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REVIEW ARTICLE

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Pemphigus and COVID-19: Critical overview of management with a focus on treatment choice

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Abstract

COVID-19 is a serious multisystem disease caused by severe acute respiratory syndrome coronavirus 2. Due to the COVID-19 crisis, that still keeps its impacts worldwide, numerous scheduled medical activities have been postponed and this interruption has a potential to modify the management of many cutaneous conditions including pemphigus. This narrative review aims to discuss the management of pemphigus in the era of COVID-19, considering the necessity to balance suitable pemphigus treatment with minimal risk of COVID-19-related mortality and morbidity. The data on the effect of treatments used for pemphigus on COVID-19 are limited. However, the evidence to manage patients properly is evolving and our knowledge is updated. Current expert recommendations include that patients with pemphigus should be informed clearly to avoid mismanagement and they should be monitored regularly for symptoms of COVID-19. Patients with mild disease can be managed with topical or intralesional corticosteroids, dapsone, or doxycycline. Systemic corticosteroids should be tapered to the lowest effective dose during the pandemic. Prednis(ol)one ≤10 mg/d can be continued in patients with COVID-19 while prednis(ol)one >10 mg/d may be reduced considering the activity of the disease. Conventional immunosuppressive therapies should only be discontinued in confirmed cases of COVID-19. Postponing rituximab treatment should be considered on a case by case basis. Intravenous immunoglobulin is not likely to increase the risk of infection and may be considered a safe option in patients with COVID-19. Given the psychological burden brought by COVID 19, online or face-to-face psychological support programs should be considered.

KEYWORDS

COVID-19, IVIg, pandemic, pemphigus, rituximab, SARS-CoV-2

1 | INTRODUCTION

COVID-19 is a serious multisystem disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease has been declared a pandemic by the World Health Organization in 1 March 2020.[1] COVID-19 pandemic still keeps its impacts, worldwide. Advanced age, male sex, and certain comorbidities, including immunosuppressive conditions are considered COVID-19-related mortality risk factors.[2]

Pemphigus vulgaris is a potentially life-threatening autoimmune blistering cutaneous disorder affecting the mucocutaneous surfaces. It is caused by autoantibodies directed against desmoglein 1 and desmoglein 3 adhesion molecules of the epidermis and is associated with an increased risk of infection.[3,4] Multiple mechanisms including

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epithelial barrier disruption and treatment-caused immunosuppression have been accused of the increased risk of infection.[3]

Due to the COVID-19 crisis, numerous scheduled medical activities have been postponed. This interruption to the healthcare system can negatively modify the diagnosis and management of many cutaneous conditions.[5,6] Patients with pemphigus are susceptible to immunosuppression and circulatory failure and are more prone to infections than healthy people. Therefore, the protection and control measures for patients with pemphigus against the COVID-19 are of serious concern. To guarantee the safety and effectiveness of treatment during the pandemic, physicians should extend their communication with patients, carefully follow alterations in patients' conditions, and adapt the treatment approach, while protecting them against the COVID-19.[7]

Considering the necessity to balance suitable pemphigus treatment with a minimal risk of COVID-19-related mortality and morbidity, we aimed to review the management of pemphigus in the era of COVID-19 with a focus on treatment choices.

2 | METHODS

This narrative review includes searching PubMed, Google Scholar, and Web of Science databases using the keywords “pemphigus”, “autoimmune bullous disease”, “autoimmune blistering diseases”, “coronavirus”, “COVID 19”, and “SARS-Cov-2”. The search was supplemented by manual searching of reference lists of included articles. A total of 14 relevant articles was identified. The search was updated in July 2020. The guideline provided by the European Academy of Dermatology and Venereology Task Force Autoimmune Blistering Diseases has also been overviewed.

