Role of Desmoglein Autoantibody in the Diagnosis of Pemphigus Vulgaris: A Case Report

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ABSTRACT

Pemphigus vulgaris (PV) is a group of autoimmune diseases that cause abnormalities in the form of lesions or blisters on the skin and mucous membranes. It often presents diagnostic challenges due to its varied clinical manifestations. Accurate diagnosis and treatment are essential to reduce mortality in patients with PV. Traditional diagnostic methods, such as histopathology and direct immunofluorescence, may not always provide conclusive results, especially if the patient does not have an intact bulla. Our report emphasizes the role of desmoglein autoantibody testing using enzyme-linked immunosorbent assay to confirm the diagnosis, allowing for prompt and targeted therapeutic interventions.

Keywords: *Pemphigus vulgaris, autoantibody, desmoglein*

INTRODUCTION

Pemphigus is a group of autoimmune diseases that cause abnormalities in the form of lesions or blisters on the skin and mucous membranes.[1] The variants of pemphigus are pemphigus vulgaris (PV), pemphigus vegetans, pemphigus foliaceous, pemphigus erythematosus, paraneoplastic pemphigus, drug-related pemphigus, and immunoglobulin A pemphigus. PV is the most common type (80%) among all pemphigus cases, with an estimated prevalence rate ranging from 0.1 to 0.5 per 100,000 population. PV is believed to be a rare autoimmune disorder that targets desmosomes, protein complexes that maintain the integrity of skin cells, leading to the separation of skin cells.[1,2]

Patients with PV are at risk of serious infections combined with dehydration, which can easily occur if they have large open wound areas. Accurate diagnosis and treatment are essential to reduce mortality in patients with PV. The diagnosis of PV is based on clinical manifestations and confirmed using autoantibody testing or histopathology.[3] Histopathological examinations can sometimes be challenging as they must be performed on unruptured bullae and require precision in biopsy specimen collection. Therefore, autoantibody testing for desmoglein (DSG) is considered one of the effective

diagnostic approaches for PV.[3,4] This case report is expected to enhance the understanding of DSG autoantibody testing in cases of PV in Indonesia.

CASE ILLUSTRATION

A 33-year-old woman presented with the chief complaint of large, painful, water-filled skin blisters all over her body. She had been experiencing skin lesions for the past 5 months, starting with painful sores in the mouth cavity and progressively spreading throughout her body over the past 3 months. The patient often cut open the bulla lesions using scissors. She had previously spent 1.5 months in another hospital and received three doses of infliximab, but her condition did not improve. She had no family history of autoimmune diseases.

On physical examination, moderate pain was observed with a pain scale score of 6 and a slight increase in the heart rate of 110 beats/minute. The patient was obese with a body mass index of 44.1 kg/m^2. Head and neck examination revealed hyperpigmented macules and bullae on the face and oral ulcers on the tongue and oral cavity. Dermatological examination revealed multiple hyperpigmented macules with indistinct borders, wet with some erosion, lichenification, squama, and bullae (**Figure 1**).

Hematological examination revealed leukocytosis with neutrophilia and elevated erythrocyte sedimentation rate. Clinical chemistry examination showed a slight increase in the C-reactive protein level (5.8 mg/dL; normal: <5 mg/dL) and a decrease in the albumin level (2.76 mg/dL; normal, 3.4–5 mg/dL), while other parameters were within normal limits. Immunological testing indicated a decrease in vitamin D (21.37 ng/mL; normal, <30 ng/mL) and C3 levels (70.17 mg/dL; normal, 90–180 mg/dL) and an increase in C4 levels (40.13 mg/dL; normal, 9–36 mg/dL). Antibody (immunoglobulin G [IgG]) testing using the enzyme-linked immunosorbent assay for DSG-1 and -3 showed high levels (134 U/mL; normal, <14 U/mL and 132 U/mL; normal, <9 U/mL, respectively). Pretreatment screen for procalcitonin, interferon-releasing assay for tuberculosis, and anti-nuclear antibody test yielded normal results.

The treatment provided was methylprednisolone 500 mg IV drips from day 1 to 3, followed by rituximab on the fourth day and regularly repeated every month. The patient's condition improved, and she was discharged on the fifth day. The patient received oral therapy at home, including methylprednisolone, mycophenolic acid, and vitamin D. The patient consistently took the medication regularly. After 8 months, skin and oral mucosa lesion complaints were well-controlled.

