A Successful Treatment of Pemphigus Foliaceus Patient with Systemic Corticosteroid

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Abstract: Pemphigus is a group of IgG-related autoimmune disease of skin and mucous membrane. It cause acantholysis with blisters and erosion as the clinical manifestation. There are three main groups of pemphigus, which is vulgaris, foliaceus, and paraneoplastic. Female 68 years old, came with chief complain of blisters that were spreading on her face, body, and both extremities since 1 year ago. From dermatological examination, we found multiple bullae and erosions sized lenticular to plaque with erythematous base and multiple hyperpigmented maculae with crusts on the face, body and both extremities. Biopsy was taken from newly formed vesicle and histopathological examination supported characteristics of pemphigus foliaceus. The patient was treated with NaCl 0,9% compress for 15 minutes every 4-6 hours, fusidic acid cream twice a day, 32 mg methylprednisolone every morning, and clarithromycin 500 mg once a day. After control, the patients showed improvement in her skin lesions.

1 INTRODUCTION

Pemphigus is a group of IgG-related autoimmune disease of skin and mucous membrane resulting acantholysis with clinical manifestation of blisters and erosion (Payne et al, 2012; Kasperkiewicz et al, 2017). Pemphigus can be classified into three main groups, such as vulgaris, foliaceus, and paraneoplastic (Kasperkiewicz et al, 2017). In pemphigus vulgaris (PV), the blisters can be found on the suprabasal layer, whereas in pemphigus foliaceus (PF) on granular layer (Payne et al, 2012; Kasperkiewicz et al, 2017). Patients with paraneoplastic pemphigus usually have neoplasm associated with lymphoid tissues and caused by combination of autoimmune humoral and cellular reaction (Kasperkiewicz et al, 2017). Both PV and PF have their variants. Variants of PV usually appear locally, such as pemphigus vegetans of Hallopeau and pemphigus vegetans of Neumann. While, PF that appear locally is pemphigus eritematosa (Payne et al, 2012).

Epidemiology of pemphigus varies throughout the world (Payne et al, 2012; Kasperkiewicz et al, 2017). The incidence is quite rare, which is 2-10 cases per one million population in some areas of the world and the prevalence is 0,1-0,7 per 100.000 population (Dimarco, 2016). Pemphigus vulgaris is a subtype that often found in Europe, United States and Japan, especially in women aged 50-60 years old. Pemphigus foliaceus is less common compare to PV and commonly found as endemic disease in South America and North Africa (Kasperkiewics et al, 2017; Pollmann et al, 2018). The age of onset of PF is 40 to 60 years old. However, the endemic form of PF can appear in second or third decades (James et al, 2011). Paraneoplastic pemphigus is less common that PV and PF, usually can be found in adult aged 45 to 70 years old (Kasperkiewicz et al, 2017). Pemphigus seldom found in children (Payne et al, 2012). The different onset of age is related to genetic, hormonal, and environmental factors (Kasperkiewicz et al, 2017).

In addition to anamnesis and physical examination, the diagnosis of pemphigus can be supported by histopathology and serology examination. Direct immunofluorescence examination can also be done to detect IgG antibody on the surface of keratinocytes. Also, measurement of IgG antibody titers to desmoglein can be done through enzyme-linked immunosorbant assay (ELISA) (Dimarco, 2016; Pollmann et al, 2018). Through this case report, we would like to present patient with pemphigus foliaceus.

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2 CASE

The patient, female 68 years old, came with chief complain of blisters that were spreading on her face, body, and both extremities since 1 year ago. At first, the blisters were only found on her left hand, then after a couple of months it started spreading to her legs and body. One month ago, the blisters are also appeared on her face. The blisters especially appear after being exposed to friction and scratch, easily ruptured, leaving painful erosion. There were no blisters on her mouth, eyes, or genital area. The patient denied any drug allergy and similar lesion in family. She also denied any other medical condition or consumes any medication.