2.1 | Pemphigus diagnosis in the era of COVID-19 pandemic

Pemphigus may cause one of the largest health-related quality of life impairment among chronic cutaneous disorders. Mucocutaneous symptoms, daily treatment, and pain may lead to serious problems for patients in their everyday lives. It has been shown that pemphigus may lead to a substantial economic burden on the community, essentially driven by productivity loss and informal care.[8] On the other hand, pemphigus is a potentially life-threatening disease. Therefore, timely diagnosis and management are crucial to achieve a favorable prognosis in pemphigus. An obstacle in the diagnosis and treatment initiation can be related to increased rates of morbidity and mortality. Pandemic-related delays in pemphigus diagnosis and management may also have serious consequences on the economic burden of the disease. In this context, we recommend that in cases where pemphigus is suspected, required diagnostic procedures including biopsy, immunofluorescence, and serological studies should be carried out without delay by taking appropriate measures.

2.2 | The impact of COVID-19 infection itself on the course of pemphigus

It has not yet been reported that patients with an autoimmune bullous disorder have a greater risk to be infected with SARS-CoV-2, compared with healthy individuals. However, this seems possible because of the immunosuppressive background of the autoimmune disorder itself.[9] There are a limited number of studies investigating the course of pemphigus in patients infected with SARS-CoV-2. In an Italy-based study including 31 patients with pemphigus, 7 patients (1 male, 6 female; mean age: 68.3 ± 9.7) experienced COVID-19 suspected symptoms.[10] Five patients had comorbidities including hypertension (n = 1), neurologic/psychiatric diseases (n = 2), dyslipidemia (n = 1), and neoplasia (n = 1). Four patients (57.1%) were on systemic corticosteroid treatment with a mean dosage of 5.9 ± 6.2 mg/day while one patient received azathioprine. All patients were in remission. Four patients described contact with suspected (n = 3) or identified (n = 1) patients with COVID-19. Six (19.4%) patients experienced mild to moderate symptoms while one (3.2%) patient had “severe” symptoms that required hospitalization. This patient was a 69-years-old with a previous history of breast cancer and completely recovered. For all patients taking systemic corticosteroid treatment, the current dosage was not deemed immunosuppressive and no patient independently suspended their current treatments. Ongoing corticosteroid or immunosuppressive treatment has only been discontinued for the hospitalized patient.[10] In an Iran-based study, a total of 45 patients with pemphigus who underwent rituximab therapy between 2014 and 2020 were included. [11] The authors identified 5 cases (4 female, 1 male; mean age of 41.8 ± 9.6 years) of COVID-19 diagnosed based on a computerized tomography scan. None of them has taken rituximab within a year from the pandemic. Among these 5 patients, 4 cases had COVID-19-related symptoms. Only one female patient, who was diagnosed incidentally, was asymptomatic. None of the patients required hospitalization. None of the patients had a productive cough, rhinorrhea, and sore throat. All of the patients were managed with hydroxychloroquine 200 mg daily for 2 weeks. The mean duration of the symptoms was 10 ± 4 days. None of these cases experienced a recurrence of lesions or cutaneous manifestations of COVID-19. All patients were on prednisolone treatment with a dosage of 5 to 10 mg/day. Two patients had additionally received methylprednisolone pulse therapy and azathioprine.[11] In another Italy-based study including nine patients with pemphigus, only one patient was reported to be tested positive for SARS-CoV-2.[12] The patient was a 65-year old female with pemphigus for more than 3 years and on mycophenolate mofetil for 38 months. The patient presented with severe nausea, fever, anorexia, asthenia, and the next day she tested positive for SARS-CoV-2. She discontinued treatment after 2 days following COVID-19 diagnosis. She progressively improved and was totally free of symptoms 12 days after the diagnosis. The patient did not show pemphigus recurrence but described only some tongue discomfort. She never experienced cough, shortness of breath, anosmia, or other symptoms of the infection. The authors stated that they planned to test the patient 2 weeks after the end of symptoms to

