conditions respond poorly to the vaccine despite having low-level immunosuppression. These patients could benefit from vaccines that trigger a greater level of immunogenicity or booster doses.

Keywords: autoimmune skin diseases, Sinovac, CoronaVac, inactivated COVID-19 vaccine, immunosuppression, immunogenicity

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a global health emergency; the disease has cost millions of lives and greatly disrupt the world economy (1). Vaccination is the key to ameliorating the situation and potentially stopping this ongoing pandemic, as evidence has shown a decline of new and hospitalized COVID-19 cases in countries with high vaccination coverage (2). Inactivated Sinovac-CoronaVac vaccine (Sinovac Life Sciences, Beijing) has been used for mass vaccination in many countries as it is proven to give an acceptable level of protection against symptomatic and severe COVID-19 disease in volunteers (3). However, data regarding the vaccine's immunogenicity in autoimmune dermatological patients is not available, making it challenging to recommend whether the vaccine is suitable for these patients.

Currently, the available evidence of inactivated COVID-19 vaccine is limited to the groups of autoimmune rheumatic disease (ARD) patients, which suggests a reduced but acceptable level of the vaccine's immunogenicity (4, 5). Nevertheless, it is not possible to assume that immunosuppressed dermatological patients will have the same immunogenicity profile, as there is only a partial overlap within the disease spectrum of autoimmune rheumatologic and dermatologic conditions. Moreover, different pathogenesis leads to a distinct treatment approach and immunosuppressive agents used. To fill in this gap of knowledge, this study aims to compare humoral immune responses after a complete course of inactivated Sinovac-CoronaVac COVID-19 vaccine (referred to as CoronaVac) between adult dermatological patients receiving systemic immunosuppressive therapies and those who did not.

METHODS

Study Design and Participants

This is a prospective observational case-control study conducted in a university hospital's dermatology outpatient clinic. The study was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA 2021/446). Patients scheduled to receive the CoronaVac vaccine distributed *via* Thailand's national vaccination scheme were screened for eligibility. Under this scheme, the vaccine was administered in two 3-μg doses, 3–4 weeks apart.

Patients with immune-mediated dermatological conditions who had been treated with systemic immunosuppressive agents from 1 month before to 1 month after vaccination were recruited as cases. Individuals who did not receive systemic immunosuppressive agents were recruited as controls. In patients who had been treated with rituximab, they were categorized as cases or controls based on their post-rituximab B cell status. Those whose B cells were depleted ($CD19^+$ lymphocyte $< 5\%$) were categorized as cases. Those whose B cells were incompletely depleted or repopulated after rituximab therapy ($CD19^+$ lymphocyte $\geq 5\%$) were also defined as cases when an additional immunosuppressant is needed for disease control. These cases were classified according to their current medication. However, those who achieved complete B cell repopulation, but remained in complete remission without treatment, were classified as controls. The patients with HIV infection, cancer, non-dermatological autoimmune conditions, history of previous COVID-19 infection, positive for anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG prior to vaccination were excluded. According to the current recommendation (6), the subjects were advised to temporarily withhold methotrexate for 1 week after each vaccine dose while continuing other therapies unadjusted.

Immunogenicity Assessment

The magnitude of humoral immune responses was assessed using the serum levels of anti-SARS-CoV-2 IgG antibody and SARS-CoV-2 surrogate neutralizing antibody (sNAb). Three milliliters of whole blood were collected from each participant before vaccination and 4 weeks after receiving the second dose of the vaccine. The samples were stored in clot activator tubes (VACUETTE®, Greiner Bio-One, Austria) and allowed to clot at room temperature for at least 10–15 min before centrifuging at 3,500 g for 10 min. The serums retrieved from the supernatant were transferred to 1.5-mL sterile polypropylene tubes using Pasteur pipettes and stored at −20°C until analysis. None of the serum samples was hemolyzed, icteric, or lipemic. All serum samples were thawed once with the storage time before an analysis between 2 and 4 weeks.

Serum anti-SARS-CoV-2 IgG antibody level was quantified, before and after vaccination, using automated chemiluminescent microparticle immunoassay (Abbott Laboratories, United States), which reports the concentration of serum anti-SARS-CoV-2 IgG antibody level in an arbitrary unit (AU) with a positive cut-off threshold recommended by the manufacturer at 50 AU/milliliters. Surrogate virus neutralization assays (SARS-CoV-2-NeutraLISA, Euroimmun, Germany) were performed on post-vaccination serum samples to measure the amount of sNAb in the form of the neutralizing activity. The tests were executed per the manufacturer's instructions by trained laboratory personnel; the system reports neutralizing activity of sNAb as the percentage of inhibition. The positive cut-off threshold recommended by the manufacturer is 35%. We did not perform the surrogate virus neutralization assay on pre-vaccinated serum samples as they were negative for anti-SARS-CoV-2 IgG antibody.

Data Collection and Statistical Analysis

Baseline Characteristics

For all study participants, age, sex, and the diagnosis of skin diseases were collected. In patients who received immunosuppressive agents, the number, name, and dosage were documented. Baseline serum IgA, IgM, IgG levels, as well as the percentages of circulating $CD19^+$ B lymphocytes, $CD4^+$ T lymphocytes, and $CD8^+$ T lymphocytes (quantified by routine flow cytometry analysis), were measured. Baseline characteristics, serum anti-SARS-CoV-2 IgG antibody level, and neutralizing activity of sNAb were compared between cases and controls. In addition, subgroup analyses were explored in patients with different skin conditions and different types of immunosuppressants used. Fisher's exact tests were

employed to compare categorical variables. The between-group comparisons of normally distributed and non-normally distributed continuous variables were performed with *t*-tests and Wilcoxon rank-sum tests, respectively.

Study Outcomes

The outcome measures were serum anti-SARS-CoV-2 IgG levels, neutralizing activity of sNAb, and seroconversion rates. Seroconversion rates were calculated from the percentages of participants in the group who tested positive for sNAb post-vaccination. We did not use anti-SARS-CoV-2 IgG levels to compute seroconversion rates because its level may partly represent a cross-reactivity of anti-SARS-CoV-2 IgG to endogenous antibodies and cross-antigens (7). The measured values were compared between cases and controls using *t*-tests (for data with normal distribution) and Wilcoxon rank-sum tests (for data with non-normal distribution). Comparisons of serum anti-SARS-CoV-2 IgG antibody level and neutralizing activity of sNAb among subgroups were made using one-way analysis of variance with *post-hoc* Bonferroni tests (for data with normal distribution) and Kruskal-Wallis tests with *post-hoc* Dunn's tests (for data with non-normal distribution). Seroconversions rates were compared between subgroups with Fisher's exact tests. Statistical analysis was performed with STATA 17.0 (StataCorp LLC, TX, US). The graphical illustrations were created with the R software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) using ggplot2 data visualization package. *P*-value < 0.05 was considered statistically significant.

RESULTS

Thirty-two patients who received a complete course of the CoronaVac vaccine were enrolled in the study. Baseline characteristics of the study participants are shown in **Table 1**. Fourteen patients with pemphigus, psoriasis and chronic spontaneous urticaria were recruited as cases. The participants who served as controls (mostly patients with acne, melasma, androgenetic alopecia, seborrheic keratosis) did not use topical or systemic immunosuppressive therapies. The cases and controls were age- and sex-matched. The medications used among the cases included azathioprine (25–150 mg/day), mycophenolate mofetil (1,000 mg/day), cyclosporin (50 mg/day), methotrexate (7.5–10 mg/week), prednisolone (5–20 mg/day), biologics (i.e., secukinumab, ixekizumab, and omalizumab at standard doses for their respective disorders); 42.8% of the patients received ≥ 2 of these medications. Three pemphigus cases had a history of rituximab use 2 years before recruitment; all had $CD19^+$ B cells $\geq$ 5%. Two patients who were in complete remission under minimal adjuvant therapy were classified as cases, while one patient, who was in complete remission off therapy, was assigned to a control group. At baseline, flow cytometry studies for the number of circulating total lymphocytes, $CD19^+$ B lymphocytes, $CD4^+$ T lymphocytes, and $CD8^+$ T lymphocytes and serum concentration of total immunoglobulins demonstrated comparable results between groups. Serum SARS-CoV-2 IgG antibody level was undetectable in the pre-vaccinated serum samples of both cases and controls. The most common side effects experienced among

TABLE 1 | Baseline characteristics of the study participants.

Characteristics	Case ($N = 14$) *n* (%)	Control ($N = 18$) *n* (%)	*p*-value
Age (mean, 95% CI)	43.9 (36.6–51.2)	44.6 (37.1–52.0)	0.890[a]
Sex, male (%)	4 (28.6)	7 (38.9)	0.712[b]
Autoimmune skin diseases (%)			<0.001*[b]
- Pemphigus	7 (50.0)	1 (5.6)	
- Psoriasis	6 (42.9)	1 (5.6)	
- Chronic spontaneous urticaria	1 (7.1)	1 (5.6)	
- No autoimmune skin diseases	0 (0)	15 (83.2)	
Baseline peripheral blood flow cytometry (percentages among total lymphocytes, mean, 95%CI)			
- $\%CD4^+$ T-lymphocytes	61.3 (56.6–66.0)	59.6 (55.1–64.0)	0.585[a]
- $\%CD8^+$ T-lymphocytes	31.1 (27.1–35.1)	30.8 (26.5–35.0)	0.902[a]
- $\%CD19^+$ B-lymphocytes	14.9 (11.6–18.1)	14.2 (11.7–16.7)	0.742[a]
Baseline immunoglobulin level (g/L)			
- IgM (median, IQR)	1.0 (0.6–1.8)	1.0 (0.7–1.5)	0.718[c]
- IgG (median, IQR)	12.5 (11.4–14.4)	12.8 (10.4–14.7)	0.909[c]
- IgA (mean, 95%CI)	2.9 (2.4–3.3)	2.4 (2.1–2.8)	0.082[a]
Systemic immunosuppressive medications (% of participants who used the medications)			
- Azathioprine	5 (35.7)	0	
- Cyclosporin	1 (7.1)	0	
- Mycophenolate mofetil	1 (7.1)	0	
- Moderate-to-high dose prednisolone (≥10 mg/day)	2 (14.3)	0	
- Low-dose prednisolone (<10 mg/day)	3 (21.4)	0	
- High-dose methotrexate (>10 mg/week)	0 (0)	0	
- Low-dose methotrexate (≤10 mg/week)	3 (21.4)	0	
- Biologics‡	6 (42.9)	0	
Number of immunosuppressants used (%)			
- 0	0 (0)	18 (100)	
- 1	8 (57.2)	0	
- 2	5 (35.7)	0	
- 3	1 (7.1)	0	
Post-vaccination immunogenicity			
- Anti-SARS-CoV-2 IgG (AU/mL, median, IQR)	666.2 (312.2–987.3)	1,208.0 (774.1–1,910.0)	0.028*[c]
- Neutralizing activity of sNAb (%inhibition, mean, 95%CI)	43.1 (29.2–57.0)	52.9 (41.3–64.6)	0.252[a]
- Post-vaccination seroconversion rate† (%)	56.3	77.8	0.180[d]

† *Seroconversion rates were calculated from the percentages of study participants who tested positive for sNAb in the group.*

‡ *Biologics include secukinumab, ixekizumab, and omalizumab at standard doses for their respective disorders.*

[a] *p-value from t-tests.*

[b] *p-value from Fisher's exact tests.*

[c] *p-value from Wilcoxon rank-sum tests.*

[d] *p-value from Chi-squared tests.*

* $p < 0.05$.

AU/mL, arbitrary unit per milliliter; CD, cluster of differentiation; CI, confidence interval; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range; sNAb, surrogate neutralizing antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

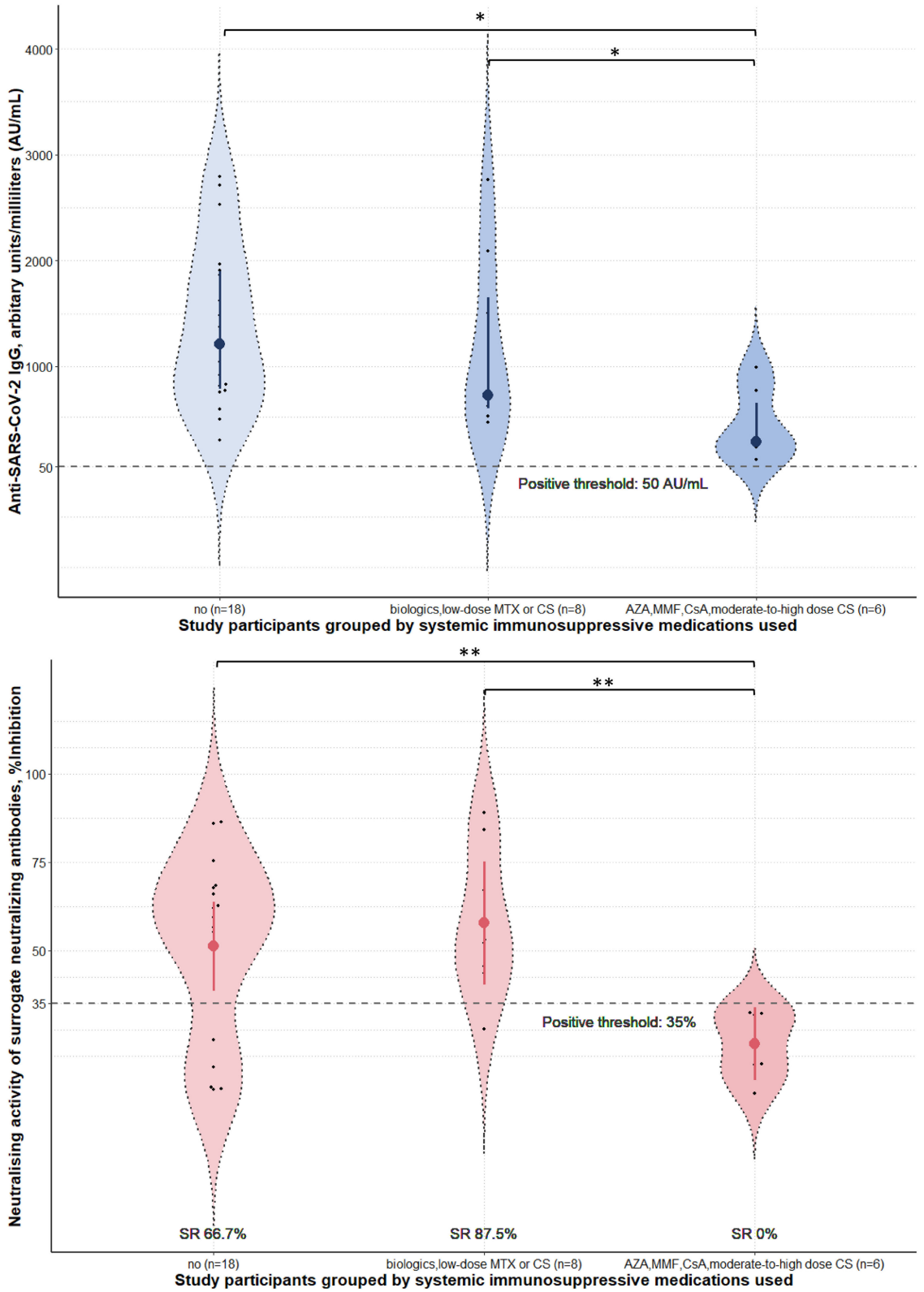

FIGURE 1 | Immunogenicity of the inactivated Sinovac-CoronaVac COVID-19 vaccine in study participants stratified by the immunosuppressive medications used. Serum anti-SARS-CoV-2 IgG antibody level and neutralizing activity of surrogate neutralizing antibody were measured 4 weeks post-second dose of the vaccine. Data

(Continued)

FIGURE 1 | were presented with violin plots containing medians and interquartile range for anti-SARS-CoV-2 IgG antibody level and means and 95% confidence interval for neutralizing activity. Seroconversion rates (SR) for each subgroup were calculated from the percentages of study participants who tested positive for sNAb in the group. Prednisolone <10 mg and ≥10 mg were considered low-dose and moderate-to-high dose. Methotrexate ≤ 10 mg/week was defined as low-dose. AZA, azathioprine; CS, corticosteroids; CsA, cyclosporin; MTX, methotrexate; MMF, mycophenolate mofetil; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SR, seroconversion rates. *p-value from Kruskal-Wallis tests *post-hoc* Dunn's tests < 0.05. **p-value from one-way analysis of variance with *post-hoc* Bonferroni tests < 0.05.

study participants were low-grade fever, myalgia, mild tenderness at the injection site, and somnolence. One psoriasis patient had a flare-up after vaccination, while the others remained under control.

Four weeks after the second vaccine dose, all participants had positive results of serum anti-SARS-CoV-2 IgG antibody. Albeit statistical insignificance, there was a trend toward lower sNAb levels and seroconversion rates in cases than controls (**Table 1**). Subgroup analyses showed that participants using azathioprine, cyclosporin, mycophenolate mofetil, or moderate-to-high-dose corticosteroids (prednisolone ≥ 10 mg/day) had a substantially lower neutralizing activity of sNAb than those who received low-dose methotrexate (≤10 mg/week), low-dose systemic corticosteroids (prednisolone < 10 mg/day), or the biologics (**Figure 1**). Moreover, none of the study participants within the former group developed seroconversion after vaccination (**Table 2**). In contrast, patients who received low-dose methotrexate, low-dose systemic corticosteroids, or the biologics had a similar immunogenicity profile to the study participants without immunosuppressive therapies. Despite the lack of statistical significance, a reduction of humoral immune responses was observed among participants who used ≥2 immunosuppressants. Likewise, pemphigus patients had lower humoral immune responses than other conditions, although this analysis did not reach a statistical significance level (**Figure 2**). None of the participants developed symptomatic COVID-19 infection during a minimum of 3-month follow-up period after vaccination.

TABLE 2 | Subgroup analyses of seroconversion rates in patients stratified by skin diseases and the number of immunosuppressants used.

Subgrouping by	Seroconversion† (%row)		*p*-value
	Yes *n* (%)	No *n* (%)	
Types of immunosuppressants used			0.003*[a]
■ Azathioprine, Cyclosporin, Mycophenolate mofetil, Prednisolone ≥ 10 mg/day.	0 (0)	6 (100.0)	
■ Methotrexate ≤ 10 mg/week, Prednisolone < 10 mg/day, Biologics‡	7 (87.5)	1 (12.5)	
■ No immunosuppressants used	12 (66.7)	6 (33.3)	
Skin diseases			0.288[a]
■ Pemphigus	3 (37.5)	5 (62.5)	
■ Psoriasis	4 (57.1)	3 (42.9)	
■ Others#	12 (70.6)	5 (29.4)	
The number of immunosuppressants used			0.347[a]
■ 0	12 (66.7)	6 (33.3)	
■ 1	5 (62.5)	3 (37.5)	
■ ≥2	2 (33.3)	4 (66.7)	

†*Seroconversion rates were calculated from the percentages of study participants who tested positive for sNAb in the group.*
‡*Biologics include secukinumab, ixekizumab, and omalizumab at standard doses for their respective disorders.*
#*Other diseases include chronic spontaneous urticaria, acne, melasma, androgenetic alopecia, and seborrheic keratosis.*
[a]*p-value from Fisher's exact tests.*
**p < 0.05.*
sNAb, surrogate neutralizing antibody.

