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Case Report
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Covid-19 In A Patient With Pemphigus: A Case Report

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ABSTRACT

Background: Pemphigus disease, especsially Pemphigus Vulgaris (PV), is an autoimmune disease resulting in blisters on the skin and mucosa due to autoantibodies attacking desmogleins (DSG) 1 and 3. Autoimmunity development in PV may be idiopathic or induced by neoplasms, drugs, infections, or inflammatory processes. Besides affecting the respiratory tract, COVID-19 may also affect other systems, such as the skin. The pathogenesis of autoimmune diseases and COVID-19 have similarities, which is an overreaction of the immune system. **Purpose:** To report a case about the association between PV autoimmune disease and COVID-19. **Case:** A 30-year-old woman presented with full-body pain and ulcers. Three days before the skin lesions, the patient complained of a mild cough, and the SARS-CoV-2 examination was positive. The patient was treated with systemic and topical corticosteroids along with broad-spectrum antivirals. The patient was discharged with an improved lesion condition and a negative SARS-CoV-2 PCR on day 5 of treatment. **Discussion:** Prolonged viral infection or viral infection itself, such as COVID-19 can cause immune system dysregulation leading to autoimmune skin lesions with different mechanisms. The use of corticosteroids or immunosuppressants in autoimmune diseases increases the risk of COVID-19 infection in a pandemic. **Conclusion:** In the COVID-19 pandemic, COVID-19 and autoimmune diseases such as pemphigus vulgaris are interrelated with the presence of immune dysregulation leading to skin lesions.

Keywords: Autoimmune, COVID-19, Pemphigus vulgaris

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BACKGROUND

Pemphigus disease is a life-threatening autoimmune blister disease, caused by autoantibodies targeting the desmosomes (DSG). Pemphigus vulgaris (PV) is one of the pemphigus diseases caused by autoantibodies targeting desmogleins 1 and 3, which serve as the adhesion layer of the skin epidermis.[1–4] Epidemiologically, PV typically occurs between 50 and 70 years of age and is more prevalent in men.[1] Autoimmune diseases are caused by various factors, including genetic and environmental (nutrition, drugs, viral infections, UV light, pesticide exposure), where viral infections are the most common factor.[1,4,5]

Coronavirus (COVID-19) is a new infection that has become a pandemic since March 11, 2020. This disease is caused by a novel strain of severe acute respiratory syndrome (SARS) coronavirus 2, known as SARS-CoV-2. The spread of COVID-19 was initiated by animal-to-human transmission and followed by human-to-human transmission with symptoms of fever, cough, weakness, headache, hemoptysis, diarrhea, shortness of breath, and lymphopenia.[6] Besides affecting the respiratory tract, COVID-19 can also manifest as a systemic disease affecting multiple organs such as the skin, kidneys, cardiovascular system, gastrointestinal tract, nervous system, and hematological system.[5,7,8] The pathogenesis of the COVID-19 cytokine storm is suspected to be one of the causes of autoimmune diseases.[7]

Without treatment, PV carries a high mortality and morbidity rate due to the failure of the skin barrier, which causes fluid loss and electrolyte disturbances and increases mortality.[2] The main therapy for PV is systemic steroids and immunosuppressants, but reducing the dose of immunosuppressants due to the risk of infection has

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made COVID-19 an exacerbating or precipitating factor of PV.[2,3,9] This study discusses the possible relationship between COVID-19 and Pemphigus Vulgaris.

CASE

A 30-year-old female labor worker recently returned to Indonesia. The patient complained of pain and ulcers all over her body for 2 weeks before entering the hospital. In the beginning, there were ulcers all over the body that broke out like burn wounds. The patient also complained of itching on the left cheek, which radiated to the right arm, chest, back, both limbs and then to the whole body. Three days before skin lesions appeared, the patient complained of a mild cough, and a SARS-CoV-2 PCR examination was performed with a positive result. The patient had already been vaccinated, but only for the first dose of the Sinovac vaccine.