repeat a swab and restart the immunosuppressive treatment.[12,13] In another study conducted in Italy, the authors interviewed 83 patients (30 males, 53 females; average age 58.6 years) with the autoimmune bullous diseases.[14] Of these patients under immunosuppressive treatment, 18 reported having had infection-related symptoms in the last month. Only one of these patients tested for SARS-CoV-2, and had resulted positive. He was a 53-year-old, on azathioprine 100 mg/day and prednisone 4 mg/day. Since then, he has suspended both immunosuppressive treatments. The author recommended the patient to restart the treatment as soon as clinical healing is totally achieved, confirmed by a negative swab result. The authors did not provide further information about the course of the infection and the treatment given for this patient. The clinical condition of the other 17 patients was, such as, to not need additional diagnostic procedures to identify SARS-CoV-2.[14]

Pemphigus is not a common disease and it is hard to accumulate large cohorts to validate the abovementioned observations. This would need more time, which is hardly compatible with the urgency associated with the COVID-19 crisis. Hence, it is very important that the centers involved in the management of pemphigus share their experiences.

2.3 | The utility of teledermatology for patients with pemphigus in the era of COVID-19

In the era of COVID-19 pandemic, accurate evaluation of the clinical condition of patients with pemphigus poses significant challenges. Many centers suspended the on-site registration and physicians should consider the utility online platform for a preliminary evaluation. Chen et al monitored 38 AIBD patients by telemedicine during the COVID-19 pandemic and found that the majority of them had two main issues: discontinuation of treatment and anxiety. Of the 38 patients, 17 patients stopped their treatment and 21 patients admitted that they were worried about COVID-19 infection. Therefore, providing medication guidance and psychological support for patients with pemphigus is of utmost importance. The author recommended daily monitoring of vital signs, blood sugar, and blood pressure, looking for side effects, complete room disinfection regularly, and keeping a social distance. It is obvious that telemedicine does not resolve all obstacles, particularly for severe cases. For patients with pemphigus, the online platforms can be flexibly utilized to guide about whether and how they should come to the hospital. In the case of the expanded lesional area, complications, such as, infection and electrolyte disturbance, insufficiency of ongoing treatment, obvious side effects of the drug, and fever or secondary infection, a detailed assessment in the clinical setting is required.[7] The use of teledermatology during the COVID-19 crisis has raised concerns about the ethical and legal implications of this care system. The protection of patient data must be guaranteed and it should be noted that mobile platforms used for teledermatology, such as, WhatsApp, Telegram, and Viber are not exempt from the relevant ethical and legal regulations and principles.[15]

2.4 | Treatment considerations for pemphigus in the era of COVID 19

Patients with pemphigus on immunosuppressive treatments usually tend to develop different types of infections including viral infections, and infectious agents may trigger and worsen the disease. Pemphigus is associated with increased risk of mortality due to pneumonia but there is currently limited information specifically concerning the impact of SARS-CoV-2 on the course of pemphigus. Hence, a careful assessment should be carried out in order to balance suitable pemphigus treatment with a minimal potential risk of COVID-19-related mortality and morbidity.

2.5 | Systemic corticosteroids

Systemic corticosteroids are usually the mainstay therapy in pemphigus. Although corticosteroids have led to significant improvement in the course of the pemphigus, treatment complications including the risk of infections, are still of considerable concern. This concern has become more pronounced in the era of COVID-19 pandemic. Given the anti-inflammatory effect of systemic corticosteroids, these agents attracted the attention of physicians due to the presence of lung inflammation triggered by host immune responses in SARS-CoV-2 infections.[16-18] It has been recently shown that the cytokine storm in patients with SARS-CoV-2 infection involves the excessive production of proinflammatory cytokines that causes increased vascular permeability. Despite the concerns that corticosteroids may disturb viral clearance, the low dose systemic corticosteroids appear to have a role in the treatment of severe COVID-19 infections.[16] In their expert recommendations for the management of autoimmune bullous diseases during the COVID-19 pandemic, Kasperkiewicz et al. suggested that immunomodulatory therapies including systemic corticosteroids should be maintained when required as unjustified withdrawal can cause disease exacerbation associated with high morbidity and mortality. They also suggested that topical corticosteroids and prednis(ol)one ≤10 mg/d can be continued in patients infected with SARS-CoV-2 while prednis(ol)one >10 mg/d may be reduced considering the activity/severity of the disease, co-morbidities, age, and severity of COVID-19 in collaboration between the dermatologist and physician in charge of COVID-19. They emphasized that withdrawal or significant dose reduction of systemic corticosteroids should be avoided, especially in patients with severe forms of autoimmune bullous disorders.[19]