DISCUSSION

We studied a humoral immune response after receiving the CoronaVac vaccine among adult dermatological patients receiving systemic immunosuppressive therapies. According to the Infectious Diseases Society of America definition of immunosuppression, these patients are categorized as having low-level immunosuppression (8). Suboptimal immune response to the vaccine was observed in a subset of participants treated with azathioprine, cyclosporin, mycophenolate mofetil, and moderate-to-high dose prednisolone (≥10 mg/d) during vaccination; in which the majority of these participants are pemphigus patients. Meanwhile, the vaccine can induce an appreciable level of immune response in participants who used biologics (i.e., secukinumab, ixekizumab, and omalizumab), low-dose methotrexate (≤10 mg/d), and low-dose systemic corticosteroids (<10 mg/d); equivalent to controls without immune-mediated skin diseases.

Previous studies investigating CoronaVac's immunogenicity in immunosuppressed patients have yielded conflicting results. For instance, Pestana et al. demonstrated a clinically insignificant seroconversion rate of 15.2% among kidney transplant recipients (9), while Karacin et al. found that more than half of cancer patients receiving chemotherapy were able to seroconvert (10). In patients with autoimmune diseases, the vaccine has demonstrated a reduced yet acceptable level of immune response among ARD patients in which 56.3% of them developed detectable neutralizing antibodies post-vaccination without statistically significant difference in neutralizing activities between ARD patients and healthy controls who seroconverted (4). Our study also observes the same trend in psoriasis patients. By contrast, another cohort study of patients with various immune-mediated diseases found a significant number of patients with low SARS-CoV2 specific antibody titers (5) despite a substantial overlap of immunosuppressants used by participants of this study and the one mentioned above. A similar finding is noticeable among pemphigus patients in our study, as

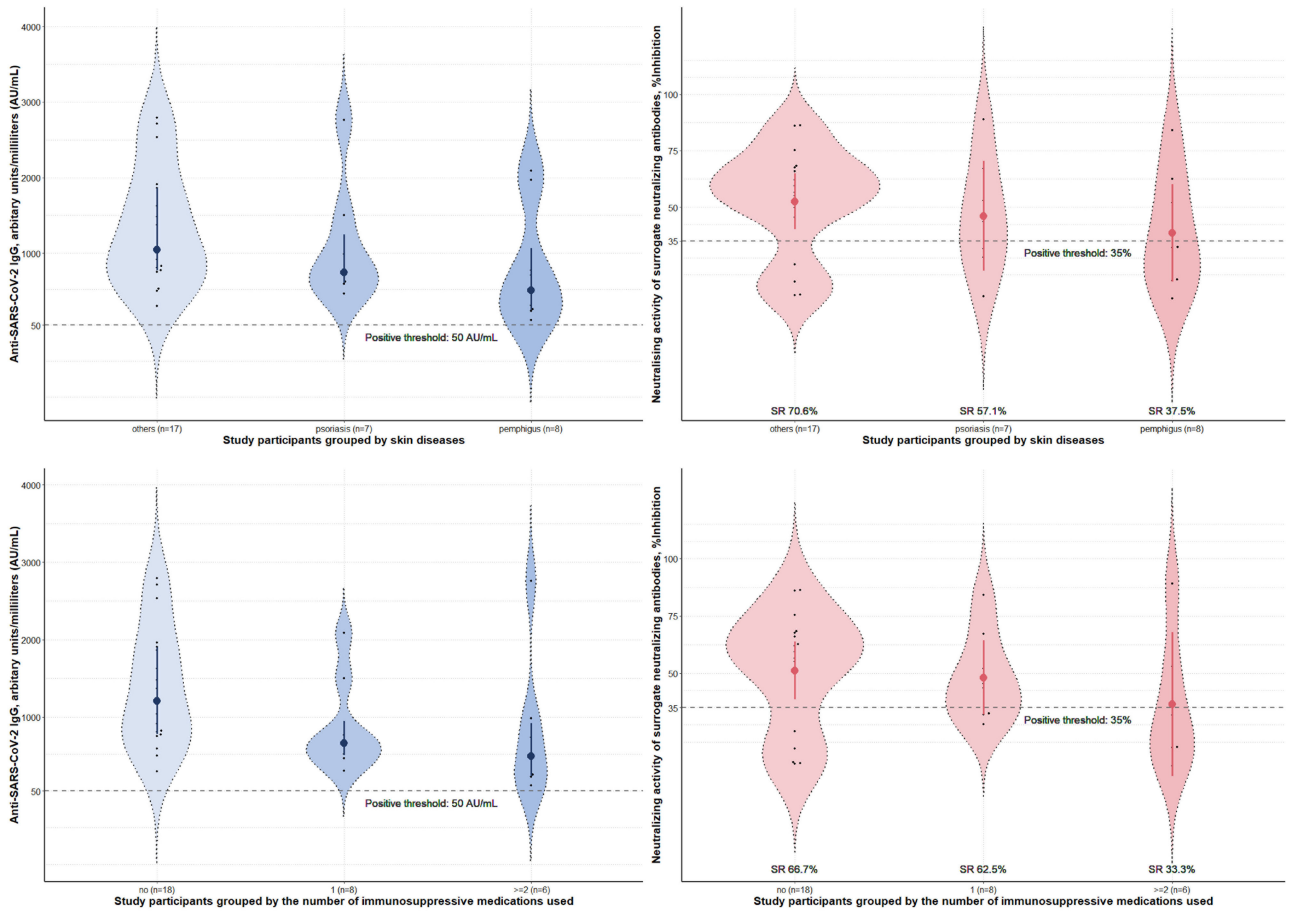

FIGURE 2 | Immunogenicity of the inactivated Sinovac-CoronaVac COVID-19 vaccine in study participants stratified by skin diseases and the number of immunosuppressants used. Serum anti-SARS-CoV-2 IgG antibody level and neutralizing activity of surrogate neutralizing antibody measured 4 weeks post-second dose of the vaccine. Data were presented with violin plots containing medians and interquartile range for anti-SARS-CoV-2 IgG antibody level and means and 95% confidence interval for neutralizing activity. Seroconversion rates (SR) for each subgroup were calculated from the percentages of study participants who tested positive for sNAb in the group. No statistically significant difference was found between groups. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SR, seroconversion rates.

a majority of those who received systemic immunosuppressive therapies did not develop seroconversion. These data suggest that the interaction between hosts' comorbidities and their treatment, rather than individual factors, determines humoral immune responses to inactivated COVID-19 vaccines, resulting in the discrepancy in vaccine response patterns between patients with different immune-mediated diseases. Therefore, for immunocompromised patients to achieve an effective response to inactivated COVID-19 vaccine, it is imperative to evaluate the immunogenicity and efficacy of the vaccine in the context of the specific patient groups of interest.

The main limitation of this study is the small sample size and heterogeneity of the patients recruited; hence, the observed trends from our research should be confirmed by larger studies. Besides, the cellular immune response was not assessed; however, as the previous study of the vaccine has demonstrated a low cellular response in healthy volunteers (11), the same or worse can be expected among these patients. Moreover, the immunosuppressive effects caused by the medications (especially rituximab) extend beyond the drug half-life, further complicated by its distinctive actions on specific B cell subpopulations which was not thoroughly assessed by this study. There is also a lack of participants who received methotrexate > 10 mg/week in this study; immunogenicity in this setting may either be below or equivalent to patients who received methotrexate ≤ 10 mg/week. Further studies with a more variety of medications and detailed lymphocyte subset characterization may uncover a more intricate vaccine response pattern among these patients.

CONCLUSION

We present immunogenicity data of the CoronaVac vaccine in a specific target group of dermatological patients who used immunosuppressive therapies. Currently, there are only a few studies that investigate immunogenicity of the vaccine in these patients. The identification of the poor

responders is crucial as they could benefit from vaccine platforms that trigger a greater level of immunogenicity. They may require booster doses using COVID-19 vaccines with adequate safety data in immunocompromised patients (12, 13). Further studies are needed to explore the effects of individual immunosuppressive medications and the immune responses in patients with other autoimmune skin diseases not presented in this study (e.g., bullous pemphigoid, dermatomyositis, and vitiligo).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CS-a, CP, and YR conducted the investigation. CS-a collected and prepared the samples, performed data curation, data visualization, formal analysis, and wrote the original draft of the manuscript. CS-a and TS provided laboratory resources and performed the experiments. KC, PR, and PS supervised the project administration. PS and KC acquired funding support for the project and revised the manuscript. All authors involved in the conceptualization, methodology planning of the study, and approved the final version of the manuscript.

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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.

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frontiers in Medicine

CASE REPORT
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Case Report: Circulating Anti-SARS-CoV-2 Antibodies Do Not Cross-React With Pemphigus or Pemphigoid Autoantigens

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It is hypothesized that SARS-CoV-2 has the potential to elicit autoimmunity due to molecular mimicry between immunogenic proteins of the virus and human extracellular molecules. While *in silico* and *in vitro* evaluation of such immune cross-reactivity of human antibodies to SARS-CoV-2 proteins with several different tissue antigens has been described, there is limited information specifically pertaining to the immunological effects of COVID-19 and vaccines against SARS-CoV-2 on the development of autoimmune bullous diseases (AIBDs). Twelve seropositive post-COVID-19 individuals and 12 seropositive healthy volunteers who received two doses of the mRNA COVID-19 vaccine from Pfizer-BioNTech have been included in this case series investigation. Serum samples of these blood donors were tested for autoantibodies to the main immunobullous autoantigens, i.e., desmoglein 1, desmoglein 3, envoplakin, BP180, BP230, and type VII collagen. Our study revealed that none of the 24 anti-SARS-CoV-2 IgG-positive subjects had concomitant antibody reactivity with any of the tested autoantigens. These results argue against a relationship between SARS-CoV-2 infection/vaccines and AIBDs with respect to disease-triggering antibody cross-reactivity.

Keywords: SARS-CoV-2, COVID-19, autoimmune blistering diseases, ELISA, molecular mimicry

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KEY POINT

A link between COVID-19 or vaccines against SARS-CoV-2 and the evolution of autoimmunity has been proposed. Here, we found no evidence of an immune cross-reactivity between anti-SARS-CoV-2 protein antibodies and the major target autoantigens of pemphigus and pemphigoid.

INTRODUCTION

A link between COVID-19 or newly developed vaccines against SARS-CoV-2 and the evolution of autoimmunity has been proposed, although the molecular mechanisms underlying these putative associations and the risk factors predicting the onset of autoimmune diseases following infection or vaccination are not well-understood (1, 2). Recently, reaction of human antibodies to SARS-CoV-2 proteins with several different tissue antigens has been described, suggesting that this molecular mimicry-based serological cross-reactivity may at least partly be responsible for the multi-organ system disorder found in some patients with COVID-19 (2).

TABLE 1 | Characteristics of anti-SARS-CoV-2 IgG-positive subjects.

No.	COVID-19 vaccine*	Anti-SARS-CoV-2 S1 IgG	Anti-SARS-CoV-2 NCP IgG	COVID-19 symptoms
1	−	+	+	+
2	−	+	+	+
3	−	+	+	+
4	−	+	+	+
5	−	+	+	+
6	−	+	+	+
7	−	+	+	+
8	−	+	+	+
9	−	+	+	+
10	−	+	+	+
11	−	+	+	+
12	−	+	+	−
13	+	+	−	−
14	+	+	−	−
15	+	+	−	−
16	+	+	−	−
17	+	+	−	−
18	+	+	−	−
19	+	+	−	−
20	+	+	−	−
21	+	+	−	−
22	+	+	−	−
23	+	+	−	−
24	+	+	−	−

**Anti-SARS-CoV-2 antibodies directed to the S1 domain of the viral spike protein and/or nucleocapsid protein (NCP) were analyzed by commercially available anti-SARS-CoV-2 ELISA kits. Eleven out of 12 non-vaccinated, seropositive post-COVID-19 individuals reported at least one of the typical COVID-19 symptoms (e.g., fever, cough, fatigue, muscle/body aches, headache, loss of taste/smell, or sore throat) that appeared in the last 12 weeks prior to blood sampling for the serological analyses. Vaccinated individuals were monitored for the presence of anti-SARS-CoV-2 IgG within 3–5 weeks of the last dose of the vaccine.*

So far, there is only limited information specifically pertaining to the effects of COVID-19 and vaccines on the development of autoimmune bullous diseases (AIBDs) (3–5). Therefore, we sought to determine, for the first time, whether immune reactivity also occurs between anti-SARS-CoV-2 protein antibodies and the main target autoantigens of pemphigus and pemphigoid.

CASE SERIES

Twelve post-COVID-19 individuals and 12 healthy volunteers immunized with two doses of the mRNA COVID-19 vaccine from Pfizer-BioNTech, who were all part of a previous study cohort reported by Mantej et al. (6), have been included in this investigation (**Table 1**). Serum samples of these blood donors were tested for autoantibodies to desmoglein 1, desmoglein 3, envoplakin, BP180, BP230, and type VII collagen. The presence of anti-SARS-CoV-2 antibodies and these pemphigus/pemphigoid antibodies was analyzed by anti-SARS-CoV-2 enzyme-linked immunosorbent assay (ELISA) (IgG) kits and a multi-variant Dermatology Profile ELISA (all from Euroimmun, Germany), respectively. Usage of human biological material was approved by the bioethics committee of the regional medical chamber in Gdańsk (Poland), and written informed consents were obtained in accordance with the Declaration of Helsinki.

Our examination revealed that none of the 24 anti-SARS-CoV-2 IgG-positive subjects had concomitant antibody reactivity with any of the six tested autoantigens.

These results together with a recent related report on heat shock protein autoantibodies argue against a relationship between SARS-CoV-2 infection/vaccines and AIBDs with respect to disease-triggering antibody cross-reactivity, as previously hypothesized (1, 6). Our findings also encourage COVID-19 vaccination in patients with AIBDs, as previously recommended (7). Nevertheless, it cannot be excluded that the infection or immunization may possibly induce or aggravate autoimmunity in genetically predisposed persons by alternative modalities such as non-specific bystander activation of immune cells. Further experimental approaches, including epitope mapping studies, are required to confirm our preliminary results as well as to clarify whether and how COVID-19 or respective vaccinations may potentially drive AIBDs.

LIMITATIONS AND STRENGTHS

Our study has some limitations. For instance, long-term follow-up observations are required to prove the immunological effects of COVID-19 vaccination (both mRNA and viral vector) and infection on the development of AIBDs in a larger cohort. However, although *in silico* sequence alignment analyses and *in vitro* evaluations of cross-reactivity of anti-SARS-CoV-2 antibodies with several different tissue antigens have been previously described, we are not aware of any other study focusing on potential cross-reactivity between naturally generated SARS-CoV-2 IgG and pemphigus/pemphigoid autoantigens *in vivo*.

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 Bioethics Committee at Regional Medical Chamber in Gdańsk, Poland. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK and ST: study design and conceptualization, supervision, original draft preparation, and data interpretation and critical revision of the manuscript. ST and MB: analysis. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Exacerbation of Psoriasis Following COVID-19 Vaccination: Report From a Single Center

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The temporal association had been reported between vaccination and exacerbation of psoriasis, and episodes of psoriasis flare-up have recently been attributed to COVID-19 vaccines. We recruited 32 unimmunized controls and 51 vaccinated psoriasis patients, 49 of whom were under biological therapy, with regular clinic visits receiving a total of 63 shots of vaccines, including 30 doses of Moderna mRNA-1273 and 33 doses of AstraZeneca-Oxford AZD1222. Fifteen episodes of exacerbation attacked within 9.3 ± 4.3 days, which is higher than two episodes in the control group ($p = 0.047$). The mean post-vaccination severity of the worsening episodes increased from PASI 3.1 to 8.0 ($p < 0.001$). Three patients showed morphologic change from chronic plaque-type to guttate psoriasis. Deterioration of psoriasis following COVID-19 vaccination was not associated with age, sex, disease duration, psoriatic arthritis, family history of psoriasis, history of erythroderma, current biologics use, comorbidities, vaccine types, human leukocyte antigen (HLA)-C genotypes, baseline PASI nor pre-vaccination PASI. For those who received two doses of vaccination, all but one patient aggravated after the first shot but not the second. The mechanism of psoriasis exacerbation in immunized individuals is unclear, but Th17 cells induced by COVID-19 vaccines may play a role. In the pandemic era, psoriasis patients and physicians should acknowledge the possibility of fluctuation of disease activity when vaccinated against COVID-19. Nevertheless, compared to a treatable dermatologic disease with rapid resolution of exacerbation, psoriasis patients who do not have contraindications to vaccination should benefit from COVID-19 vaccines in the prevention of severe COVID-19 infection and fatality.

Keywords: psoriasis, COVID-19, vaccine, exacerbation, HLA, human leukocyte antigen, Th17, biologics

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INTRODUCTION

Psoriasis is a chronic immune-mediated cutaneous inflammatory disease that may be precipitated by drug, infection, stress, physical trauma, and vaccination (1–6). A lower rate of influenza vaccination in psoriasis patients may be attributed to the fact that vaccines may be a triggering factor for aggravation (7). "Psoriasis vaccinalis" had been described in different types of vaccines, including influenza, Bacillus Calmette-Guerin, tetanus-diphtheria, and pneumococcal polysaccharide vaccines (8). Patients may present as widespread severe psoriasis or new-onset guttate psoriasis. Recently, coronavirus (COVID-19) vaccinations have been linked to the exacerbation of psoriasis (9–11).

This study aims to evaluate the clinical characteristics and genetic factors in the aggravation of psoriasis after COVID-19 vaccination.

METHOD

The study was approved by the Research Ethics Committee of National Taiwan University Hospital (201904124RINC). Consecutive patients with moderate to severe psoriasis who received COVID-19 vaccines in our dermatologic outpatient clinic between June 2021 and October 2021 were enrolled for analysis. Therapeutic inclusion criteria include patients under biologics and patients under remission after discontinuation of biologics, currently with/without traditional systemic treatment. The types of COVID-19 vaccine were documented, either Moderna mRNA-1273 or AstraZeneca-Oxford AZD1222. All patients were tested for human leukocyte antigen-C (HLA-C) genotypes. The baseline Psoriasis Area Severity Index (PASI) was defined as the most severe PASI before the initiation of current biological treatment, while the pre-vaccination PASI was defined as the PASI before receiving COVID-19 vaccines. Worsening of vaccinated patients was defined as (1) worsening of 50% PASI from a prior visit, which was based on an interval of 4–12 weeks depending on the biological agents, or (2) morphologic change, for example, chronic plaque-type to guttate, pustular or erythrodermic psoriasis, without other identifiable aggravating factors within 14 days of vaccination. Psoriasis area and severity index (PASI) was assessed at each clinic visit by the same physician. Aggravation of unvaccinated patients was defined as worsening 50% PASI compared to baseline PASI or morphological change. Possible precipitating factors, including upper respiratory tract infection, excess ultraviolet light exposure, alterations of medications, and psychological stress, are inquired orally.

Statistics analysis was performed using SPSS version 25. Parametric data are presented as mean ± SD. To compare intergroup differences, Shapiro-Wilk test was applied to determine the data normality of distribution. Based on the result, Mann-Whitney or Student's *t*-test was employed for quantitative variables. Pearson Chi-square test or Fisher's exact tests were applied for categorical data. The analysis results are two-tailed, with a significance level of 0.05.

TABLE 1 | Comparison between psoriasis patients vaccinated and unvaccinated against COVID-19.