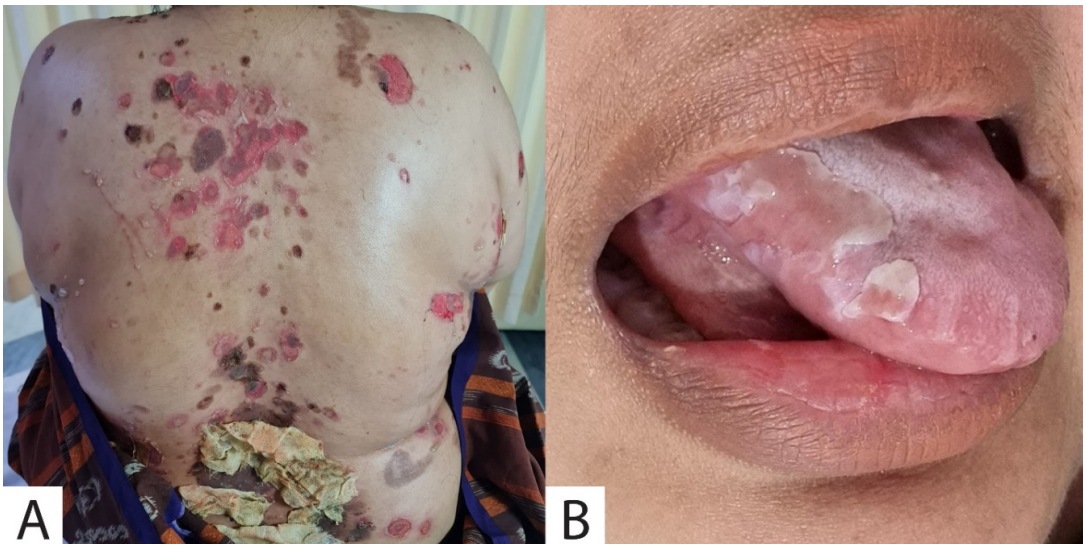

Figure 1. Clinical appearance before therapy. Hyperpigmented macules with indistinct borders, wet with some erosion, and burst bullae on the skin of the back (A). *Oral ulcer* on the tongue and mouth mucosa (mucocutaneous) (B).

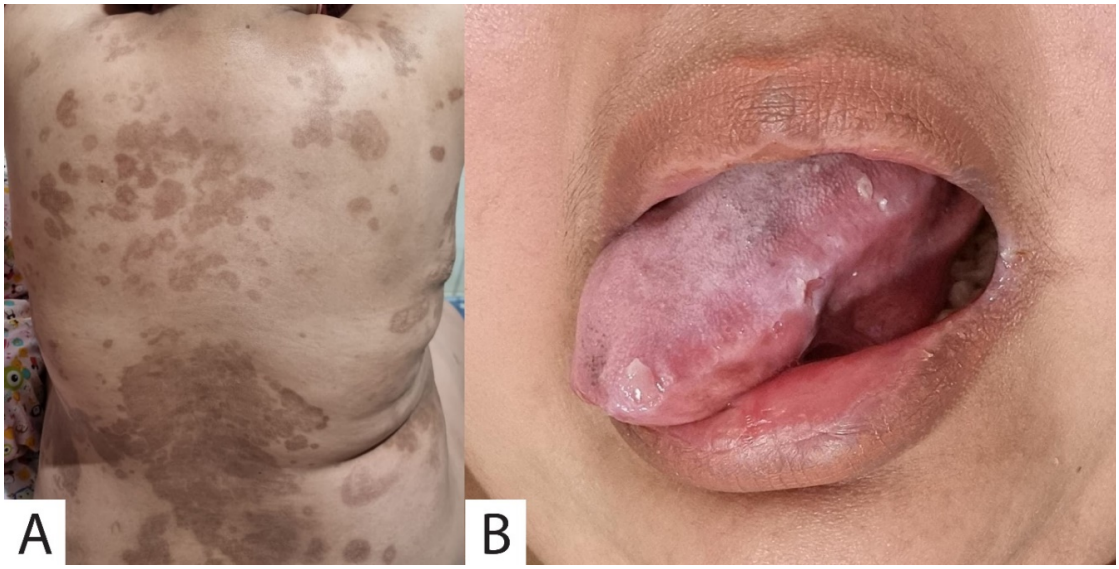

Figure 2. Clinical appearance 3 months after therapy. The hyperpigmented macules had dried up, and no active erosions or blisters were visible (A). The oral ulcer on the tongue and mucocutaneous areas had improved (B).