There is no history of comorbid diseases, skin diseases, or allergies. There was no consumption of drugs or herbs in the last 2 months before the lesions appeared. Three days after the lesions appeared, the patient was given medication, but the patient did not know the medicine. Physical examination of vital signs was within normal limits; from cutaneous examination, generally, there were erythematous bullae with mostly erosion, discrete-confluent, and lenticular placard-size crust. Laboratory examination revealed an increase in CRP (5.40 nn < 1.00); other laboratory examinations were within normal limits. The results of histopathological examination taken from a lesion on the back reveal that the epidermis layer shows the basket-weave stratum corneum. A suprabasal cleft image showing acantholytic keratinocytes. It is also seen that basal keratinocytes adhere to the basement membrane and lose cohesiveness with the surrounding keratinocytes, forming a tombstone appearance. In the dermis, there is a mild coating of perivascular inflammatory lymphocytes and eosinophils. Morphological features showing a suprabasal cleft containing acantholytic keratinocytes, a tombstone appearance, and a perivascular inflammatory lymphocyte and eosinophil splinter are consistent with pemphigus vulgaris

The patient was treated for 5 days with dexamethasone injection, diphenhydramine injection, antibiotic injection (levofloxacin), antiviral injection (remdesivir), topical therapy of NS compress, and ointment compounds (burnazine, mometasone, and gentamicin). The patient was discharged on day 6 of treatment with improvement in skin lesions and a negative SARS-CV-2 PCR.

Figure 1. A 30-year-old woman with full-body blisters (a-d).

DISCUSSION

Pemphigus refers to a group of autoimmune blistering diseases of the skin and mucous membranes that are characterized histologically by intraepidermal blisters due to acantholysis. One type of pemphigus, pemphigus vulgaris (PV), is an autoimmune disease whereby the autoantibodies attack either only DSG3 or both DSG1 and DSG3.[10] DSG3 is well-known as a key mediator associated with desmosome remodeling, epidermal proliferation and differentiation, cell migration, and apoptosis, signaling molecules that may affect skin tissue integrity. As a result, the separation of the epidermis and epithelial layers is accompanied by acantholysis (separation of keratinocytes from their respective layers).[12] Symptoms include blisters in the oral mucosa, pharynx, larynx, esophagus, urethra, glans penis, vulva, and perianal area.[1,4] PV can be pruritic or painful, the incidence of PV is 1.6 per 100,000 per year. The sex ratio is commonly found in men compared to women, with an average age of onset between 50 and 70 years.[13]

Coronavirus disease 2019 (COVID-19) is a multisystemic disease caused by SARS-CoV-2. SARS-CoV-2 has four structural proteins: envelope (E), membrane (M), nucleocapsid (N), and spike (S) proteins. The spike protein forms large protrusions from the virus surface, giving the appearance of a crown and, therefore, the name "coronavirus". The spike binds to human ACE2 (hACE2) in the cell membrane through the S1 subunit of the receptor-binding domain (RBD).[8]

Pemfigus vulgaris represents damage to epidermal keratinocytes, resulting in acantholysis due to the production of autoantibodies against desmoglein-1 and desmoglein-3. Autoimmunity development in PV is a complex process and may be idiopathic or induced by neoplasms, drugs, infections, or inflammatory processes.[8] In another study, the SARS-CoV/SARS-CoV-2 spike protein was observed in the basal keratinocytes, which suggests a possible pathological link between SARS-CoV-2 and the onset of PV. Interestingly, a recent study showed high expression levels of angiotensin-converting enzyme 2 (ACE2), a cellular receptor of COVID-19, on keratinocytes in human skin and indicated that keratinocytes are potential target cells for the viral infection when a patient has a COVID-19 infection.[16]