	Vaccinated	Unvaccinated	*P*-value
Number of patients, n	51	32	NA
Doses of vaccines, n	63	0	NA
Moderna mRNA-1273	30	0	NA
AstraZeneca-Oxford AZD1222	33	0	NA
Age (years), mean ± SD	55.3 ± 11.6	50.4 ± 12.7	0.077
Female, n (%)	14 (27%)	14 (44%)	0.155
Body weight (kg), mean ± SD	78.0 ± 15.5	71.6 ± 13.3	0.111
Disease duration (years), mean ± SD	18.0 ± 10.0	18.1 ± 9.6	0.771
Psoriatic arthritis, n (%)	31 (61%)	16 (50%)	0.370
History of erythroderma, n (%)	8 (16%)	9 (29%)	0.263
Family history of psoriasis, n (%)	15 (29%)	7 (22%)	0.610
Comorbidities			
Hypertension, n (%)	13 (26%)	7 (22%)	0.796
Diabetes mellitus, n (%)	9 (18%)	4 (13%)	0.758
Cardiovascular disease, n (%)	3 (6%)	0	0.281
Hepatitis B virus infection, n (%)	5 (10%)	4 (13%)	0.728
Hepatitis C virus infection, n (%)	2 (4%)	0	0.520
Numbers of exacerbation episodes, n (%)	15 (29%)	2 (6)	0.047
Interval between exacerbation and vaccine (days), mean ± SD	9.3 ± 4.1	NA	NA
Morphology change, n (%)	3 (5%)	0	0.548
HLA-C allele frequency (%)			
C*01	40.5	31.3	0.267
C*03	12.7	20.3	0.201
C*04	3.2	4.7	0.690
C*06	2.4	3.1	>0.999
C*07	26.2	23.4	0.727
C*08	4.8	6.3	0.735
C*12	4.0	4.7	>0.999
C*14	3.2	1.6	0.665
C*15	3.2	4.7	0.690
Current treatment			
Non-biologic only, n (%)	3 (6%)	1 (3%)	>0.999
Biologics, n (%)	48 (94%)	31 (97%)	>0.999

HLA, human leukocyte antigen; NA, not applicable.

RESULTS

A total of 83 patients were recruited, including 51 vaccinated patients receiving 63 doses of vaccines and 32 patients who did not receive COVID-19 vaccines (**Table 1**). COVID-19 vaccines include 30 doses of Moderna and 33 doses of AstraZeneca-Oxford. The age in the vaccinated group was 55.3 ± 11.6 years with a body weight of 78.0 ± 15.5 kg. Female patients comprise 27% ($n = 14$) of the vaccinated group. In the unvaccinated control, age was 50.4 ± 12.7 years, body weight was 71.6 ± 13.3, and female patients accounted for 44%. Age, sex, and body weight are not statistically different between the vaccinated and control group. All of the patients suffered from long-lasting psoriasis, with a mean disease duration of 18.0 ± 10.0 and 18.1 ± 9.6 years in the vaccinated and unvaccinated group, respectively. In patients who received COVID-19 vaccines, psoriatic arthritis was diagnosed in 61%, history of erythrodermic change was recorded in 16%, and positive family history was found in 31%. Among individuals not receiving COVID-19 vaccines, the percentages of psoriatic arthritis, history of erythroderma, and family history of psoriasis stood at 50, 29, and 22%, respectively, showing no difference when each was compared with the unvaccinated counterpart.

The comorbidities include hypertension in 13 (26%), diabetes mellitus in 9 (18%), cardiovascular disease in 3 (6%), hepatitis B virus infection in 5 (10%), and hepatitis C virus infection in 2 (4%) vaccinated patients, whereas 7 (22%) have hypertension,

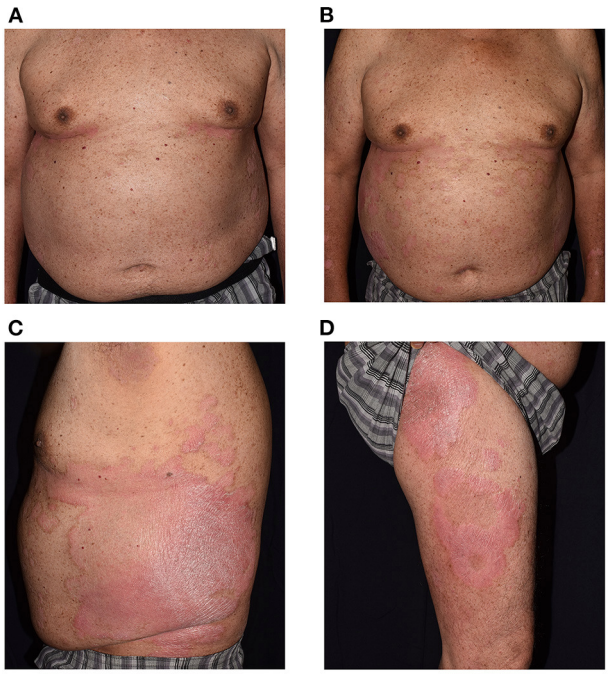

FIGURE 1 | Clinical exacerbation of a 68-year-old man from baseline **(A)** Psoriasis Area Severity Index (PASI) at 5.4. Extensive erythematous scaly patches developed 14 days after Moderna vaccine, covering more than 13% of total body surface area, with PASI score at 10.0 **(B–D)**.

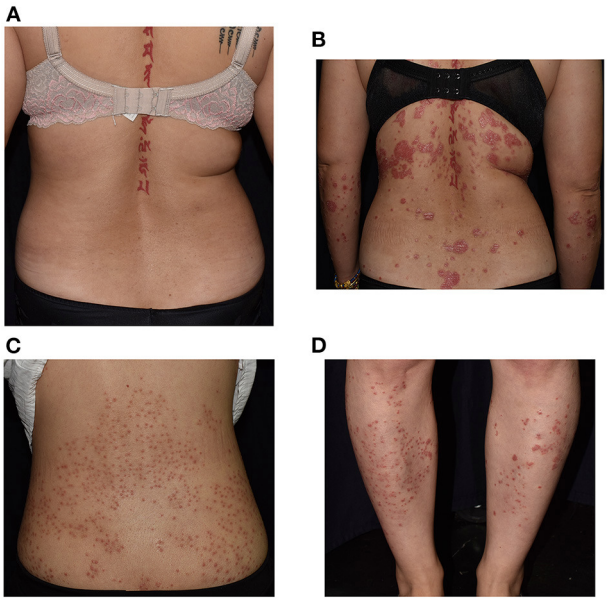

FIGURE 2 | Severe exacerbation with morphological change in a 40-year-old woman with a history of psoriasis for more than a decade, worsening from Psoriasis Area Severity Index (PASI) 2.8 **(A)** to 10.7 **(B)**. Photos of the back **(C)** and lower legs **(D)** of a 39-year-old woman with chronic plaque-type psoriasis who developed guttate and/or follicular form 3 days after receiving AstraZeneca-Oxford vaccine.

4 (13%) have diabetes mellitus, and 4 (13%) hepatitis B virus infection in the unvaccinated group. None of the patients in the control group have documented cardiovascular disease or hepatitis C virus infection.

Fifteen worsening episodes following administration of COVID-19 vaccine in psoriasis patients were observed (**Figure 1**), which is higher than two episodes recorded in the control group ($p = 0.047$). No specific aggravating factors, such as upper respiratory infection, excess ultraviolet exposure, change of medications, nor psychological stress, were reported in all patients. In the immunized group, three patients experienced morphologic changes from chronic plaque-type to guttate type (**Figure 2**).

The mean pre-vaccination PASI scores between those who deteriorated and the counterpart group are not significantly different ($p = 0.571$). The mean post-vaccination PASI of the worsening episodes significantly increased from 3.1 to 8.0 ($p < 0.001$), while the BSA increased from 2.4 to 8.0 ($p = 0.061$). In comparison, the mean post-vaccination PASI of the episodes not associated with exacerbation was stable over time (4.3–3.6, $p = 0.329$), and the BSA are not significantly different (3.5–2.6, $p = 0.614$).

The mean duration between vaccine injection to psoriasis deterioration was 9.3 ± 4.3 days. Among them, 11 showed improvement of disease severity in the following clinic visits, with an interval of 64.6 ± 29.7 days. As shown in **Table 2**, no specific HLA-C genotype is found to be related to worsening of skin manifestations. The result of the intergroup analysis is shown in **Table 2**. There was no difference between the exacerbation group and its counterpart regarding age, sex, disease duration, psoriatic arthritis, family history of psoriasis, history of erythrodermic psoriasis, current biologics use, comorbidities, nor the baseline PASI.

The same brands of vaccines were given to all the patients receiving two shots. A total of 12 patients received two doses of COVID-19 vaccination, including seven patients without aggravation, four patients showing exacerbation following the first injection but not the second one, and one patient repeatedly aggravated after vaccination, in whom AstraZeneca-Oxford was administered. In the subgroup of patients who only had worsening episodes once after the first dose of the COVID-19 vaccine, three of them received AstraZeneca-Oxford, and one received Moderna vaccine. Four and three patients were given AstraZeneca-Oxford and Moderna vaccines, respectively, in those whose disease severity was not worsened due to COVID-19 vaccines.

Regarding the treatment, only three patients were not receiving biologics; one was applying topical steroids, another taking methotrexate, and the other was taking acitretin. Forty-nine patients (94%) in the immunized group were under biological therapy, including guselkumab ($n = 16$), ixekizumab ($n = 12$), risankizumab ($n = 6$), etanercept ($n = 4$), adalimumab ($n = 4$), adalimumab plus methotrexate ($n = 3$), secukinumab ($n = 2$), and brodalumab ($n = 1$). In 14 individuals with disease aggravation, they are receiving guselkumab ($n = 3$), ixekizumab

TABLE 2 | Comparison between the exacerbation episodes and the exacerbation-free episodes in patients who received COVID-19 vaccines.

	Exacerbation episodes	Exacerbation-free episodes	*P*-value
Female sex, n (%)	7 (46%)	11 (23%)	0.104
Age (years)	53.6 ± 12.2	55.5 ± 11.5	0.591
Vaccine type, AstraZeneca-Oxford/Moderna	8/7	25/23	>0.999
Disease duration (years)	20.1 ± 9.8	18.1 ± 10.3	0.378
Psoriatic arthritis, n (%)	7 (47%)	31 (65%)	0.241
Family history of psoriasis, n (%)	6 (40%)	15 (31%)	0.545
History of erythroderma, n (%)	3 (20%)	10 (21%)	>0.999
Baseline PASI	14.9 ± 8.8	12.5 ± 7.5	0.429
Pre-vaccination PASI	3.1 ± 1.8	4.3 ± 4.4	0.571
Current biologics use, n (%)	13 (87%)	47 (98%)	0.138
Comorbidities			
Hypertension, n (%)	5 (33%)	11 (23%)	0.501
Diabetes mellitus, n (%)	2 (13%)	7 (15%)	>0.999
Cardiovascular disease, n (%)	1 (7%)	3 (6%)	>0.999
Hepatitis B virus infection, n (%)	0	6 (13%)	0.321
Hepatitis C virus infection, n (%)	1 (7%)	2 (4%)	0.564
HLA-C allele frequency (%)			
C*01	38.5	46.7	0.523
C*03	11.5	16.7	0.531
C*04	3.1	3.3	>0.999
C*06	3.1	0	>0.999
C*07	27.1	23.3	0.814
C*08	6.3	0	0.334
C*12	4.2	3.3	>0.999
C*14	4.2	0	0.572
C*15	2.1	6.7	0.240

($n = 2$), risankizumab ($n = 2$), etanercept ($n = 1$), adalimumab ($n = 1$), adalimumab plus methotrexate ($n = 2$), secukinumab ($n = 1$), methotrexate ($n = 1$), and topical steroid ($n = 1$). Whether receiving biological agents or not was not associated with disease exacerbation following COVID-19 vaccination ($p = 0.138$).

DISCUSSION

Reports of COVID-19 vaccines associated with psoriasis exacerbation were emerging (8, 9, 11). In an international registry of 414 individuals with cutaneous reactions after Pfizer-BioNTech and Moderna vaccines, two patients experienced psoriasis exacerbation (12). Besides worsening of pre-existing psoriatic lesions, a *de novo* generalized pustular psoriasis following administration of the first dose of AstraZeneca-Oxford COVID-19 vaccine was also reported (10). Recently, Ricardo et al. reported *de novo* nail psoriasis triggered by Pfizer-BioNTech in a 76-year-old woman (13).

Previously, psoriasis following Streptococcal infections is commonly reported, but its association with HLA-Cw6 is controversial (14). The relationship between genetic factors and vaccination in psoriasis aggravation has not been studied. However, widespread and unstable diseases were found in HLA-C positive patients (14). Whether worsening after COVID-19 vaccination results from the complex interplay between HLA and unstable disease remains to be clarified. A new insight provided by our report is that all patients received genetic testing for HLA-C. The relatively low HLA-Cw6 positivity in Chinese patients has been reported, especially in high need patients (biologic users) with moderate to severe psoriasis in which HLA-Cw1 was thought to play a more significant role (15). However, there was no significant association between a specific HLA-C allele and aggravation of disease activity after COVID-19 vaccination.

In our report, episodes of worsening of psoriasis were defined as 50% of deterioration of PASI scores, which is mainly based on the definition of minimal significant psoriasis efficacy endpoint (16) and relapse in clinical trials after discontinuation of biological agents, which is 50% of reduction of PASI improvement (17, 18). We suggest that changing clinical morphology should be regarded as a sign of disease exacerbation after receiving the COVID-19 vaccine. It is consistent with the definition of adverse events of trials of biologics for psoriasis. Three patients in our cohort developed guttate psoriasis even though all of them were diagnosed with chronic plaque-type psoriasis for more than a decade. More than hundreds of guttate lesions erupted four days after vaccination in one of the chronic plaque-type psoriasis patients.

The mean interval between COVID-19 vaccination and disease exacerbation was 9.3 days in our cohort, which was similar to another preliminary report from Greece (10.36 days) (8). In consistence with previous reports, no specific type of vaccine was associated with a significantly higher rate of exacerbation (8). In our cohort, there is one patient who showed exacerbation of psoriasis after both doses of COVID-19 vaccination. She is a 50-year-old woman receiving AstraZeneca-Oxford vaccines, showing surges of PASI scores 8 and 11 days after the first and second injections, respectively. Under regular ixekizumab administration, the disease severity was later controlled. The HLA-C serotyping showed she has HLA-Cw1/Cw10.

Psoriasis in four patients worsened after the first dose but not after the second. Three of them received AstraZeneca-Oxford vaccine, and one of them received Moderna vaccine. In addition to the possible triggering effect of COVID-19 vaccines, psoriasis severity may be altered by the effect of biologics, for example, time of initiation of the treatment course, duration of therapy, and the interval between COVID-19 vaccination and clinic visit. In our patients, two of them initiated guselkumab within 3 months before the first shot of COVID-19 vaccination. PASI response of patients receiving guselkumab increases with the duration of treatment (19). Another patient shifted from guselkumab to risankizumab after exacerbation following the first dose of Moderna. Since exacerbation are defined by physician-assessed PASI scores, mild attacks may occur between clinic visits but are not documented.

COVID-19 vaccination may be a triggering factor for psoriasis, as suggested by the short time intervals between vaccination and psoriasis exacerbation, which is supported by

this and previous reports (8). Most of the currently used COVID-19 vaccines are based on adenovirus as vector or mRNA; thus, the immunologic reaction to the COVID-19 vaccine may be distinct from the influenza vaccine, which is mediated by T-helper (Th)1 and Th17 responses (7). Previous studies reported an increase in tumor necrosis factor (TNF)-α and interferon (IFN)-γ production by CD4+ T cells after AstraZeneca-Oxford COVID-19 vaccine (20). TNF-α is well-known as a potent proinflammatory cytokine in psoriatic skin lesions (21), whereas IFN-γ has been recognized as one of the pathogenic cytokines that can trigger inflammatory cascades of psoriasis with the potential to become a severity marker (22, 23). The critical role of the Th17 subset of CD4+ T cells, possibly IL-6-induced, in COVID-19 immunopathology and vaccine-induced immune enhancement was highlighted by recent studies (24–26). Interwoven with Th17, TNF-α, and IFN may be the link between psoriasis exacerbation and COVID-19 vaccines, yet further investigations are required to unravel the immunologic reactions. Further investigations and large controlled studies are warranted to elucidate the relationship between psoriasis and COVID-19 vaccines.

The limitations of the study are the small number of patients and possible fluctuation of disease course in patients with moderate to severe psoriasis. Although more patients under COVID-19 vaccination can be included, we included only patients who received severity assessment immediately before and after the vaccination. Besides, only patients with stable disease conditions for at least 3 months prior to vaccination without other identifiable aggravation factors were included. Although we only included psoriasis patients who aggravated in 2 weeks after vaccination to avoid recollection bias, this may result in over-estimation of the incidence of vaccine-induced psoriasis aggravation, based on the possibility that aggravation may urge the patients to seek medical attention before the scheduled visit. However, the proportion of patients with an unscheduled return to the clinic is low, at 6.3%.

Vaccination for COVID-19 is currently recommended for all patients with psoriasis, irrespective of the severity and current mediation, although temporary discontinuation may be needed for some oral systemic agents, but not biologics for psoriasis (27). This recommendation is based on the documented efficacy of the COVID-19 vaccine in the prevention of severe COVID-19 infection and fatality (28). In a large international series of patients with psoriasis and COVID-19 infection, 348 patients (93%) fully recovered from COVID-19, 77 (21%) were hospitalized, and 9 (2%) died (29). Patients under biological agents were associated with a lower risk of COVID-19-related hospitalization compared to those under systemic therapies (29). COVID-19 infection, rather than COVID-19 vaccine, can also exacerbate psoriasis (30, 31). Compared to a treatable dermatologic disease with rapid resolution of exacerbation, patients with psoriatic disease who do not have contraindications to vaccination should follow the guidance statements published by the National Psoriasis Foundation to receive an mRNA-based COVID-19 vaccine as soon as it becomes available to them (32).

In some patients, COVID-19 vaccinations may be associated with disease exacerbation of psoriasis, with an average interval of approximately 10 days. These abrupt clinical deteriorations are irrelevant to the type of vaccines injected, the baseline or pre-vaccination PASI, or the HLA-C genotyping. Psoriasis patients should be consulted before getting vaccinated for COVID, and prompt clinical visit should be available if exacerbation develop. However, more studies are needed to identify the true incidence and factors contributing to the aggravation.

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 Research Ethics Committee of National Taiwan University Hospital (201904124RINC). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-WH and T-FT contributed to conception and design of the study. Y-WH organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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frontiers in Medicine

CASE REPORT
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Case Report: Rowell Syndrome–Like Flare of Cutaneous Lupus Erythematosus Following COVID-19 Infection

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The current COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had an important impact on dermatology practice, posing diagnostic and therapeutic challenges especially in patients with inflammatory and autoimmune skin disorders. Disease-specific and nonspecific cutaneous manifestations have been increasingly reported in the spectrum of COVID-19 but the influence of the infection on pre-existing dermatologic diseases has not been clearly defined. There has been a debate in the literature as to whether patients suffering from autoimmune dermatoses, including cutaneous lupus erythematosus (CLE), are at increased risk of SARS-CoV-2 infection, as well as if they experience worsening of their lupus erythematosus (LE)-related clinical symptoms. This article reports on a case of Rowell syndrome occurring after COVID-19 in a 67-year old woman with pre-existing chronic CLE manifesting with few discoid lesions on the face, scalp, and upper chest, successfully controlled with topical corticosteroids and photoprotection. Erythema multiforme (EM)-like eruption developed approximately two weeks after the SARS-CoV-2 infection, the latter being confirmed by positive nasopharyngeal swab and successfully treated with systemic antibiotics and antiaggregants. Diffuse hair loss and patches of cicatricial alopecia were also present upon scalp examination. Laboratory workup, including routine tests, histologic, immunofluorescent, and serologic investigations, was supportive to the diagnosis. Administration of topical and systemic corticosteroids along with peroral hydroxychloroquine resulted in the progressive improvement of the cutaneous lesions. Rowell syndrome is a rare entity in the spectrum of LE, characterized by EM-like lesions, photosensitivity, and positive antinuclear and anti-Ro antibodies, that is currently considered to be a variant of subacute CLE (SCLE). Several cases of SCLE have been described in association with medications, including anti-SARS-CoV-2 vaccines but only a few reports incriminate the infection itself as a potential exacerbating factor. Based on the clinical course of the disease, we suggest that the observed Rowell syndrome-like flare of CLE was related to the COVID-19 infection in this patient.