DISCUSSION

Pemphigus is a potentially dangerous mucosal and/or skin disorder characterized by thin-walled blisters that easily rupture and rapidly spread throughout the body, resulting in open skin erosions.[2] Specific IgG autoantibodies produced against extracellular membrane proteins of keratinocytes lead to acantholysis (loss of desmosome molecule adhesion between keratinocytes).[5] Skin lesions are preceded by oral mucosa abnormalities in 70%–90% of PV cases.[1,2] Clinical examination and the patient's history showed complaints of skin lesions in the form of blisters that become erosions when they rupture, starting from the oral mucosa and spreading throughout the body, consistent with the description of PV.[5]

Epidemiologically, PV often occurs in women aged 50–60 years, although some cases have been reported in younger women. Several human leukocyte antigen types have been identified as risk factors, but the correlation between them is still unclear. Some studies suggested that it can lead to structural changes in peptide binding, affecting antigen presentation and the secretion of inflammatory molecules by keratinocytes bound by autoantibodies. Others suggested that genetic factors alone are not sufficient to cause PV, and it needs environmental triggers such as certain drugs, such as penicillin, cephalosporin, captopril, and aspirin, and viral infections, such as herpes simplex infection, that can disrupt keratinocytes.[1,2,6]

Several methods can be used for diagnosing PV, including histopathology, direct immunofluorescence microscopy, and serological tests for the levels of autoantibodies. In direct immunofluorescence microscopy, biopsied specimens from patients with PV generally show deposits of IgG antibodies and complement C3.[3,7,8] This finding may explain the decrease in serum C3 levels, while C4 levels remain normal. The sensitivity and specificity of the autoantibody test range from 96% to 100%. These indicate that almost all patients have anti-DSG antibodies, which are not found in healthy individuals. Histopathological biopsies were not performed on this patient because most of the blisters had already been ruptured, and it is best to perform a biopsy when the bulla is intact and less than 24 hours old, preferably from the advancing edge of the lesion.[3]

DSG-1 and -3 are glycoprotein membrane components of the cadherin family, serving as "glue" in desmosomes.[9] Their expression differs between the oral mucosa and skin. DSG-1 is expressed in the epidermal layer of the skin (superficial layers), while DSG-3 is expressed

in the basal and parabasal layers. Oral mucosa has a different expression pattern, with both of them being expressed in the squamous layers, but DSG-1 levels are lower than those of DSG-3. The levels of DSG-1 and -3 autoantibodies also correlate with clinical presentation and examination results of patients with PV (**Figure 3**).[1,2] The levels of DSG-1 and -3 antibodies in this patient were extremely high (134 U/mL and 132 U/mL, respectively), which aligns with the clinical presentation of the patient's lesions, supporting a diagnosis of mucocutaneous PV. Antinuclear antibody testing was performed for this patient to detect the possibility of other autoimmune diseases, but the result was negative.

A patient's low vitamin D levels can be one of the factors in the pathophysiology of autoimmune diseases. Several studies have shown insufficient levels of serum 25(OH)D in patients with PV compared with those in healthy control individuals.[10] Moreover, low vitamin D levels were suggested to contribute to the development of PV.[11] Calcitriol can prevent the onset of autoimmune diseases by inhibiting Th1 cytokines (interleukin-2, tumor necrosis factor-α, and interferon-γ) while promoting the action of T helper 2 (Th2) cytokines (IL-4 and IL-10), inhibiting Th-17 activity, IL-17 production, and, most importantly, stimulating regulatory T cells (Tregs) to downregulate the immune response. Recent studies indicated that the control of DSG-3-reactive lymphocytes by Tregs can prevent the exacerbation of PV.[12,13]

PV therapy is considered successful if no new skin blisters are formed after 2 weeks of treatment, and previous skin lesions show signs of healing. The first-line therapy is corticosteroids because they have a rapid effect (short-term, high-dose methylprednisolone). Subsequent therapy involves steroid-sparing agents, which can include mycophenolate mofetil and/or azathioprine. Some studies have shown that mycophenolate mofetil has a faster and more long-lasting therapeutic response when combined with steroid therapy.[1,2,5] Some studies also reported using rituximab as a first-line therapy for patients with pemphigus, with 59%–100% of patients achieving complete