Prolonged viral infections or viral infections with multiple targets induce the immune response to attack optimally. However, in some individuals, such compensation leads to autoimmunity. Different mechanisms result in autoimmunities in, such as molecular mimicry, immune activation by exposure to self-antigens, and the subsequent expansion of autoreactive T cells by the epitope-spreading phenomenon in some cases.[8] However, hypersensitivity reactions due to COVID-19 have been reported, even though there is no clear mechanism. It is suspected that COVID-19 causes immune dysregulation, leading to hypersensitivity and skin lesions.[14] In another study, COVID-19 triggers immune reactions in which T cells are the main control center. Overproduction and release of chemokines and pro-inflammatory cytokines can cause severe organ damage, which also occurs in autoimmune diseases.[5,7] Since COVID-19 may impair immune tolerance and trigger immune responses, it is suspected that it can also cause autoimmune diseases.[7]

The main therapeutic strategies for PV include systemic corticosteroids and immunosuppressants (azathioprine, methotrexate, and cyclosporine).[1,4] Corticosteroids are tapered off if the patient has no blisters within 2 weeks and the healing rate is approximately 80%. The dose will be escalated if the lesions do not improve within 10-15 days. Relapse occurs in 50% of patients. PV patients with moderate symptoms can be treated non-aggressively with systemic corticosteroids, dapsone, and doxycycline.[3,5]

The administration of corticosteroids can reduce the mortality rate from 75% to 30%. However, 65% of patients experience severe side effects due to immunosuppressants.[1] This has become a concern during the COVID-19 pandemic as autoimmune patients have a high risk of infection, so it is necessary to monitor PV patients to prevent fatal outcomes.[3] Corticosteroid administration should be maintained as needed to prevent exacerbations and increased morbidity and mortality rates.[9]

The use of immunosuppressant agents such as azathioprine, mycophenolate mofetil, methotrexate, or cyclosporine should be maintained in PV patients without COVID-19, although some recommendations suggest discontinuing their use if there are symptoms of COVID-19. Rituximab is an anti-CD20 monoclonal antibody agent that reduces the expression of B cells. The use of rituximab can improve PV remission and accelerate corticosteroid dose reduction, but according to its mechanism of action, this agent can increase the risk of infection.[15]

Studies have shown that patients who were given rituximab for a period of 1 year experienced more severe COVID-19 compared to patients without rituximab. IVIG is an anti-inflammatory and immunomodulator that does not increase the risk of

infection.[11] IVIG reduces and eliminates autoantibodies, thus normalizing immune system regulation. Other therapeutic agents such as dapsone, nicotinamide, sulfapyridine, and doxycycline do not increase the risk of infection and, when necessary, can be used during the COVID-19 pandemic (Table 1). PV is also associated with high-stress factors. This can influence the onset and complications of PV; therefore, standard management of PV should also pay attention to mental health.

Patients suffering from autoimmune diseases, such as PV, are vulnerable to infections, including COVID-19. On the other hand, COVID-19 infection may also result in autoimmune diseases due to dysregulation and overproduction of the immune system. Therefore, corticosteroid administration in PV patients with COVID-19 is recommended for continuation to prevent recurrence and fatal outcomes.

Table 1. Therapeutic considerations for pemphigus vulgaris patients with COVID-19.[9]

Therapy	Infection Risk	Recommendation
Topical and intralesional corticosteroids	Minimum to no risk of infection	Patients with moderate symptoms can be given safely
Systemic corticosteroids	Increased risk of infection, especially with doses >10 mg/day	Prednisone <10 mg/day can be continued, while prednisone >10 mg/day can be reduced based on patient characteristics
Conventional immunosuppressing agents	Increases the risk of infection	It is recommended to discontinue the use of immunosuppressants in the presence of COVID-19 symptoms
Rituximab	Increases the risk of infection	Delaying rituximab administration in consideration of various studies
IVIG	No increased risk of infection	May become a treatment option for patients with PV and COVID-19
Dapsone, nicotinamide, sulfapyridine, doxycycline	No increased risk of infection	Can be given to patients with mild symptoms

IVIG: Intravenous immunoglobulin

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