Keywords: COVID-19, Rowell syndrome, erythema multiforme-like, subacute cutaneous lupus erythematosus, flare

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INTRODUCTION

The outbreak of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had an important impact on dermatology practice, posing diagnostic and therapeutic challenges especially in patients with inflammatory and autoimmune skin disorders. Disease-specific and non-specific cutaneous manifestations have been increasingly reported in the spectrum of COVID-19 but the influence of the infection on pre-existing dermatologic diseases has not been clearly defined. There has been a debate in the literature as to whether patients suffering from autoimmune skin diseases, including the various subtypes in the broad spectrum of cutaneous lupus erythematosus (CLE), are at increased risk of SARS-CoV-2 infection, as well as if they experience worsening of their lupus erythematosus (LE)-related clinical symptoms. In recent months, there have been multiple publications in the form of case reports, case series, observational and retrospective studies on COVID-19 in patients with systemic LE (1); however, not much information is present in the literature on the effect of coronavirus infection on multiple subtypes and clinical variants of CLE including chronic CLE and subacute CLE (SCLE).

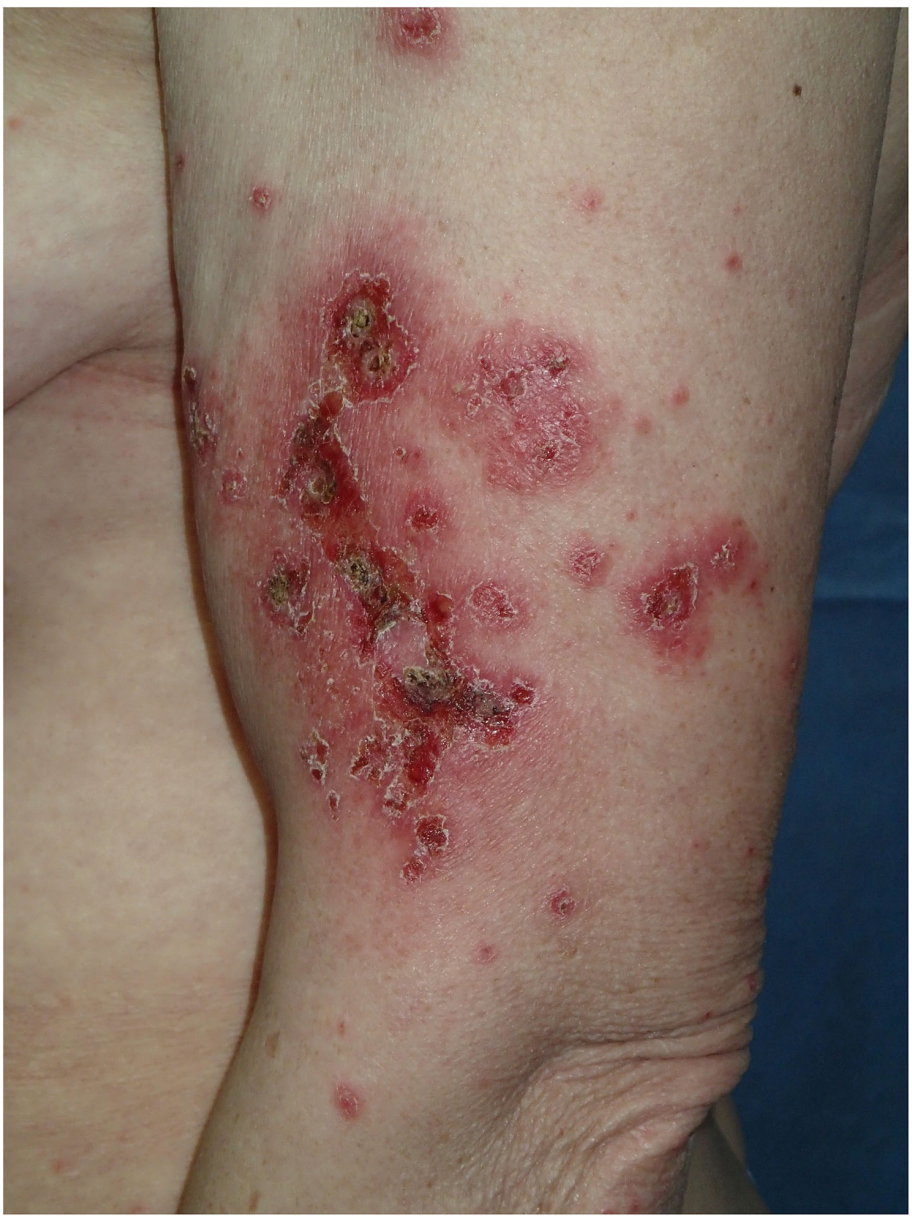

FIGURE 1 | Annular-polycyclic photosensitive eruption of subacute cutaneous lupus erythematosus (SCLE) occurring after COVID-19 illness; note the trailing scale in the periphery of the lesions.

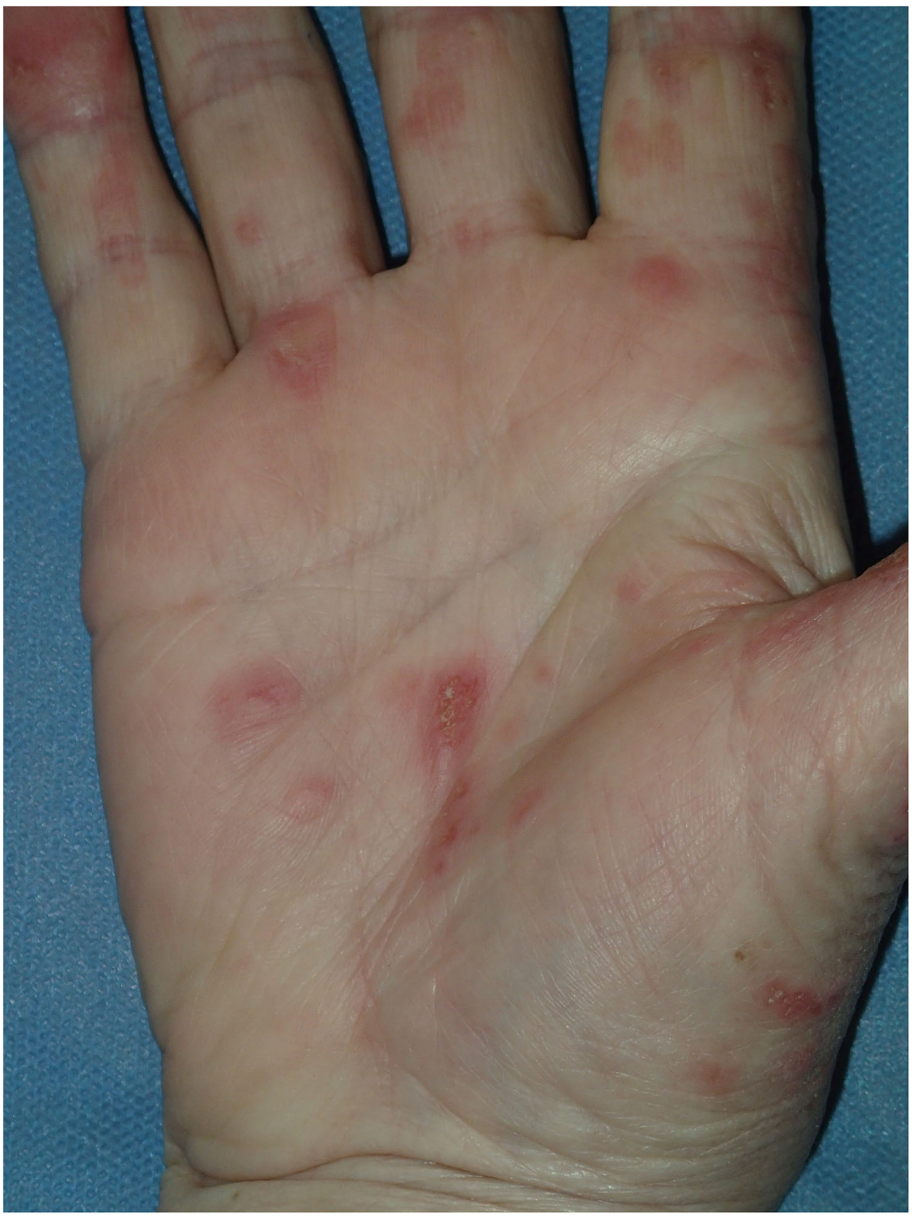

FIGURE 2 | Flat targetoid erythema multiforme (EM)-like lesions on the palmar skin, compatible with Rowell syndrome.

Though skin manifestations of COVID-19 are rare, they are diverse (2) and some of them might create confusion with the wide range of skin changes in the spectrum of CLE (3). In this respect, it is of interest to record all cases of occurrence of SARS-CoV-2 infection in the setting of cutaneous lupus and vice versa.

We present a case of Rowell syndrome-like flare of CLE following COVID-19.

CASE REPORT

A 67-year-old Caucasian woman was admitted to our Dermatology department in April 2021 for a non-pruritic and slightly burning erythematous and scaly cutaneous eruption affecting sun-exposed areas that started two weeks after a mild COVID-19. The patient reported that she had been suffering from "photosensitivity" since her young age and had been diagnosed 6 years ago with chronic CLE manifesting with few discoid lesions on the face, scalp, and upper chest, successfully controlled with topical corticosteroids and photoprotection. In February 2021 she experienced intermittent fever up to 38°C, dry cough, and malaise. Reverse-transcription PCR (RT-PCR) on a nasopharyngeal swab tested positive for SARS-CoV-2 but there was no need for hospital care because of the patient's good general condition with oxygen saturation within normal limits and no signs of pneumonia. Therefore,

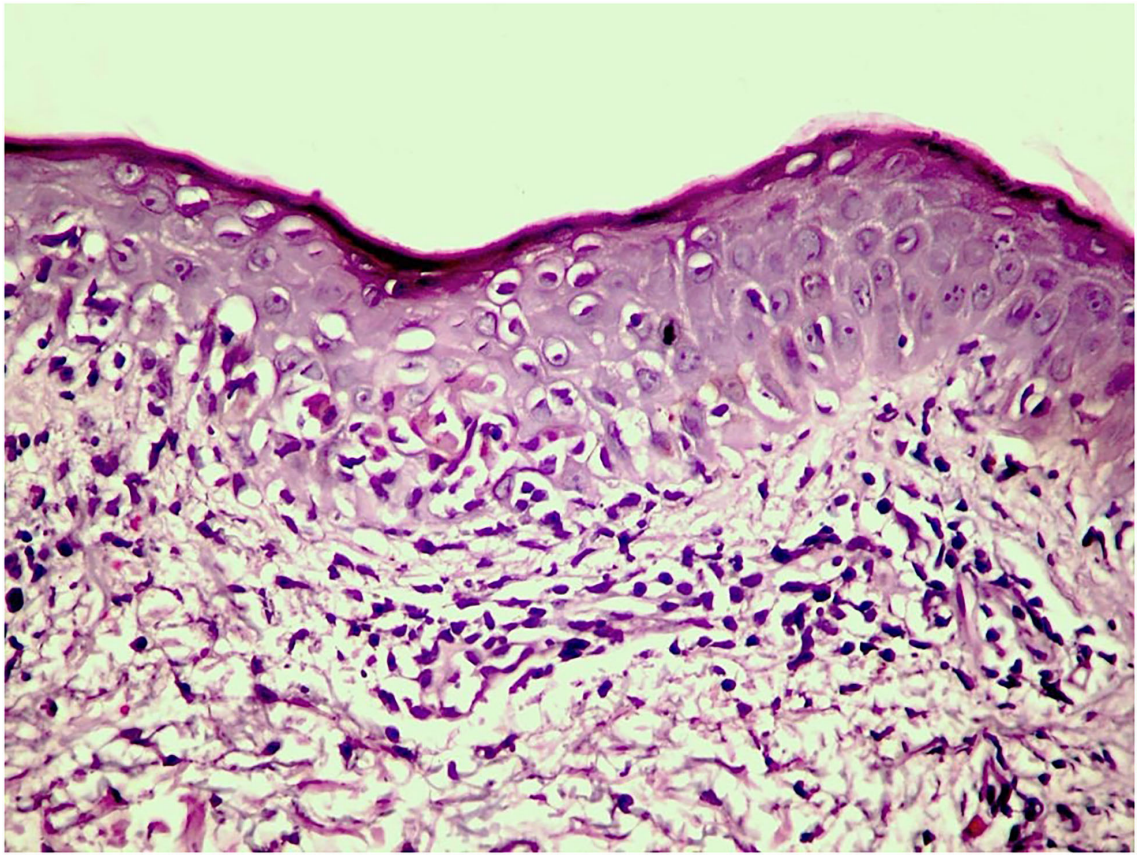

FIGURE 3 | Hematoxylin and eosin stain of a biopsy from the periphery of an annular lesion showing SCLE features: epidermal atrophy, interface dermatitis, and lymphohistiocytic dermal infiltrate.

she underwent outpatient quarantine and peroral treatment with azithromycin.

Physical examination revealed a widespread erythematous scaly annular and polycyclic eruption symmetrically distributed on the extensor aspects of the arms, lower legs, lateral parts of the face, and scalp (**Figure 1**). A "trailing scale" was present at the borders of all annular plaques. In addition, multiple targetoid, erythema multiforme (EM)-like lesions were observed on the chest, back, neck, and dorsal hands, and on the lower lip vermilion (**Figure 2**). Diffuse hair loss and patches of cicatricial alopecia were also present upon scalp examination. Mucous membranes were not affected. Apart from the skin rash, no other systemic signs or symptoms of rheumatic disease were present.

The results of laboratory tests upon hospital admission showed a negative rapid SARS-CoV-2 antigen test and normal complete blood count, erythrocyte sedimentation rate, C-reactive protein, blood chemistry, electrolytes, liver and kidney function tests, and urinalysis. On the other hand, immune serology for lupus markers revealed positive anti-SS-A native (60 kDa) (Ro/SSA), 34 U/ml (<10 U/ml), anti-SSA (Ro-52 recombinant), 44 U/ml (<10 U/ml), and anti-ribosomal P antibodies, 63 U/ml (<10 U/ml), as well as low complement C4, 0.064 (0.20–0.65 g/l), whereas anti-La/SSB, Sm, dsDNA, RNP, anti-histone, anti-cyclic citrullinated peptide, anti-phospholipid antibodies, rheumatoid factor (RF), and immunofluorescence antinuclear antibody (ANA) test (HEp-2 substrate) were all negative. Photo testing with a standardized protocol revealed positive results for ultraviolet (UV)-A and UV-B.

A skin biopsy from the active border of an EM-like lesion on the dorsal forearm showed epidermal atrophy and vacuolar interface dermatitis with an intense hydropic degeneration of the basal layer and few necrotic keratinocytes, as well as lymphohistiocytic infiltrate beneath the epidermis, along the dermo-epidermal junction (DEJ), together with some degree of leukocytoclasia (**Figure 3**).

Direct immunofluorescence revealed the presence of a positive lupus band of immune reactants at the DEJ in both lesional (IgA, IgM, complement C3) and clinically uninvolved non-exposed skin (IgM) (**Figure 4**). Dust-like epidermal fluorescence was not found in any of the biopsy specimens.

According to the above clinical, histologic, immunologic, and serologic findings, the diagnosis of subacute cutaneous LE presenting as Rowell syndrome was established. Treatment with systemic methylprednisolone at a dose of 40 mg/daily and hydroxychloroquine 200 mg twice/daily resulted in progressive clinical improvement of the cutaneous lesions including signs of

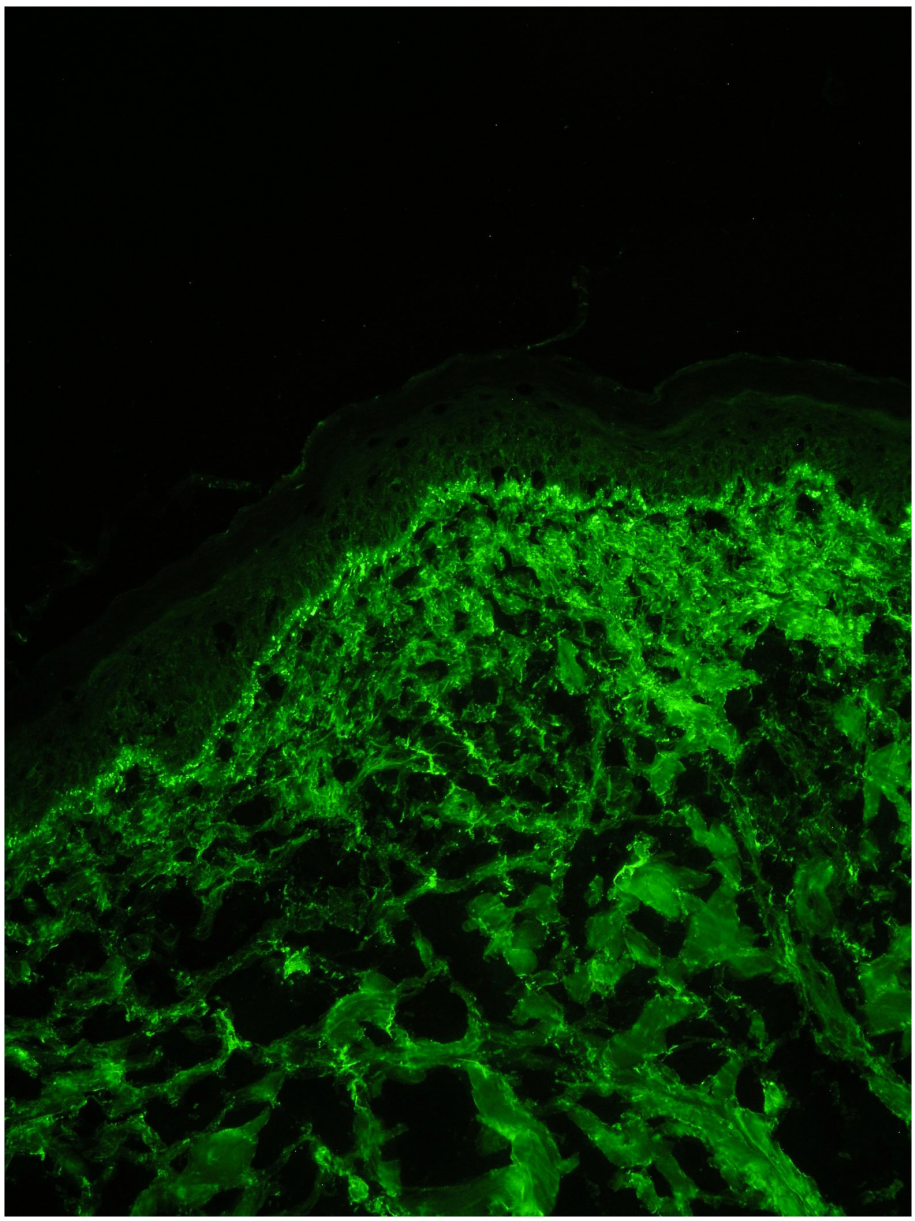

FIGURE 4 | Direct immunofluorescence on a biopsy from a lesion on photo exposed skin showing a granular band of immuno-reactant deposition along the dermal-epidermal junction.

hair loss over a 2-week hospital stay. The patient was followed up for 6 months, during which period she remained in clinical remission on a maintenance corticosteroid dose of 4 mg/day, hydroxychloroquine 400 mg/day, topical corticosteroids, and photo protection.