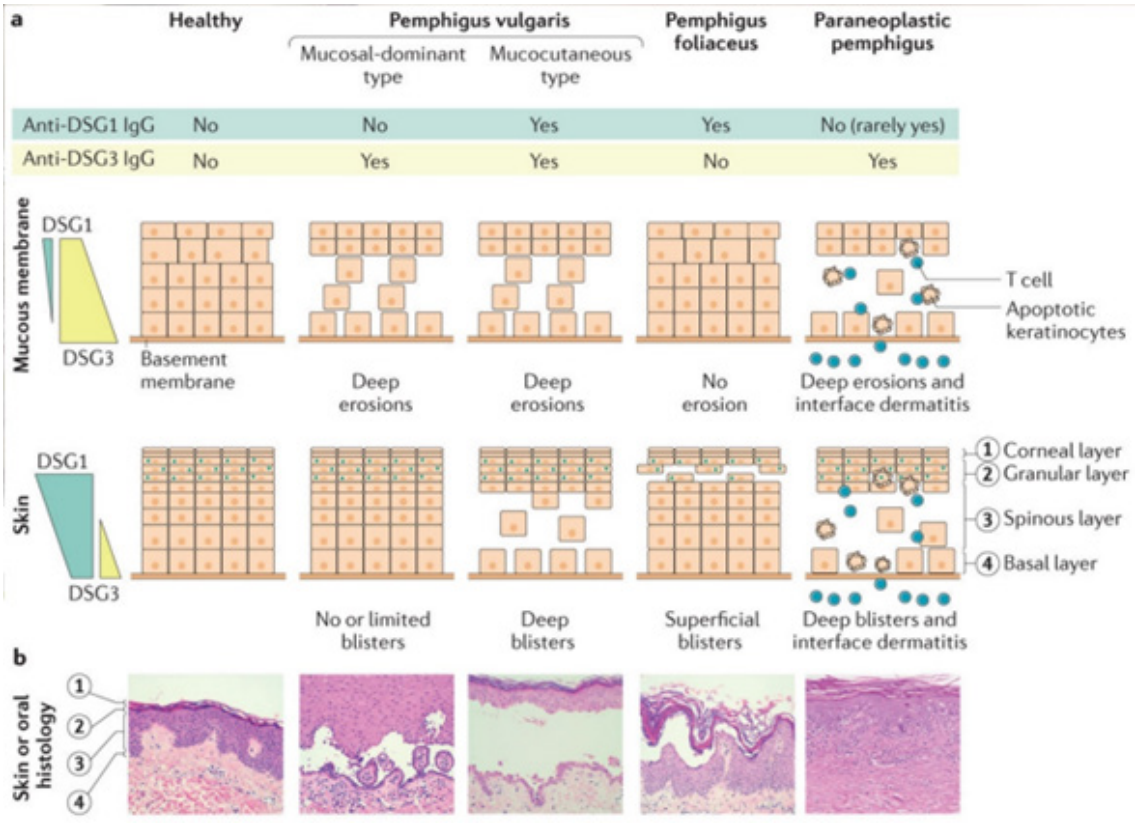

Figure 3. Pemphigus pathogenesis was related to the location of desmoglein 1 and 3 on the skin.[2]

remission after 15–19 months of therapy.[6,14,15] This finding aligns with the patient's history, who did not respond to infliximab therapy but showed a good response to the combination of pulse-dose methylprednisolone, mycophenolate mofetil, and rituximab. The skin lesions had improved since the fifth day of hospitalization, and no skin lesions were visible 2 months after therapy (**Figure 2**). A study performed in 2009 discussed the role of autoantibodies DSG-1 and -3 in evaluating the success of therapy and predicting the likelihood of relapse. The cutoffs of 20 U/mL and 130 U/mL for anti-DSG-1 and anti-DSG-3 antibodies, respectively, are considered to have good sensitivity and specificity in predicting relapse of the mucosa and skin.[16]

CONCLUSION

PV is an autoimmune disorder with a tendency to affect the oral mucosa and skin, which, if not diagnosed properly, may lead to incorrect therapy and death. Early diagnosis and therapy provide a good prognosis for the patient. Therefore, the levels of DSG-1 and -3 autoantibodies are expected to be widely used in diagnosis, evaluating treatment outcomes, and predicting the likelihood of relapse in Indonesian patients with PV to improve their quality of life.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest in this study.

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