The guideline provided by the European Academy of Dermatology and Venereology Task Force Autoimmune Blistering Diseases recommended not to stop or reduce ongoing treatment unless there is a particular reason. The guideline suggested to discuss reducing the dose of systemic corticosteroids for COVID-19 positive patients.[9] Shakshouk et al. also recommended that systemic corticosteroids should be tapered to the lowest effective dose during the pandemic.[3]

2.6 | Immunosupressive treatments

Azathioprine or mycophenolate mofetil are usually considered first-line immunosuppressive agents for the treatment of pemphigus. These drugs are mainly used for their corticosteroid-sparing effect. Currently, there are limited data regarding the use of these drugs during the COVID-19 pandemic. Kasperkiewicz et al. suggested that immunosuppressive therapies including azathioprine, mycophenolate mofetil/sodium, cyclophosphamide, methotrexate, and cyclosporine should be maintained for patients without SARS-CoV-2 infection during the pandemic while they recommended that these agents may be stopped for the patients with COVID-19 related symptoms.[19] Shakshouk et al. recommended that these drugs only be discontinued in confirmed cases of COVID-19.[3] According to the guideline provided by the European Academy of Dermatology and Venereology Task Force Autoimmune Blistering Diseases, it may be advisable to temporarily stop these immunosuppressants during COVID-19 symptoms.[9]

2.7 | Rituximab

Rituximab is a monoclonal anti-CD20 antibody that leads to the reduction of CD20-expressing B cells. Early treatment of pemphigus with rituximab is associated with higher remission rates and quick tapering of systemic corticosteroids compared with traditional immunosuppressive treatments. Therefore, it can be used as first-line therapy in pemphigus. Rituximab has been associated with severe infections, including Pneumocystis jiroveci pneumonia and tuberculosis and the reactivation of hepatitis B virus. Prolonged B-cell depletion, B-cell-T-cell crosstalk, and neutropenia are considered the possible mechanisms of increased risk of infection. The risk of infectious complications may also be associated with personal patient characteristics.[20] Since long-lived SARS-CoV-2-specific plasma cells are presumed not to be present in most people, pemphigus patients treated with rituximab within the last 1 year may have a more serious SARS-CoV-2 infection compared with healthy individuals.[3] In a recent study including a total of 45 patients with pemphigus who underwent rituximab therapy, the authors identified five cases of COVID-19, without the need for hospitalization. However, none of them have taken rituximab within a year from the pandemic.[11] Shakshouk et al. suggested postponing rituximab treatment temporarily to delay peak patient immunosuppression during peak COVID-19 incidence to reduce the risk of adverse results while Kasperkiewicz et al. recommended that initiation of rituximab must be weighed against the risks of traditional immunomodulatory therapy.[3,19] International Pemphigus and Pemphigoid Foundation also suggested personalized discussion with the physician in charge to determine the risk of disease vs the risk of rituximab therapy.[21]