DISCUSSION

The occurrence of EM-like lesions in the setting of cutaneous LE is referred to as Rowell syndrome. The latter was first described by Rowell et al. (4) as the combination of chronic discoid LE and EM-like annular lesions in the presence of typical serologic findings including positive RF, speckled pattern of ANA, and a saline extract of human tissue (anti-SJT), now known to be similar to anti-Ro/SSA antibodies. With the description of SCLE by Gilliam and Sontheimer (5) in the 1970s, it became increasingly clear that the latter can present with several unusual clinical subtypes, such as erythrodermic, acral, vitiligo-like, or poikilodermatous SCLE (6, 7) and SCLE with EM-like lesions (8). The existence of Rowell syndrome as a distinct entity has been therefore questioned and it was attributed to the diverse clinical spectrum of SCLE and considered to be rather a limited

form of expression of SCLE with EM-like, or Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)-like lesions (9). Currently, Rowell syndrome is widely considered to be a variant of SCLE (10).

Our patient met the diagnostic criteria for Rowell syndrome, i.e. occurrence of a photo-distributed annular-polycyclic eruption together with EM-like lesions, and positive anti-Ro/SSA and anti-Ro-52 antibodies present in up to 90% of SCLE cases (7). The negative RF, on the other hand, does not rule out the diagnosis since it has been found in less than half of the published cases of Rowell syndrome. The diagnostic significance of anti-Ro/SSA antibodies is much higher for SCLE because they have been found in more than two-thirds of a large cohort of patients with SCLE, while anti-La/SSB antibodies were only present in one-third of them (11). In addition, the possibility of EM merely occurring in a patient with CLE following SARS-CoV-2 infection was ruled out in our patient based on the clinical, histopathologic, and immunofluorescence findings that strongly supported the diagnosis of SCLE.

It is commonly recognized that SCLE skin lesions and Ro/SS-A autoantibody production can be triggered by a number of drugs, the majority of which are capable of producing photosensitivity drug reactions (12). The past medical history of the patient described herein, including the treatment received for COVID-19, did not include any of the drugs reported to induce SCLE (13). Other reported eliciting/exacerbating factors include cigarette smoking, psychological stress, and infection (12), the latter of which merits attention in this case.

Various pathogens have been implicated in the pathogenesis of systemic LE (SLE), namely, viruses, such as human endogenous retroviruses, parvovirus B19, herpes-zoster virus, cytomegalovirus, human immunodeficiency virus type 1, hepatitis A and C virus, rubella virus, and recently, coronaviruses (14–17).

The occurrence of several autoimmune diseases has been described secondary to COVID-19 including Guillian-Barré syndrome, immune thrombocytopenia, Miller Fischer syndrome, anti-phospholipid syndrome, type 1 diabetes mellitus, and Kawasaki disease-like syndrome (16, 18). There is also an increasing number of reports published in the literature of SLE developed after COVID-19 (19–22). Exposure to foreign peptides homologous to human peptides, i.e. molecular mimicry between the virus and human peptides, has been proposed as the main cause of the autoimmune phenomena observed in SARS-CoV-2 infection during which the immune responses raised against the virus may cross-react with human proteins that share peptide sequences with the virus leading to autoimmune pathologic sequelae. Epigenetic dysregulation of angiotensin-converting enzyme 2 and interferon (IFN)-regulated genes has been suggested to increase the sensitivity to SARS-CoV-2 in patients with lupus and to lead to new flares (3). COVID-19 infection causes a dysregulated cytokine response with a high resultant expression of IFN-gamma and pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-7, IL-10, and tumor necrosis factor-alpha, which in turn could potentially be exacerbated by the shift in Th1 to Th2 response seen in SLE (16). Various autoantibodies have been reported in the serum of patients with COVID-19, including anti-nuclear antibodies, such as anti−52 kDa SSA/Ro and anti−60 kDa SSA/Ro, and various anti-phospholipid antibodies (23). It is interesting to point out that Ro52 is an IFN-inducible protein, and it is also induced by viral infection or Toll-like receptor (TLR) engagement *via* type I IFN induction (24). In contrast to SLE, there are limited reports of CLE in association with SARS-CoV-2 infection. A case of chilblain LE has been described to occur in a previously healthy 24-year-old man after COVID-19 3 months earlier (25). The worsening of SCLE with the enlargement of pre-existing plaques on the trunk and emergence of new lesions has been observed in a 50-year-old woman with positive SARS-CoV-2 PCR (26). In addition, cases of Rowell syndrome and SCLE have been reported after COVID-19 vaccines but only a few reports incriminate the infection itself as a potential exacerbating factor (27–30). Based on the clinical course of the disease, we suggest that the observed Rowell syndrome-like flare-up of CLE was related to the COVID-19 infection in our patient.

AUTHOR CONTRIBUTIONS

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

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BRIEF RESEARCH REPORT
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Bullous Pemphigoid Associated With COVID-19 Vaccines: An Italian Multicentre Study

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Bullous pemphigoid (BP) is an autoimmune bullous disease caused by circulating autoantibodies toward the hemidesmosomal antigens BP180 and BP230. Cases of BP have been described following vaccinations against tetanus, poliomyelitis, diphtheria, influenza, pneumococcus, meningococcus, hepatitis B and rabies. The putative mechanism by which COVID-19-vaccines may induce BP has not been clarified. An Italian multicentre study was conducted to collect clinical, histopathological and immunopathological data of patients with BP associated with COVID-19-vaccines. Twenty-one cases were collected, including 9 females and 12 males (M/F = 1.3) with a median age at diagnosis of 82 years. Seventeen patients received the COMIRNATY Pfizer-BioNTech vaccine, two the Moderna mRNA-1273 vaccine, one the ChAdOx1/nCoV-19-AstraZeneca/ Vaxzevria vaccine and one received the first dose with the ChAdOx1/nCoV-19-AstraZeneca/Vaxzevria vaccine and the second dose with the COMIRNATY Pfizer-BioNTech vaccine. Median latency time between the first dose of anti-SARS-CoV-2 vaccine and the onset of cutaneous manifestations was 27 days. Median BPDAI at onset was 42. Eleven out of seventeen patients (65%) had positive titres for anti-BP180 antibodies with a median value of 106.3 U/mL on ELISA; in contrast, only five out of seventeen (29%) were positive for anti-BP230 antibodies, with a median of 35.3 U/mL. In conclusion, in terms of mean age, disease severity at diagnosis and

clinical phenotype vaccine-associated BP patients seem to be similar to idiopathic BP with an overall benign course with appropriate treatment. On the other hand, the slight male predominance and the reduced humoral response to BP230 represent peculiar features of this subset of patients.

Keywords: bullous pemphigoid, vaccine, COVID-19, autoantibodies, SARS-CoV-2, triggering factors, BP180, BP230

INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune bullous disease caused by circulating autoantibodies toward the hemidesmosomal antigens BP180 and BP230 (1).

Although the majority of cases are considered idiopathic, several trigger factors have been described in literature, such as UV light, radiation, drugs and trauma. Moreover, cases of BP developed following vaccine injection have recently been reported, with a variable latency time, mostly <1 month (2–5). Specifically, multiple vaccinations are reported as trigger for BP, including the ones for influenza (4, 6), pneumococcus (7), meningococcus (2, 8), varicella-zoster (3), rabies (9) and hexavalent (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and Haemophilus influenzae B) (2, 10).

More recently, both new onset and reactivation of BP have been observed after the inoculation of SARS-CoV-2 vaccines (11–14). The putative mechanism by which COVID-19 vaccines may induce BP has not been thoroughly investigated.

Autoimmune mechanisms following SARS-CoV-2 infection may be associated with molecular mimicry (15, 16). On the other hand, vaccination may activate B and T-cell immunity, triggering an autoimmune response in genetically predisposed individuals (17).

The present multicentre study aimed at investigating the demographics, clinical and immunopathological features of SARS-CoV-2 vaccine-associated BP.

METHODS

SARS-CoV-2 vaccine-associated BP patients examined between February 1, 2021, and November 15, 2021, were included in the present multicentre study involving six Dermatology Clinics (Milan, Cagliari, Florence, Genoa, Bergamo and Rome). The following eligibility criteria were adopted: (1) age of 18 years or older; (2) recent anti-SARS-CoV2 vaccination (<2 months after either the I or II dose); (3) a Naranjo score of 4 or above concerning the association between BP and SARS-CoV-2 vaccine; (4) absence of newly prescribed medications (in the 3 months preceding BP onset) or dipeptidyl peptidase 4 inhibitors; (5) diagnosis of BP based on typical findings on clinical, histopathological and/or immunopathological [IgG and/or C3 deposits along the dermal-epidermal junction (DEJ) on direct immunofluorescence (DIF) and/or indirect immunofluorescence (IIF) microscopy] examinations. The study was conducted in accordance with the Declaration of Helsinki guidelines and all patients gave written informed consent. The present study is a combined retrospective and prospective study. Clinical data were collected from electronic charts but also directly from patients at baseline or during the follow up visit. Skin manifestations were directly evaluated by a dermatologist. Each patient was examined at least twice (during the period of skin manifestations and after 3 months). Response to treatment was evaluated according to the recommendations from the International Pemphigoid Committee (18). Each participating center was asked to provide the following data: sex; age at onset; SARS-CoV-2 vaccine type; first and second dose date; time from SARS-CoV2 vaccine administration and BP onset; Naranjo score; comorbidities and concomitant medications; clinical scores [Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and Bullous Pemphigoid Disease Area Index (BPDAI), histopathological and immunopathological features (direct and/or indirect immunofluorescence, ELISA-tests); COVID-19 medications and duration of follow-up.

To identify anti-BP180 and anti-BP230 autoantibodies in patients' serum, commercial ELISA kits (Euroimmun, Padova, Italia) were used, in accordance with the manufacturer's instructions. A cut-off value of >20 U/mL was used for both type of test. As for DIF microscopy the sections stained with fluorescein isothiocyanate-conjugated goat anti-human Ig and C3 (Kallestad Diagnostic, Chaska, MN, USA), were analyzed under a fluorescence microscope. DIF results were recorded by taking into consideration the nature of the immune deposits (IgG, IgA, IgM, C3), the location of the immune deposits and the extent and the pattern of immune complex deposits (granular or linear). IIF was performed on slides containing human epithelial substrate and human salt-split skin as described (19).

RESULTS

Twenty-one cases of SARS-CoV2 vaccine-associated BP were collected, including 9 females and 12 males (M/F = 1.3) with a median age at diagnosis of 82 (IQR: 74–85.5) years (**Table 1**). Seventeen patients received the COMIRNATY Pfizer-BioNTech vaccine, two the Moderna mRNA-1273 vaccine, one the ChAdOx1/nCoV-19-AstraZeneca/ Vaxzevria vaccine and one received the first dose with the ChAdOx1/nCoV-19-AstraZeneca/Vaxzevria vaccine and the second dose with the COMIRNATY Pfizer-BioNTech vaccine. Median latency time between the first dose of SARS-CoV2 vaccine and the onset of cutaneous manifestations was 27 (IQR: 7–34) days (**Table 1**). The onset of clinical manifestations occurred in eight patients after the first dose and in 13 after the second dose. Among those with BP appearance between the first and the second dose, median latency time was 6.5 (IQR: 4–7) days from the first dose, whereas

TABLE 1 | Demographics and clinical features of reported cases.

N.	Sex, age (years)	Vaccine	Concomitant medications	Latency from the 1st dose (days)	Naranjo score#	Baseline BPDAI	Baseline ABSIS	Treatment	BPDAI at 3 months	ABSIS at 3 months
1	F, 84	Pfizer	Alendronate	25	6	70	21	Topical and systemic CS plus doxycycline	0	0
2	M, 83	Pfizer	Allopurinol, amiodarone, amlodipine, bicalutamide, clonidine, furosemide, insulin, valsartan, warfarin	32	6	50	18	Topical and systemic CS plus doxycycline	0	0
3	F, 56	Moderna	none	7	6	17	4.5	Topical CS plus doxycycline	0	0
4	M, 79	Pfizer	ASA, amiodarone, atorvastatin, clopidogrel, hydrochlorothiazide, olmesartan, pantoprazole, tamsulosin	4	6	23	10	Topical CS plus doxycycline	0	0
5	M, 86	Pfizer	Amiodarone, atorvastatin, clopidrogrel, domperidone, escitalopram, hydrochlorothiazide, levodopa/benserazide	37	6	20	12	Topical CS	0	0
6	M, 91	Pfizer	Allopurinol, atorvastatin, furosemide, insulin, nebivolol	28	6	80	30	Topical and systemic CS	0	0
7	M, 86	Pfizer	ASA, fenofibrate, isosorbide, ivabradine, pyridostigmine	36	6	52	20	Topical and systemic CS plus doxycycline	0	0
8	F, 84	Moderna	Amlodipine, glimepiride, metformin, levothyroxine	7	6	40	15	Topical and systemic CS plus doxycycline	0	0
9	M, 84	Pfizer	None	23	6	37	54	Systemic CS	0	0
10	F, 82	Pfizer	None	34	6	52	90	Systemic CS	6	27
11	M, 76	Pfizer	Candesartan, hydrochlorothiazide	34	6	47	70	Systemic CS	NA	NA
12	M, 78	Pfizer	none	4	4	42	NA	Topical CS	0	NA
13	F, 90	Pfizer	Allopurinol, hydrochlorothiazide, losartan	28	4	142	NA	Topical and systemic CS	25	NA
14	M, 90	Pfizer	Alfuzosin, allopurinol, darbepoetin alfa, furosemide, levothyroxine, pregabalin, warfarin	64	6	20	NA	Systemic CS	0	NA
15	M, 72	Pfizer	Insulin, telmisartan	16	6	80	NA	Topical and systemic CS plus MTX	29	NA
16	M, 80	Pfizer	ASA, amlodipine, atenolol, atorvastatin, finasteride, salmeterol/fluticasone, zofenopril	6	6	71	90	Topical and systemic CS	51	70
17	F, 77	AstraZeneca	Amlodipine, bisoprolol, furosemide, ramipril, sertraline	3	8	42	60	MTX	0	0
18	F, 60	Pfizer	None	75	6	10	36	Systemic CS	0	0
19	F, 70	Pfizer	None	27	6	15	35	Systemic CS	1	5
20	F, 72	AstraZeneca (1st dose), Pfizer (2nd dose)	ASA, amlodipine, levothyroxine, perindopril, simvastatin	7	6	15	NA	Systemic CS plus dapsone	3	NA
21	M, 85	Pfizer	ASA, atenolol, dutasteride, indapamide, perindopril, tamsulosin	27	6	15	30	Systemic CS	41	50

#*Naranjo scale interpretation: doubtful (≤0), possible (1-4), probable (5-8), definite (≥9).*

CS, corticosteroids; MTX, methotrexate; NA, not available; ABSIS, Autoimmune Bullous Skin Disorder Intensity Score; ASA, acetylsalicylic acid; BPDAI, Bullous Pemphigoid Disease Area Index.

TABLE 2 | Immunopathological features of reported cases.

N.	Histopathology[§]	DIF	IIF	ELISA IgG anti-BP180 (U/mL)	ELISA IgG anti-BP230 (U/mL)
1	+	Linear IgG/C3 deposits along the DEJ	IgG along the DEJ. SSS: roof	40	8.5
2	+	Linear IgG/C3 deposits along the DEJ	IgG along the DEJ. SSS: roof	492.1	425
3	+	Neg	IgG along the DEJ. SSS: roof	136.8	73.6
4	+	Linear IgG/C3 deposits along the DEJ	IgG along the DEJ. SSS: roof	237.5	0
5	+	Linear IgG/C3 deposits along the DEJ	IgG along the DEJ. SSS: roof	46.9	9.7
6	+	Linear IgG/C3 deposits along the DEJ	IgG along the DEJ. SSS: roof	14.9	0
7	+	Linear IgG/C3 deposits along the DEJ	NA	NA	NA
8	+	Linear IgG/C3 deposits along the DEJ	IgG along the DEJ. SSS: roof	247.2	5.7
9	+	Linear C3 deposits along the DEJ	NA	0	0
10	+	Linear IgG/C3 deposits along the DEJ	NA	0	0
11	+	Linear C3 deposits along the DEJ	NA	0	0
12	+	NA	IgG along the DEJ. SSS: roof	29.1	29.6
13	+	Linear IgG deposits along the DEJ	IgG along the DEJ. SSS: roof	106.3	2.9
14	+	Linear C3 deposits along the DEJ	neg	3.3	1.3
15	+	Linear C3 deposits along the DEJ	neg	140.4	0
16	+	Linear IgG/C3 deposits along the DEJ	IgG along the DEJ. SSS: roof	NA	NA
17	+	Linear C3 deposits along the DEJ	IgG along the DEJ. SSS: roof	52.9	22.2
18	+	Granular C3 deposits along the DEJ	IgG along the DEJ. SSS: roof	23.7	35.3
19	+	Linear C3 deposits along the DEJ	IgG along the DEJ. SSS: roof	5.5	1.8
20	+	NA	NA	NA	NA
21	+	NA	NA	NA	NA

[§]*Consistent with bullous pemphigoid, i.e., subepidermal blistering and eosinophil-rich infiltrates.*

DIF, direct immunofluorescence; IIF, indirect immunofluorescence; DEJ, dermal-epidermal junction; SSS, salt-split skin; NA, not available.

among those with BP onset after the second dose, the median latency was 7 (IQR: 4–14.5) days from the second dose [and 32 (IQR: 27–36.5) days from the first one]. Nineteen patients had a Naranjo score ≥6 while two had a Naranjo score of 4. Baseline BPDAI scores were available for all patients. Median BPDAI at onset was 42 (IQR: 18.5–61). Baseline ABSIS scores were available for 16 out of 21 patients. Median ABSIS at onset was 30 (IQR: 15.75–58.5) (**Table 1**). Laboratory exams were within normal ranges. Eleven out of seventeen patients (64.7%) had positive (>20 U/mL) titres for anti-BP180 antibodies with a median value of 106.3 U/mL on ELISA (IQR: 40–237.5 U/mL); in contrast, only 5 out of 17 (29.4%) were positive for anti-BP230 antibodies, with a median of 35.3 U/mL on ELISA (IQR: 25.9–249.3 U/mL) (**Table 2**). The clinicopathological picture was typical across our cohort (**Figures 1**, **2**). DIF showed linear IgG and C3 deposits along the DEJ (9 out of 18 cases), isolated linear C3 deposits along the DEJ (6/18), isolated linear IgG deposits along the DEJ (1/18), isolated granular C3 deposits along the DEJ (1/18). DIF turned out negative in one case. IIF performed on salt-split human skin revealed epidermal side binding in all tested cases (13/21) (**Table 2**).

Treatment included systemic corticosteroids (7), topical and systemic corticosteroids (3), topical and systemic corticosteroids plus doxycycline (4), topical corticosteroids plus doxycycline (2), topical and systemic corticosteroids plus methotrexate (1), systemic corticosteroids plus dapsone (1) and topical corticosteroids alone (2), methotrexate alone (1) (**Table 1**).

At 3 months, 13 patients achieved a complete response, whereas 6 had a partial response and one had stable disease [mean ABSIS percentage change = −80.75% (SD ± 44.25; $n = 15$); mean BPDAI percentage change = −78.14% (SD ± 60.21; $n = 20$)] (**Table 1**).

DISCUSSION

Vaccination has rarely been associated with new-onset dermatoses as well as flaring of pre-existent dermatological disease (11). SARS-CoV-2-vaccine-associated cutaneous eruptions encompass a growing spectrum of clinicopathological varieties, including local injection site reactions, urticarial eruptions, morbilliform eruptions, pernio/chilblain-like lesions, cosmetic filler reactions, herpes zoster and herpes simplex flares, pityriasis rosea-like eruptions (11, 20, 21). Autoimmune bullous skin diseases have also been observed following SARS-CoV-2-vaccination, with approximately 34 individual cases of vaccine-associated BP currently described (12, 14, 17, 22–28) (**Supplementary Table 1**). According to the registry-based studies by McMahon et al., BP-like eruptions accounted for 20% (12/58) of biopsy-proven SARS-CoV-2-vaccine-associated cutaneous reactions and 1.5% overall (11, 22).

The present multicentre study reports 21 cases of SARS-CoV-2 vaccine-associated BP, representing the largest case series to date.

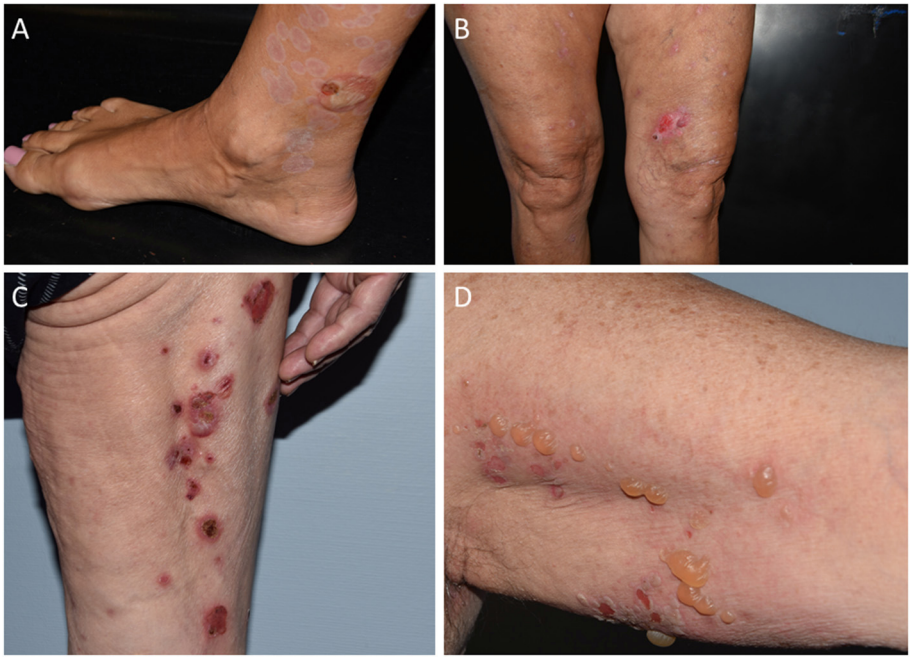

FIGURE 1 | Clinical spectrum of vaccine-associated BP patients. **(A)** Acral distribution of active blister associated with older lesions in partial resolution, resulting in mild erythema and hypopigmentation. **(B)** Sero-hemorrhagic bullous, pruritic eruption on medial surface of left thigh, surrounded by multiple prurigo-like specific lesions. **(C)** Linear distribution of erythematous blisters, resulting in crusts and erosions. **(D)** Blisters and erosions with mild erythema located on left axilla.

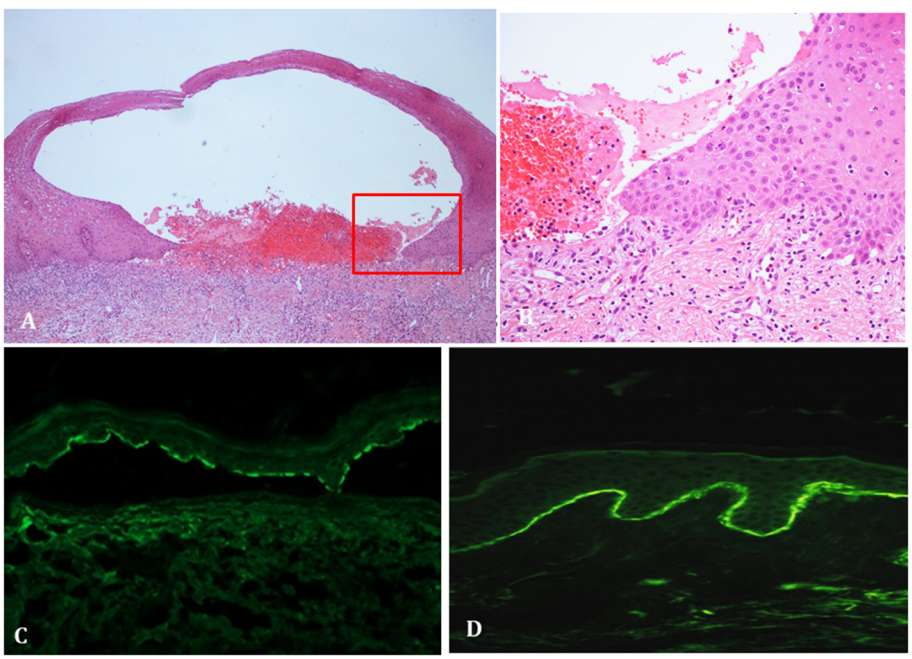

FIGURE 2 | Histopathological and immunopathological findings of vaccine-associated BP patients. **(A)** Histopathology showing subepidermal detachment accompanied by inflammatory infiltrates in the dermis (hematoxylin and eosin staining). **(B)** Close-up view revealing the supepidermal detachment with a dermal inflammatory infiltrate, mainly consisting of lymphocytes and eosinophils (hematoxylin and eosin staining). **(C)** Salt splin skin in indirect immunofluorescence shows IgG deposits along the dermo-epidermal junction. **(D)** Direct immunofluorescence shows linear IgG/C3 deposits along the dermo-epidermal junction.

Median age at onset (81 years) was in line with published observations [82.5 (IQR: 71.25–84.75) years; $n = 24/34$ with age available] (23–28). Likewise, sex distribution showed a slight male sex preference in both our cohort (M:F = 1.3) and available reports (M:F = 1.2; $n = 22$ with gender available) (23–28).

Vaccine-induced BP was more frequently associated with the Pfizer vaccine (80.1 vs. 67.6% of available reports), as compared with other mRNA- (Moderna mRNA-1273, 9.5 vs. 29.4% of available reports) or vector-based vaccines (ChAdOx1/nCoV-19-AstraZeneca/Vaxzevria, 9.5 vs. 2.9% of available reports). In line with our data McMahon and coworkers have recently found more BP cases associated with Pfizer vaccine than with Moderna (64 vs. 36%) (21). It is unclear whether this association depends on the greater employment of the Pfizer vaccine or if it underlies a deeper pathogenetic link. In fact, at the time of this study the percentage of Pfizer administration to adult patients was much higher (69.4%) in comparison with Moderna (18.3%), AstraZeneca (10.6%) and Janssen (1.7%) (29). In addition, in the present and all reported studies the sample size is too small to get meaningful result in term of association with a specific vaccine. To assess a possible link further studies with a large sample size standardized by specific vaccine administration should be performed.

Overall, the median latency time between the first dose and onset of cutaneous lesions was 27 days, which is notably higher than that of available reports [median latency time from the first dose to onset: 7 (IQR: 4–22.5) days, $n = 17$ with timing data available]. However, direct comparison with published cases is hindered by the lack of precise reporting of vaccination timings—especially in the case of vaccines with longer, variable time intervals between doses (e.g., Moderna mRNA-1273 vaccine, ChAdOx1/nCoV-19-AstraZeneca/Vaxzevria). Latency time from last dose was the preferred way of reporting across the literature. In our study, among those with BP appearance between the first and the second dose ($n = 8$), the median latency time was 6.5 (IQR: 4–7) days after the first dose, in line with available reports [median = 6 (IQR: 3–7.75) days, $n = 12$]. Similarly, those with BP onset after the second dose ($n = 13$) had a median latency time of 7 (IQR: 4–14.5) days from the latter, which is in agreement with the literature [median = 7 (2.5–14) days, $n = 9$]. Speculatively, a latency time shorter than a week (i.e., the minimum time required for antibody production) since the first dose may hint at a role for the stimulation of pre-existent autoimmunity in the pathogenesis of SARS-CoV-2-vaccine-associated BP. Conversely, late onset SARS-CoV-2-vaccine-associated BP may result from a dysregulated primary immune response triggered by the vaccine. Of note, it has been suggested that a one-month latency period from the time of vaccination may be appropriate for anti-basement membrane antibody induction (30).

Clinically, the presentation of SARS-CoV-2-vaccine-associated BP appears to be typical with tense bullae on an erythematous base, various degrees of cutaneous involvement, and an overall benign course with appropriate treatment (only patient n. 21 had stable disease at 3 months). Although many published reports describe a similarly favorable course (17, 24–28), in the study by Tomayko *et al.*, five patients had ongoing disease after a follow-up period ranging from 23 to 105 days (12). Our sample size prevents the possibility to reliably compare different treatments. However, most of the subjects were easily controlled with treatment regimens concepted for milder forms of BP (i.e., topical steroids, low-to-moderate doses of systemic corticosteroids, doxycycline), supporting the assumption that the majority of COVID-19 induced BP cases would be non-severe (17, 24–26). Systemic corticosteroids as well as immunosuppressive adjuvants required to achieve disease control in BP may affect the efficacy of anti-SARS-CoV-2 vaccines. Humoral and cellular immune responses to COVID-19 mRNA vaccines are reduced in patients with immune-mediated inflammatory diseases on background methotrexate (31). Moreover, treatment with mycophenolate mofetil and rituximab also compromise anti-SARS-CoV-2 antibody responses (32). However, according to the updated international recommendations for the management of autoimmune bullous diseases during COVID-19 pandemic, lowering the dosage of immunomodulatory medications before or during the vaccination is not advisable due to the risk of exacerbations (33).

Immunopathological findings also seem to be typical, highlighting linear IgG/C3 deposits along the DEJ on DIF and epidermal side binding on SSS IIF in the vast majority of cases. The serological landscape of SARS-CoV2 vaccine-associated BP is dominated by the presence of anti-BP180 autoantibodies with a frequency (65%) comparable with literature data (34, 35). Of note, positivity for anti-BP230 autoantibodies was infrequent in our cohort with a frequency of reactivity (29%) sharply lower than that previously reported (34, 35). Previous studies, investigating the dynamics of immune response to BP antigens, described that it involves at first extracellular antigens/epitopes (BP180-NC16A domain) followed by intracellular ones (BP230) possibly exposed after tissue damage (36, 37). In the light of these findings, it could be speculated that in vaccine-associated BP, due to very short disease duration, the induction of secondary response to BP230 is not always detectable.

Vaccine-induced BP could stem from vaccine-mediated stimulation of pre-existent, sub-clinical autoreactivity against hemidesmosomal components, as seen in a proportion of pruritic dermatoses of the elderly characterized by IgG-mediated autoimmunity against BP230 (38). However, limited anti-BP230 reactivity across our cohort and published reports would not encourage this interpretation. SARS-CoV-2 vaccine-associated BP may be driven by a specific pathogenetic process in genetically predisposed individuals. Prior to translation, mRNA vaccines could trigger several pro-inflammatory pathways via Toll-like receptor (TLR)-3, TLR7 and TLR8 binding (39). Moreover, through cytokine modulation, novel antigens and adjuvants could promote T-cell-dependent immune responses leading to the production of self-reactive B cells. Indeed, SARS-CoV-2-reactive T cell clones have been reported in the infiltrate of two elderly men with vaccination-induced BP (17). A contributing role of hollow needle-induced tissue disruption during vaccination has also been hypothesized (14, 40). Although no new medications were introduced in our cohort in the 3 months preceding BP onset, the

majority of our patients was receiving polypharmacy for various indications. Indeed, drugs potentially linked to drug-induced BP, including antihypertensives, salicylates and diuretics, had been administered for years in some of our cases (**Table 1**). It is not unconceivable that anti-SARS-CoV-2 vaccines may have created a suitable immune environment to make these individuals more prone to drug-induced BP (41).

In conclusion, SARS-CoV-2-vaccine-associated BP seems to be superimposable to idiopathic BP in terms of median age at onset and clinical presentation. On the other hand, slight male predominance and reduced humoral response to BP230 could represent peculiar features of this subset of patients. A close relationship between vaccination and BP onset is difficult to prove considering the extensive vaccination of the adult population during COVID-19 pandemic. However, the recent immunopathological findings by Gambichler *et al.* (17) as well as timing reported across our cohort and published cases support the hypothesis of a causal link between SARS-CoV-2 vaccine and BP development. Further research is warranted to better define the nature of SARS-CoV-2-vaccine-associated immune dysregulation leading to BP.

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 Istituto Dermopatico dell'Immacolata (IDI)-IRCCS. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MC, GD, and AM: designed the study. CAM GGe, PV, PS, EC, GGa, AP, EA, LA, RM, MC, EM, AC, SP, BD, and AM: enrolled patients. FM, RM, and GP: carried out the experiment. CAM, CM, GG, MC, GD, and AM: wrote the manuscript. CAM, MC, and GD: contributed to the interpretation of the results. GD and AM: conceived and planned the experiments. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.841506/full#supplementary-material

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Vaccination for SARS-CoV-2 in Patients With Psoriatic Arthritis: Can Therapy Affect the Immunological Response?

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Background: A few studies on vaccination in patients with rheumatic diseases, including arthritis, connective tissue diseases, vasculitis, and psoriatic arthropathy (PsA), demonstrated reduced production of neutralizing antibodies to SARS-CoV-2 Spike RBD (receptor-binding domain contained in the N-terminal of the S1 globular head region) when compared to the general population.

Objective: The aim of our study was to observe whether different therapies for PsA [methotrexate, anti-TNF antibodies, soluble TNF receptor (etanercept) or IL-17 inhibitors] have a different impact on SARS-CoV-2 vaccination in a homogeneous population of patients.

Methods: We enrolled 110 PsA patients in remission, assessed with Disease Activity in PSoriatic Arthritis (DAPSA). Of these: 63 were in treatment with anti-TNF-α therapy (26 etanercept, 15 certolizumab, 5 golimumab, 17 adalimumab); 37 with anti-IL17 secukinumab; 10 with methotrexate. All patients underwent vaccination for SARS-CoV-2 with mRNA BNT162b2 vaccine. Assessment of absolute and percentage lymphocyte subsets and anti-SARS-CoV-2 Spike RBD IgG antibody value 3 weeks after the second vaccine dose were performed. In addition, the serum antibody levels of 96 healthy healthcare workers (HCW) were analyzed.

Results: The mean disease activity assessed with DAPSA score was 2.96 (SD = 0.60) with no significant differences between patients under different medications ($p = 0.779$). Median levels of neutralizing antibodies to SARS-CoV-2 Spike RBD were 928.00 binding antibody unit (BAU)/mL [IQR 329.25, 1632.0]; 1068.00 BAU/ml [IQR 475.00, 1632.00] in patients taking MTX, 846.00 BAU/ml [IQR 125.00, 1632.00] in patients taking etanercept, 908.00 BAU/mL [IQR 396.00, 1632.00] in patients taking anti-IL17 and 1148.00 BAU/ml [IQR 327.00, 1632.00] in patients taking TNF-α inhibitors, without statistically significant

differences between these groups. Mean serum antibody level of HCW group was 1562.00 BAU/ml [IQR 975.00, 1632.00], being significantly higher than in the patient group ($p = 0.000816$). Absolute and percentage count of lymphocyte subsets were not statistically different between the subgroups under different treatments and when compared with HCW.

Conclusions: As for other rheumatic diseases on immunomodulatory treatment, our data showed a reduced humoral response in PsA patients compared to the control group. However, antibody response did not significantly differ between groups treated with different medications.

Keywords: SARS-CoV-2 vaccination, psoriatic arthritis, BNT162b2, mRNA COVID-19 vaccine, DMARDs, biologics

INTRODUCTION

Psoriatic arthritis (PsA) is a clinical heterogeneous, progressive and chronic inflammatory condition potentially leading to irreversible joint damage with negative impact on patient's quality of life (1–4). Many factors, including disease's subset (peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis, nail psoriasis), and severity, along with failure to previous lines of treatment, need to be considered when setting up a therapy for active PsA according with current guideline recommendations (5–7). Treatment options for PsA include non-biologic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, ciclosporin, and leflunomide, biologic therapies such as infliximab, golimumab, adalimumab, etanercept, certolizumab pegol, abatacept, ustekinumab, secukinumab, and ixekizumab and targeted synthetic DMARDs (i.e., apremilast and tofacitinib). These biologic and targeted therapies are used with optional concomitant DMARDs treatment. Due to immune dysregulation, PsA patients often receive corticosteroids (CS) and immunosuppressive therapies as well as other rheumatic disease. Moreover, they frequently have comorbidities such as diabetes, obesity, hypertension or may show lung or kidney involvement (8). For these reasons, patients with PsA have been included in the fragile patient's category, according to the Italian Ministry of Health, with the priority to SARS-CoV-2 vaccination, being considered a category at higher risk of developing coronavirus disease (COVID-19) with severe outcome (9, 10). The international community of rheumatologists have been focused on the effects of COVID-19 on their patients receiving different anti-rheumatic therapies. Thus, both European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) in 2020 developed a guidance for the management of rheumatic diseases in adult patients during the COVID-19 pandemic (11, 12) but did not reach a consensus over the withholding of all the drugs at disposal, in the peri-vaccination period.

In fact, while the effect of immunosuppressive agents on the immunogenicity of other vaccines has been largely investigated, to reach a consensus over their effect on anti-SARS-CoV-2 vaccines more data are needed. Studies on the effect of vaccination in rheumatic patients with arthritis, connective tissue diseases, vasculitis and PsA have demonstrated a low level of neutralizing antibodies to SARS-CoV-2 compared to the general population (13–15). In particular, it has been reported that methotrexate impairs serological response SARS-CoV-2 vaccine-induced immunity, even in absence of significant impact on seroconversion rate (16–18), while TNF-α inhibitors seems not to affect the ability to mount a sufficient serological and cellular response to two doses of SARS-CoV-2 mRNA BNT162b2 vaccine in psoriasis patients (17). Moreover, according to recent evidence, anti-IL17 and secukinumab, in particular, do not seem to interfere significantly with seroconversion rate following mRNA SARS-CoV-2 vaccine also (15, 17, 19).

The aim of our study was to acquire more data over the impact of different therapies for PsA such as methotrexate, anti-TNF-α antibodies, soluble TNF receptor (etanercept) or IL-17 inhibitors, on SARS-CoV-2 vaccination.