2.8 | IVIG

Intravenous immunoglobulin (IVIg) has anti-inflammatory/immunomodulatory properties and not considered to increase the risk for infections. It can decrease and eliminate autoantibodies, probably by restoring immune regulation. IVIg can provide prolonged remission lasting at least 2 years in patients with recalcitrant pemphigus. Considering its effectivity as an adjuvant treatment in both pemphigus and COVID-19, IVIg may be a useful option in pemphigus patients with COVID-19. However, there are no data on the use of IVIg in this setting. Hence, it should be weighed against possible adverse effects, such as, thromboembolic complications, particularly in severe cases.[3,18,19,22] Although evidence of plasmapheresis efficiency is mainly anecdotal in pemphigus and COVID-19, it could also be considered as another option.[19]

TABLE 1 Treatment considerations for patients with pemphigus in the setting of COVID-19

Treatment	The associated risk for infections	Recommendations
Topical and intralesional corticosteroids	Minimal to no risk for infections	Patients with mild disease can be safely managed with topical or intralesional corticosteroids.
Systemic corticosteroids	Increased risk for infections, particularly at a dose of more than 10 mg/day.	Prednis(ol)on<10 mg/day can be continued in patients infected with COVID-19 while prednis(ol)one>10 mg/d may be reduced considering individual patient characteristics.
Conventional immunosuppressant agents	Increased risk for infections	It may be advisable to temporarily stop conventional immunosuppressants during COVID-19 symptoms
Rituximab	Increased risk for infections	Postponing rituximab treatment temporarily should be considered on a case by cases basis.
IVIg	Usually not considered to increase the risk for infections	IVIg may be a useful option in pemphigus patients with COVID-19
Dapson, sulfapyridine nicotinamide, doxycycline, tetracycline	No increased risk for infections	Patients with mild disease can be managed with Dapson, sulfapyridine, nicotinamide, doxycycline, tetracycline

2.9 | Other treatments

Dapsone, nicotinamide, sulfapyridine, doxycycline, and tetracycline are unlikely to increase the risk of infection, thus may be preferred in the setting of the COVID-19 pandemic where appropriate.[9,19] Tocilizumab, an anti-interleukin 6 monoclonal antibody, has been suggested to treat the hyperinflammatory stage of COVID-19 and has been anecdotally reported to be beneficial in pemphigus.[3] Treatment considerations for patients with pemphigus in the setting of COVID-19 have been summarized in Table 1.

2.10 | Psychological support

Studies showed that pemphigus is associated with the high rates of psychiatric morbidity and impaired quality of life. Psychogenic factors can be considered an inducing factor for pemphigus onset, or a possible complication of the disease. The conventional treatments may also adversely affect the mental health in patients with pemphigus.[23,24] Considering the great psychological burden brought by COVID 19, online or face-to-face psychological support programs for patients with pemphigus should be evaluated and provided with necessary precautions.

3 | CONCLUSIONS

The data on the effect of treatments used for pemphigus on COVID-19 are limited. However, the evidence to manage patients properly is evolving and our knowledge is updated. It is essential that the patients and their caregivers should be informed clearly to avoid mismanagement and the patients should be monitored regularly for symptoms of COVID-19. Patients with mild disease can be managed with topical or intralesional corticosteroids, dapsone, and doxycycline. Systemic corticosteroids should be tapered to the lowest effective dose during the pandemic. Prednis(ol)one ≤10 mg/d can be continued in patients with COVID-19 while prednis(ol)one >10 mg/d may be reduced considering the activity of the disease. Conventional immunosuppressive therapies should only be discontinued in confirmed cases of COVID-19. Postponing rituximab treatment should be considered on a case by case basis. IVIG is not likely to increase the risk of infection and may be considered a safe option in patients with COVID-19.

CONFLICT OF INTEREST

The author declares no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Ömer Faruk Elmas, Abdullah Demirbaş, Ümit Türsen: Literature searching, designing and writing the manuscript.

Ömer Faruk Elmas, Abdullah Demirbaş, Mustafa Atasoy, Torello Lotti: Substantial contributions to conception and design, interpretation of data.

Ömer Faruk Elmas, Abdullah Demirbaş, Ümit Türsen, Torello Lotti: Editing, revising and final approval of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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