METHODS

We studied 110 PsA patients enrolled at the Rheumatology Unit of the S. Giovanni di Dio Hospital (Florence) from July to October 2021. Concurrently, 96 healthy healthcare workers (HCW group) were enrolled as healthy controls. The following characteristics were considered as inclusion criteria: age above 18 years; previous administration of both first and second dose of SARS-CoV-2 BNT162b2 vaccine; stable therapy regimen from at least 12 months; PsA in clinical remission, intended as a value ≤ 4 resulted from the assessment with Disease Activity in PSoriatic Arthritis (DAPSA) score at the time of enrolment (20). Conversely, previous SARS-CoV-2 infection, concomitant systemic corticosteroid treatment and autoimmune or immunodeficiencies comorbidities were designed as exclusion criteria. All the patients included in the study were on immunomodulatory treatment and on monotherapy regimen at the time of their enrollment: 63 were in treatment with anti-TNF therapy; 37 with secukinumab (150 mg every 4 weeks); 10 with methotrexate (MTX, 10 mg weekly). Among the patients treated with anti-TNF: 26 were on etanercept (50 mg weekly), 17 on adalimumab (40 mg every 2 weeks), 15 on certolizumab pegol (200 mg/every 2 weeks), 5 on golimumab (50 mg every 4 weeks). The patients under methotrexate were told to withhold the administration of the drug 1 week after each vaccine dose,

while subjects undergoing biological agents did not change their treatment schedule, as recommended by the latest available ACR COVID-19 vaccine clinical guidance at the time of enrolment (21) (version 2.0, July 2021).

All the enrolled PsA patients underwent evaluation of the lymphocyte subpopulations (CD3+, CD3+/ CD4+, CD3+/CD8+, CD4+/CD8+ ratio, CD3-/CD19+, CD3-/CD56+CD16+) by a flow cytometry analysis (FACS CANTO II, BD Biosciences) and the titer of anti-SARS-CoV-2 Spike RBD (receptor-binding domain contained in the N-terminal of the S1 globular head region) IgG antibodies (quantified by FEIA ThermoFisher, Uppsala Sweden) was also determined in both patients and HCW groups. All the mentioned analysis were conducted 3 weeks after the second vaccine injection. All patients gave their written informed consent based on the prospective nature of the study according to the Declaration of Helsinki and to the Italian legislation (Authorization of the Privacy Guarantor n.9, 12 December 2013). Local scientific ethic committee and health department examined and approved this research and the use of clinical and laboratory data of common clinical practice, in compliance with the Privacy Law, for clinical and scientific studies and publications.

Statistical Analysis

Statistical analysis was performed using R 3.5.2 GUI 1.70 El Capitan build (7612) software. For the descriptive statistics, continuous variables were tested for normality of distribution using Shapiro- Wilk test and represented by indicating the average and standard deviation in case of normality. Non-normally distributed variables were indicated as median and interquartile range [IQR]. Categorical variables were described by frequency distribution. Parametric (One way ANOVA) or non-parametric (Kruskall Wallis) tests, as appropriate, were than performed to compare antibody levels between patients under different therapies and between patients and controls. Linear regression analysis with stepwise selection based on *p*-value was performed considering as outcome variable binding antibody unit (BAU)/ml levels and as predictors the variables concerning characteristics of patients (sex, age, DMARD, DAPSA). Correlation between BAU/ml levels and demographical variables (sex, age) was also assessed *via* linear regression analysis in the control group.

RESULTS

The patient cohort consisted of 71 (65%) females and 39 (35%) males with a mean age of 61.72 years (SD 12). The prevalence of several comorbidities was collected: two patients (1.8%) had previous history of myocardial infarction, while angina pectoris was reported in three cases (2.7%). Twenty-five subjects were affected by arterial hypertension (22.7%) and one case by peripheral vascular disease (0.9%). Other cardiovascular diseases accounted for 16.3% of the enrolled subjects ($n = 18$). Regarding metabolic comorbidities, diabetes mellitus' cohort prevalence was 9.09% ($n = 10$) while 19 patients presented dyslipidemia (17.2%) and the body mass index of 20 subjects resulted in obesity (18.1%). Finally, eight patients were affected by thyroiditis (7.27%) and 2 by chronic obstructive pulmonary disease (1.81%).

The control group (HCW) included 96 healthy health care workers. Of these, 31 (32.3%) were males and 65 were females (67.7%). The mean age of the control group was 50.54 years (SD 11.66). Mean disease activity calculated with DAPSA was 2.96 (SD 0.60) and it did not differ between patients undergoing different treatments ($p = 0.779$). Lymphocyte subpopulations (CD3+, CD3+/CD4+, CD3+/CD8+, CD3-/CD19+, CD3-/CD56+CD16+) did not show any differences between groups too (**Table 1**). All the PsA patients had a detectable humoral response, as well as for the subjects enrolled in HCW group. The median of anti-SARS-CoV-2 Spike RBD IgG antibodies levels in patients' cohort was 928.00 BAU/ml [IQR 329.25, 1632.0]. Considering the different groups, the median values were the following: 1068.00 BAU/ml [IQR 475.00, 1632.00] in patients under MTX therapy; 846.00 BAU/ml [IQR 125.00, 1632.00] in patients under etanercept treatment; 908.00 BAU/ml [IQR 396.00, 1632.00] in patients treated with anti-IL17 agents; 1148.00 BAU/ml [IQR 327.00, 1632.00] in patients under TNF-α

TABLE 2 | Differences in anti-SARS-CoV-2 Spike RBD antibody titers between psoriatic arthritis patients and HealthCare Workers control group.

	Healthy healthcare controls workers	Treated PsA patients	
N	**96**	**110**	***P*-value**
Anti-Spike IgG level median [IQR]	1562.00 [975.00, 1632.00]	928.00 [329.25, 1632.0]	0.000816

TABLE 1 | Differences in lymphocytes' subpopulations in the four subgroups.

Treatment	Anti-IL17	Anti-TNF alpha	Etanercept	Metothrexate	
N	**37**	**37**	**26**	**10**	***P*-value**
CD3 median (BAU/ml) [IQR]	1680.00 [1210.00, 1936.00]	1680.00 [1350.00, 1747.00]	1747.00 [1643.00, 1923.75]	1446.00 [1216.50, 1709.00]	0.4
CD4 median (BAU/ml) [IQR]	1073.00 [712.00, 1350.00]	1047.00 [709.00, 1350.00]	1087.00 [887.50, 1350.00]	894.50 [723.75, 1068.25]	0.498
CD8 median (BAU/ml) [IQR]	404.00 [290.00, 720.00]	414.00 [257.00, 764.00]	547.50 [306.25, 779.00]	556.50 [248.00, 738.25]	0.727
CD19 median (BAU/ml) [IQR]	204.00 [139.00, 275.00]	196.00 [139.00, 298.00]	225.00 [190.00, 311.50]	255.50 [144.75, 394.75]	0.520
CD56 median (BAU/ml) [IQR]	290.00 [166.00, 454.00]	370.00 [166.00, 527.00]	267.00 [178.75, 473.50]	268.50 [167.50, 324.50]	0.761

BAU, binding antibody unit; IQR, inter-quartile range.

inhibitors. No statistically significant differences were found between these groups ($p = 0.73$) (**Table 2**). The median serum level of HCW group was 1562.00 BAU/ml [IQR 975.00, 1632.00], significantly higher when compared to the patients' group ($p \leq 0.001$) (**Table 3**; **Figure 1**). Linear regression analysis identified the age as negative predictor of concentration levels in the PsA population ($\beta = -12.26, p = 0.016$) but not in the control group.

DISCUSSION

Recent recommendations indicate that patients with psoriatic disease who do not have contraindications to vaccination should receive an mRNA-based COVID-19 vaccine and they are invited to continue their systemic therapies for psoriasis and/or PsA in most cases (22).

Despite the lack of large studies focused on PsA populations, a reduction of the humoral response to SARS-CoV-2 vaccines in patients on immunomodulatory treatments has been repeatedly reported. Al-Janabi et al. recruited 120 participants with immune-mediated inflammatory diseases (IMIDs) in treatment with biologics, other immunomodulators or combination of therapy, reporting that 15% of patients with no prior COVID-19 failed to mount a detectable antibody response to BNT162b2 or AZD1222 vaccines while 41% had no detectable anti-SARS-CoV-2 Spike RBD S1 IgG antibodies. However, it is of note that the assessments were performed after a single dose of vaccine (23). Simon et al. enrolled 84 IMIDs patients and 182 controls, with no previous history of COVID-19, finding delayed and reduced overall responses to first or second vaccination dose in patients' group (13). Considering that patients under therapy did not show a different response compared with off-therapy patients, they concluded that the phenomenon may be related to the disease itself rather than the treatment. Geisen et al. evaluated antibody responses following the second dose of mRNA vaccines in 26 patients with IMIDs receiving biologic, conventional DMARDs and/or prednisolone compared to 42 healthy controls. They showed that all patients developed neutralizing antibodies, but mean levels of anti-S1 SARS-CoV-2 IgG titers were reduced in those under immunosuppression (15).

Similarly, we found lower antibody levels in response to vaccine in our PsA patients under immunomodulatory treatment, compared to the HCW group. In fact, the mean serum level in the PsA patients' group was 965.44 BAU/ml (SD 643.13) while it was significatively higher ($p = 0.0000276$) in the HCW group, being 1294.5 BAU/ml (SD 416.2). However, our cohort resulted in 100% seroconversion rate among patients receiving immunosuppression, as well as for healthy controls. Although reduced, detectable serological responses to vaccine in patients' group suggests successful induction of antibodies in individuals receiving methotrexate and targeted biologics.

While subgroup analysis of drug type could not be conducted (23) among the cited studies, Deepak et al. evaluated the titers of serum anti-SARS-CoV-2 spike (S) IgG in 133 adults with chronic inflammatory diseases, highlighting that patients on B-cell depletion therapy, prednisone, JAK inhibitors, and antimetabolites had statistically significant reductions in antibody titers in univariate and multivariate models. In contrast, antimalarials (i.e., hydroxychloroquine) and TNF-α inhibitors were not significantly associated with reduced antibody titers. However, most patients were able to mount an efficient immunological response to vaccine, while the highest rate of failed seroconversion was registered among patients under systemic corticosteroids or B-cell depleting therapies (24). In fact, rituximab and prednisone or prednisolone doses greater than 10 mg/die were also associated with higher risk of COVID-19 and hospitalization in patients with autoimmune or rheumatic diseases (25, 26), thus underlining the fundamental role of humoral response against SARS-CoV-2 infection.

In our case, when comparing single therapeutic regimens, no statistical difference emerged between different treatment groups.

Geisen et al. did not report significant differences in antibody levels comparing the according age groups (15); in our work, linear regression analysis revealed age as a negative predictor of

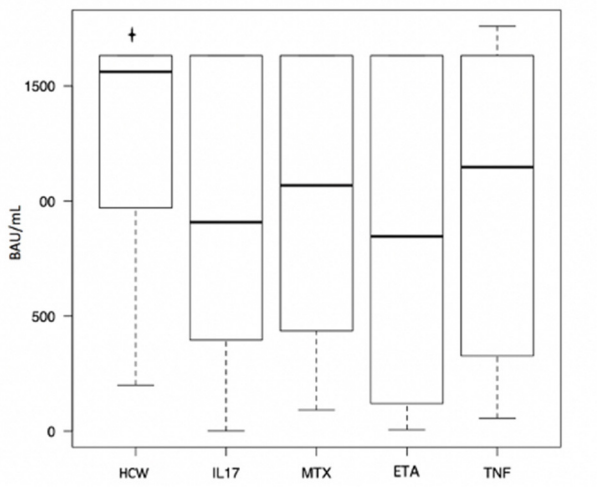

FIGURE 1 | Differences in anti-SARS-CoV-2 Spike RBD antibody titers between psoriatic arthritis patients treated with different medications. HCW, HealthCare Workers control group; IL17, anti-IL17; MTX, methotrexate; ETA, etanercept; TNF, anti-TNF.

TABLE 3 | Differences in anti-SARS-CoV-2 Spike RBD antibody titer in the four patient groups.

Treatment	Anti-IL17	Anti-TNF alpha	Etanercept	MTX	
N	37	37	26	10	*P*-value
Anti-Spike IgG levels median [IQR]	908.00 [0.70, 1632.00]	1148.00 [56.00, 1760.00]	846.00 [6.40, 1632.00]	1068.00 [92.00, 1632.00]	ns

anti-SARS-CoV-2 Spike RBD IgG levels in patients' cohort, while the same association was not found in HCW group. So, even if the significative difference between the mean age of the two groups (61.72 years, SD 12 vs. 50.54 years, SD 11.66, $p < 0.001$) could represent a limit of the study, age seemed not to influence antibodies production in control groups, thus reducing the risk of bias. Therefore, we may speculate that immunosuppressive agents could somehow enhance or anticipate the age-related immune senescence process in treated individuals. At this regard it is worth mentioning that a large cross-sectional study found a different age distribution of humoral response: in fact, the negative correlation with age was demonstrated only in people below the age of 18, while the adult population showed a positive correlation with higher antibodies titers in older age groups. Thus, other large-population studies are needed to improve the knowledge about this correlation (27).

For what concerns cellular response to vaccination, specific studies for psoriatic arthropathy are still lacking. However, a significant increase in Spike-specific B cells, T-follicular helper cells, activated CD4+ T cells and HLA-DR + CD8+ T cells was described using flow cytometry in IMIDs patients and controls, while activated CD8 + T cells and granzyme-B-producing CD8 + T cells boosting was lacking only in patients under methotrexate (16). Abatacept treatment in RA patients was also associated with reduced cellular T response, as well as with impaired production of neutralizing anti-Spike antibodies (28). With the aim to acquire more data on this topic, we evaluated lymphocyte subpopulations finding no differences between patients under different treatments. Moreover, lymphocyte subpopulations were not predictive of antibody levels according to linear regression analysis in our cohort. However, no decrease in any of the investigated subpopulations was observed, thus suggesting an adequate cellular immune response to vaccination.

To date, it is still not clear whether a reduced antibody response is invariably linked to an increased susceptibility to COVID-19. In fact, it has been reported that rates of SARS-CoV-2 infection appear to be similar between general population and patients with rheumatic diseases receiving DMARDs or biologics (29), including psoriasis (22, 30–35). In addition, those patients do not seem to have an increased risk of hospitalization or death from COVID-19, although generally burdened by higher rates of metabolic and cardiovascular comorbidities (36–40).

As already suggested by other authors (41), our results may support the decision not to suspend treatment with anti-TNF or anti-IL17 in the peri vaccination period. In fact, the latest version (4.0) of ACR guidelines Task Force failed to reach consensus on whether to temporarily interrupt these following each COVID vaccine dose, including both primary vaccination and supplemental (booster) dosing.

Among the limitations to our study immune functional tests such as plasma neutralization assay and assessment of interferon-γ produced by T-cells in response to SARS-CoV-2 peptides were not performed. Moreover, methotrexate was administered at a mean dosage of 10 mg/week. This may be not fully representative of PsA patients on methotrexate, which are often treated with higher dosages. Hence, humoral response to vaccination for PsA patients on methotrexate may not be comparable with the other drugs, despite our findings. The study did not cover all the treatment commonly used for psoriatic arthritis, i.e., abatacept, anti-IL23 and apremilast. In addition, the difference on mean age of the groups may represent a confounding factor.

While contributing to acquire more data concerning antibody response to vaccination on immunomodulatory treatments, our results do not exclude that antibody serum level may have been reduced by the disease itself rather than the treatment, as previously suggested by Simon et al. In fact, since the majority of patients underwent vaccination, as strongly recommended by the scientific community, adding a non-vaccinated PsA patients control group to the study was not possible.

CONCLUSION

Our data show that systemic therapy for psoriatic arthritis, as observed for other rheumatic diseases, may lead to a reduced quantitative humoral response when compared with healthy controls. However, global seroconversion rate seems not to be significantly affected. There seem not to be statistically significant differences between the groups treated with low dose methotrexate and biologic agents with different mechanisms of action in terms of humoral response. Antibodies production may decrease with age, while immunosuppression could represent an enhancement for this phenomenon.

As we believe that cellular response might have a fundamental role into the development of immune response against SARS-CoV-2, further studies are needed to identify reliable indicators of its involvement and to clarify whether immunomodulatory treatments may affect it and how.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

All patients gave their written informed consent based on the prospective nature of the study according to the Declaration of Helsinki and to the Italian legislation (Authorization of the Privacy Guarantor n.9, 12 December 2013). The Institutional Review Board, Health Director of the Florence Hospital, has examined and approved this research and the use of clinical and laboratory data of common clinical practice, in compliance with the Privacy Law, for clinical and scientific studies and publications.

AUTHOR CONTRIBUTIONS

MB, AD, MI, MM, BL, VG, MC, and FLG designed the study and drafted the manuscript. MB, AD, EM, and AC drafted the manuscript. CA, LQ, AV, and EA revised the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Considerations on Immunization and Immunosuppression of Patients With Autoimmune Blistering Diseases During COVID-19 Pandemic in Brazil: Case Report

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Autoimmune blistering diseases comprise a rare group of potentially life-threatening dermatoses. Management of autoimmune disorders poses a challenge in terms of achieving disease control and preventing adverse events. Treatment often requires an individualized approach considering disease severity, age, comorbidities, and infectious risk especially in the context of the ongoing COVID-19 pandemic. Knowledge regarding SARS-CoV-2 infection is still evolving and no specific antiviral therapy is available yet. We report four patients with active disease that required adjustment of treatment during the pandemic to discuss the use of immunosuppressants and immunobiologics, weighing potential risks and benefits of each therapy modality and vaccination status.

Keywords: COVID-19, SARS-CoV-2, autoimmune blistering diseases, pemphigus, immunosuppressants, rituximab, vaccine

INTRODUCTION

Since the COVID-19 outbreak, management of autoimmune blistering diseases (AIBD) became even more challenging to provide adequate immunosuppressive treatment while minimizing infectious risk. Clinicians recommend individualized approach considering disease severity, patients' age and comorbidities while no specific antiviral therapy is available.

Brazil has the third highest number of confirmed COVID-19 cases and the second highest mortality rate, with nearly 21.82 million cases and 608,000 deaths (1). The University of São Paulo Medical School is a reference center for AIBD, with 1,156 patients under follow-up (683 with pemphigus and 473 with subepidermal blistering diseases). From March until September 2020, our hospital exclusively dedicated 800 beds for the treatment of 4,500 severe COVID-19 cases (2), which limited dermatological outpatient and inpatient consultations (3). Such measures led to reschedule AIBD patients in remission and reevaluation of immunosuppressant therapy with the lowest immunosuppression for patients with active disease. We hereby report four cases that required treatment assessment during the pandemic to discuss the use of immunosuppressive and immunobiologics, weighing potential risks and benefits of each treatment and vaccination status (**Table 1**).

TABLE 1 | Summary of AIBD cases treated during COVID-19 pandemic.

No.	Age/sex	Diagnosis/ duration	Comorbidities	Treatment[a]	COVID-19 vaccine	COVID-19 infection[b]	Outcome
1	57/male	PF 3 months	Schizophrenia	Pred 80 mg/d (1 mg/kg/d) MMF 3 g/d	Unavailable	D57	Deceased
2	36/male	PV 8 months	Diabetes type I Obesity	Pred 15 mg/d (0.2 mg/kg/d) MMF 2 g/d RTX 1 g (Jan 18 and Feb 5, 2021)	Unavailable	D63	Recovery
3	45/female	PV 1 month	Pulmonary embolism	Pred 50 mg/d (0.7 mg/kg/d) RTX 1 g (Apr 22 and May 6, 2021)	Unavailable	D45	Deceased
4	61/male	PV 3 years	Diabetes type II	Pred 30 mg/d (0.4 mg/kg/d) RTX 1 g (Aug 30 and Sep 13, 2021)	PfizerBioNTech (May, Jul, Sep 2021)	N/A	N/A

[a]*Treatment in use at the time of COVID-19 infection.*

[b]*Interval between onset of immunosuppression and SARS-CoV-2 infection; MMF, mycophenolate mofetil; N/A, not applicable; PF, pemphigus foliaceus; Pred, prednisone; PV, pemphigus vulgaris; RTX, rituximab.*

CASE DESCRIPTION

Patient 1

A 57-year-old male patient with schizophrenia presented diffuse blisters and confluent erosions on the face and trunk for 3 months. He was hospitalized on March 13, 2020, and the diagnosis of pemphigus foliaceus was confirmed: histopathological analysis revealed acantholysis and cleavage at the spinous layer level. Immunofluorescence findings showed intercellular intraepidermal deposits of IgG and C3 (direct immunofluorescence) and circulating IgG autoantibodies by indirect immunofluorescence (titers >1:2,560, intercellular epidermal pattern). Initial treatment started with oxacillin 1 g 4/4 h, methylprednisolone 80 mg/d and mycophenolate mofetil (MMF) 3 g/d. On D12, he developed multiple round crusts predominantly on the periocular region, diagnosed as Kaposi varicelliform eruption and received intravenous acyclovir 5 mg/kg/dose. Disease control was achieved on D35 and the patient was discharged with prednisone 80 mg/d and MMF 3 g/d. On April 27, 2020, during the first follow-up visit, the patient complained of weakness and fever (>100.4 F) for 1 day. Infectious disease clinicians recommended influenza vaccination and prescribed oseltamivir 75 mg BID for 5 days. Once the patient did not attend his 1 week-follow-up visit, we contacted his family, who informed that he was admitted in a different hospital and passed away due to COVID-19.

Patient 2

A 36-year-old male patient with refractory pemphigus vulgaris (PV) and uncontrolled type I diabetes was referred to our institution due to persistent erythematous and squamous plaques on the scalp and confluent erosions on the trunk for 8 months. His prior treatment included prednisone (40 mg/day), azathioprine (100 mg/day) and doxycycline (200 mg/day) since September 2020, prescribed elsewhere. In December 2020, we replaced azathioprine for MMF 3 g/day due to the refractoriness of PV lesions. Once the PV activity persisted and his comorbidities such as diabetes and obesity aggravated, we decided for rituximab (RTX), two 1 g infusions, administered on January 18 and February 5, 2021 (**Figure 1A**). Within 1 month after anti-CD20 therapy, the patient achieved partial remission, with complete healing of the PV lesions on the trunk, partial clearing of crusted plaques on the scalp and adequate control of the diabetes.

However, on Mar 31, 2021, he presented with fever, pustules and exsudative plaques on the scalp for 10 days despite treatment with prednisone 15 mg/day and mycophenolate mofetil 2 g/day. He was hospitalized and SARS-CoV-2 PCR was positive on D10. Thorax CT revealed multiple ground glass opacities with multifocal and bilateral areas of consolidation involving up to 50% of the lung parenchyma. He received Heparin 5,000 UI 12/12 h and oxacillin 1 g 4/4 h for the cutaneous infection., and PV treatment changed to monotherapy with prednisone 30 mg/d. On D13, he developed hypoxemia (O_2 saturation = 88%) and required oxygen supplementation with nasal catheter (2 L/min) that progressed to non-invasive ventilation due to respiratory failure. On D16, he was transferred to the intensive care unit and put on awake prone ventilation; prednisone was replaced with dexamethasone 20 mg/day and heparin was increased to 5,000 UI 8/8 h. On D25 oxygen supplementation was progressively reduced and the patient was discharged after 27 days of hospitalization. He fully recovered of COVID-19 without sequelae. On October 25, 2021, during his last follow-up visit, PV was on remission with prednisone 7.5 mg/day (**Figure 1B**).

Patient 3

A 45-year-old otherwise healthy female patient presented lesions on the scalp for 1 month that progressed to the trunk, abdomen, and limbs along with oral and vaginal erosions. On March 22, 2021, she was admitted to the hospital for diagnostic confirmation and treatment. Histopathological examination (abdomen) revealed a suprabasilar acantholytic dermatosis. Direct immunofluorescence demonstrated IgG, C3 and IgA intercellular deposits within the epidermis and IgM and C3

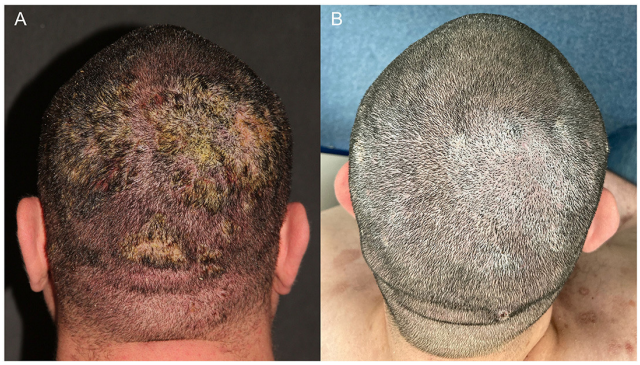

FIGURE 1 | A 36-year-old man with pemphigus vulgaris. **(A)** Confluent erosions with purulent crusts on the scalp in February 2021. **(B)** Improvement of the lesions 9 months after rituximab treatment.

focally deposited at the basement membrane zone. Indirect immunofluorescence titers of IgG on human foreskin were of 1:640 and negative on transitional murine epithelium. We then confirmed the diagnosis of PV after a complete systemic workup with no evidence of neoplasia. Additional systemic findings revealed incidental acute bilateral pulmonary embolism without thrombophilia and no cardiac dysfunction that needed anticoagulation with rivaroxaban. After 30 days, the mucocutaneous PV erosions evolved with slow central healing. However, persistent PV activity occurred despite the use of prednisone 1.4 mg/kg/d and MMF 3 g/day, thus limiting the tapering of immunosuppression. She then received two infusions of RTX 1 g within 14 days. As the patient evolved with lymphopenia (600/mm^3), MMF was withdrawn, and we added prophylactic trimethoprim/sulfamethoxazole 160mg/800mg per day.

The patient was discharged on April 25, 2021, after control of PV within 2 weeks after RTX infusion. After 3 weeks, the patient failed to attend the appointment, and after contacting the family, we were informed that she passed away in another hospital, 5 days after the onset of fever, cough, and dyspnea that progressed to respiratory failure. COVID-19 was highly suspected, as the patient had close contact with a sibling with similar symptoms.

Patient 4

A 61-year-old diabetic patient with mucocutaneous PV, with erosions on the trunk and oral mucosa since 2018, initially treated with prednisone 100 mg/day and MMF 3 g/d, progressively healed, allowing tapering of MMF from May until November 2020; by then, prednisone 15 mg/day was maintained as monotherapy due to PV remission and to a scheduled a cataract surgery.

In March 2021, he developed blisters and erosions on the oral mucosa, malar region and trunk that did not improve even after reintroduction of MMF 3 g/d and increase in prednisone to 80 mg/d (1 mg/kg/d). Secondary bacterial infection required prolonged treatment with trimethoprim/sulfamethoxazole 160/800 mg BID (**Figure 2A**). Despite risk factors for severe SARS-CoV-2 infection (male sex, age, diabetes), RTX therapy was scheduled 4 weeks after completion of COVID-19 vaccination. At the second RTX infusion, he developed herpes zoster successfully treated with valacyclovir 1 g 8/8 h for 14 days. PV lesions started improving right after RTX infusion, allowing tapering of prednisone and MMF. As of September 2021, the Brazilian Ministry of Health approved an additional booster COVID-19 vaccine dose for immunosuppressed patients, 4 weeks after vaccination completion. The patient received the additional COVID immunization, had no adverse effects and currently presents partial PV control on therapy Prednisone (30 mg/d) after 9 weeks of rituximab therapy (**Figure 2B**).

DISCUSSION

Brazil has been one of the epicenters of COVID-19 pandemic. Patient 1 highlights the difficult decision of treating a severe disease with immunosupressants such as systemic corticosteroids and MMF in a scenario during the beginning of the pandemic, when scientific knowledge regarding SARS-CoV-2 infection and treatment was scarce, whilst viral transmissibility was increasing (Reff >1) (4), with no perspective on COVID-19 immunization. He presented a severe, refractory bullous-invasive PF, only controlled with the association of prednisone and MMF.

MMF is a first line adjuvant drug in the treatment of AIBD (5) due to its corticosteroid-sparing effect with a better safety profile, when compared to other immunossupressants. MMF selectively inhibits *de novo* purine synthesis of B- and T-cells, and its active metabolite—mycophenolic acid—presents a half-life of 17.9 h (6).

Low lymphocyte levels are considered predictors of poor outcome in COVID-19 (7). The use of MMF during the pandemic became a great concern, once lymphopenia is a potential adverse effect of the drug (6). In COVID-19, it has been hypothesized that SARS-CoV-2 may present direct cytotoxic

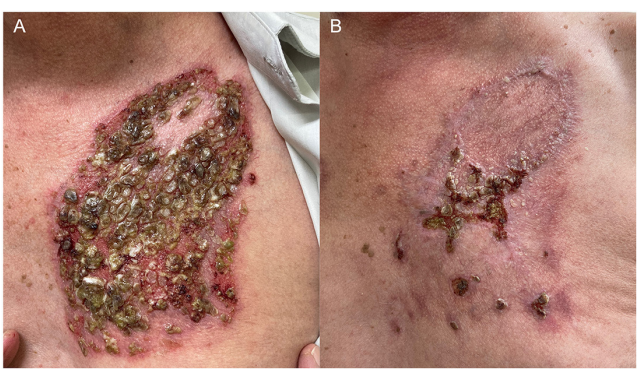

FIGURE 2 | A 61-year-old man with pemphigus vulgaris had a recurrence of the disease after withdrawn of mycophenolate mofetil in November 2021 and presented **(A)** eroded plaques with purulent crusts and keratotic areas on the trunk in July 2021. Lesions were recalcitrant to prednisone 1 mg/kg/d and mycophenolate mofetil 3 g/d, and only improved 1 month after 2 rituximab infusions **(B)**.

effects in lymphocytes, as they also express ACE2 receptor, or that lymphopenia may be a result of a dysregulated immune response to the virus and to the corticosteroid treatment for the infection (7). On the other hand, *in vitro* studies demonstrated an antiviral effect of mycophenolic acid at a concentration of 0.87 μm/mL (8), which is much lower than the therapeutic level of 1.2–8.0 μm/mL observed in patients during MMF treatment of 1–3.5 g/d (9).

A systematic review including eight studies with 732 patients with AIBD under immunomodulatory (corticosteroid, MMF, azathioprine, RTX) treatment observed no increased risk of severe SARS-CoV-2 or mortality in comparison with the general population (10). However, heterogeneity in the studied population including different AIBD with variable disease activity and treatment regimens requires caution to interpret the data.

A committee of experts currently recommends to withdraw MMF treatment during active COVID-19 (11). For patients with adequate AIBD control, it is advisable to outweigh benefits and risks of maintenance therapy with MMF. Current studies suggest mortality rates among patients with bullous pemphigoid are higher than age-matched controls (12). As potentially life-threatening diseases, AIBD flares may also require higher doses of systemic corticosteroid and hospitalization, thus aggravating the infectious risk. A retrospective single-center study demonstrates that prednisone >10 mg/d increases the risk of COVID-19 hospitalization and mortality (13).

Patient 2 had COVID-19 after 2 months of RTX treatment. He had additional risk factors for poor outcome including gender (male), obesity and diabetes; furthermore, vaccination was not available to him (young patient on immunosupressants). Nevertheless, full recovery was achieved due to adequate intensive care support at a reference hospital for COVID-19, and new recommendations for the management of severe pulmonary SARS-CoV-2 infection: anticoagulation (14), oxygen supplementation, dexamethasone (15), and awake proned ventilation (16).

Rituximab is an IgG anti-CD20 monoclonal antibody that promotes B-cell depletion and reduces antibody synthesis for 6–12 months (17). CD20+ cell recovery usually occurs within 6 to 9 months after the infusion (18). Though this prolonged effect enables AIBD remission with lower cumulative corticosteroid dose, it poses a challenge during the COVID-19 pandemic, as patients may experience a higher infectious risk and disease severity. Current studies demonstrated that AIBD and rheumatic patients treated with rituximab have an increased risk of COVID-19 mortality that reduces monthly after the infusion following B-cell recovery (11).

A retrospective study analyzed the outcomes of COVID-19 in 19 AIBD patients with confirmed SARS-CoV-2 infection. Among patients with bullous pemphigoid ($n = 11$), pemphigus vulgaris ($n = 4$), pemphigus foliaceus ($n = 3$) and mucous membrane pemphigoid ($n = 1$), the only 2 deaths occurred in patients who had been treated with rituximabe <6 months before COVID-19: a 74-year-old male PV patient with hypertension that received rituximab 2 months before the infection and a 82-year-old female BP patient with hypertension, dementia and chronic obstructive lung disease that was treated with rituximab 4 months prior to SARS-CoV-2 infection (19). Another retrospective cohort study evaluated COVID-19 outcomes in 704 AIBD patients and observed that a decrease of 38% in the relative risk of SARS-CoV-2 infection and of 45% in the relative risk of hospitalization occurs every month after rituximab infusion (13). This suggests that B-cell depletion increases the COVID-19 severity (19). As humoral response recovery is crucial for adequate response to vaccination against SARS-CoV-2, it is currently recommended to postpone rituximab infusion at least 4 weeks after vaccination completion (11).

An observational study including 3,729 patients with rheumatic diseases and suspected or confirmed COVID-19 diagnosis demonstrated that patients treated with rituximab have a 4.04 increased risk of mortality in comparison to patients receiving methotrexate in monotherapy. Limitations included a potential reporting bias, as this physician-registry study may have included more severe cases, and missing data concerning the interval between last rituximab infusion and SARS-CoV-2 infection (20).

For these reasons, maintenance treatment with rituximab infusions in patients under disease control has been discouraged. Updated expert opinion recommends treatment with rituximab for patients with recalcitrant disease and without comorbidities (17).

Patient 3 also developed COVID-19 during an active phase of anti-CD20 treatment. She received RTX due to recalcitrant PV despite high dose prednisone and MMF, that led to a prolonged hospitalization. Immunosuppressive therapy with corticosteroid and RTX, lymphopenia and bilateral pulmonary embolism may have contributed to a poor outcome despite anticoagulation therapy with rivaroxaban. Unfortunately, even after extensive evaluation, the cause of her pulmonary embolism remained undetermined and may have been related to PV activity.

Previous studies revealed that patients with active pemphigus and bullous pemphigoid have higher risk of venous thromboembolism, possibly related to increased expression of tissue factor and pro-inflammatory cytokines leading to a prothrombotic state (21, 22). An Italian multicenter cohort study demonstrated a 15-fold risk of venous thromboembolism in patients with active BP (21), whereas a Israeli population-based study showed a 2-fold risk of pulmonary embolism in pemphigus patients, mainly during the first year of the disease (22). Additional studies are necessary to determine the benefits of thromboprophylaxis in such patients, especially in the context of COVID-19 pandemic, as the SARS-CoV-2 infection may further activate the coagulation cascade and increase the risk of life-threatening thromboembolic events (14, 23).

Patient 4 presented reactivation of PV lesions following MMF withdrawn without improvement, with reintroduction of MMF treatment and increase in prednisone daily dose. He received extensive explanations regarding potential risks and benefits of rituximab therapy, as well as safety measures to prevent COVID-19 infection. Considering current knowledge regarding the outcomes of SARS-CoV-2 infection in patients with AIBD, the availability of COVID-19 vaccine enabling a reduction in the number of new cases and viral transmissibility in Brazil, we scheduled rituximab infusions in September 2021, at a better

pandemic scenario than patients 2 and 3 and 4 weeks after vaccination completion.

Randomized controlled trials focusing on the approval of COVID-19 vaccines demonstrated efficacy and safety only among healthy individuals and did not include immunosuppressed patients with autoimmune diseases. Pre-pandemic studies demonstrated that the vaccine response may also be impaired in patients treated with RTX. A systematic review and meta-analysis of 38 studies including 905 patients with autoimmune disorders or hematologic malignancies evaluated the immune response of RTX-treated patients to different vaccines. A lower vaccine response in patients treated with RTX was observed in comparison with disease controls treated with other immunosuppressants and healthy individuals, with seroconversion rates from 0 to 25% in patients under active treatment (<12 weeks between RTX infusion and vaccination) (24).

Immune responses to novel technologies incorporated in SARS-CoV-2 vaccines, such as lipid-nanoparticles including mRNA of S1 receptor binding domain used in BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), are being further evaluated in AIBD patients. It has been hypothesized that upregulation of interferon-I following COVID-19 vaccination may induce autoimmunity and trigger the onset of AIBD or disease relapse (25). Moreover, immune dysregulation induced by vaccination may precipitate an epitope spreading phenomenon thus leading to recognition of self-antigens (26), and clonal expansion of T cells exhibiting SARS-CoV-2 reactivity (27). Lesion development has been reported between 1 day and 3 weeks after the first and/or second vaccination. Current data supports vaccination completion even for patients that experienced disease flares after the first dose, as seroconversion has been documented and adequate AIBD control may be achieved with appropriate treatment adjustment (28). Observational studies including patients with immune-mediated inflammatory diseases demonstrated a similar adverse effect and safety profile as in healthy individuals (25). It is noteworthy that additional studies to evaluate COVID-19 outcomes in vaccinated AIBD patients are necessary to better understand the safety of immunosuppressive and immunobiologic treatments after immunization.

From March 2020 on, management of AIBD during pandemic is evolving along with advances in vaccination and COVID-19 treatment, although an effective and specific antiviral therapy is still missing. As a reference center for AIBD patients, we are currently receiving patients with uncontrolled disease because of initial pandemic restrictions limiting access to health care facilities. Patients are encouraged to receive COVID-19 vaccination including the booster dose, and to maintain protective measures to prevent SARS-CoV-2 infection (social distancing and protective personal equipment). For severe AIBD cases, RTX treatment is scheduled at least 4 weeks after full COVID-19 vaccination. We are now considering postponing RTX infusions following the novel recommendation to perform a booster dose at least 4 weeks after full vaccination completion. After anti-CD20 therapy, B-cell recovery monitoring may help to determine the most appropriate timing to vaccine patients to maximized seroconversion. A recent study demonstrated that CD19+ recovery is a predictor of adequate immune response after vaccination (29). In accordance to Shakshouk et al. (30), we are performing SARS-CoV-2 PCR for screening before each infusion. Meanwhile, outpatient evaluations are scheduled in a way to minimize hospital visits while maintaining frequent monitoring to adjust corticosteroid and immunosuppressants dosage to the lowest possible.

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

This study was reviewed and approved by the Ethics Committee of our institution (Comissão de Ética para Análise de Projetos de Pesquisa - CAPPesq # 56796222.6.0000.0068). All patients or next of kin provided written informed consent to participate in this manuscript and for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

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

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