Physical examination generally was within normal limits. From dermatological examination, we found multiple bullae and erosions sized lenticular to plaque with erythematous base and multiple hyperpigmented maculae with crusts on the face, body and both extremities. We then carried out punch biopsy on patient's bulla for histopathology examination. According to several examination that was done in the patients, we have differential diagnoses of pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid. The patient was treated with NaCl 0,9% compress for 15 minutes every 4-6 hours, fusidic acid cream twice a day, 32 mg methylprednisolone every morning, and clarithromycin 500 mg once a day.

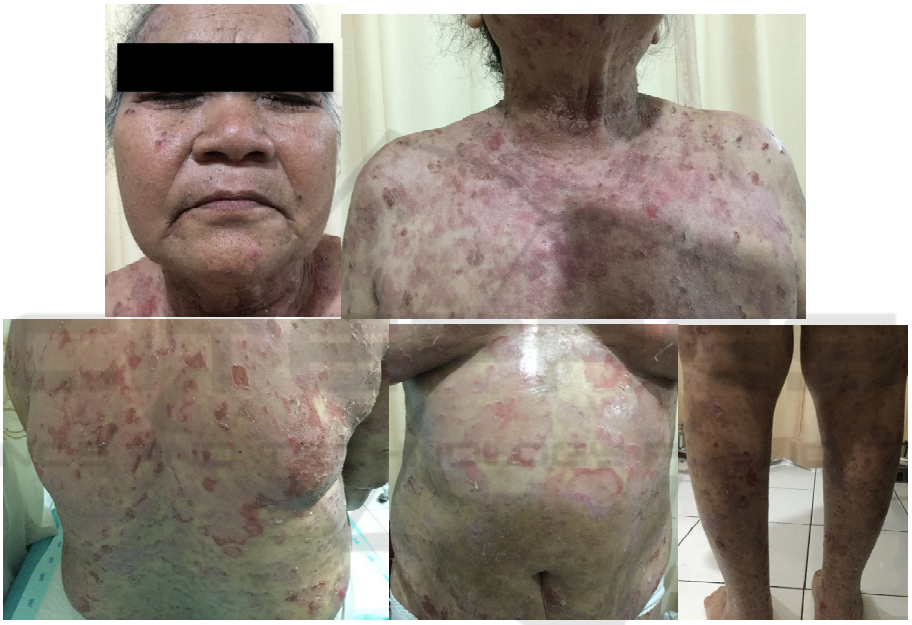

Figure 1. In generalized area, there were multiple bullae and erosions sized lenticular to plaque with erythematous base and hyperpigmented maculae with crust

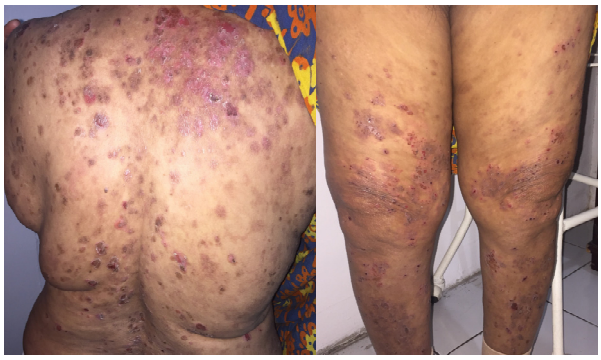

Figure 2. Multiple papule in lenticular to plaque sized with erosion, hyperpigmented maculae with crusts in her back, chest, and lower extremities

Histopathological examination showed stratified squamous epithelial cell with hyperkeratosis and thickening on stratum granulosum and acanthosis. There are subcorneal blister surrounded by lymphocyte infiltrate. It was concluded that the diagnosis was pemphigus foliaceus. After control, the patients showed improvement in her skin lesions.

3 DISCUSSION

Pemphigus is caused by autoantibody, especially IgG_4, against its antigen, which is desmoglein, a trans membrane glycoprotein of desmosome. Desmoglein is part of cell's adhesion molecule cadherin. (Payne et al, 2012; Pollmann et al, 2018). Pemphigus is mainly caused by antibodies to desmoglein 1 (Dsg1, 160-kDa) in PF, desmoglein 3 (Dsg3, 130-kDa) in PV that predominantly in mucosal membrane, or both in muco-cutaneous PV. (Payne et al, 2012;Dimarco, 20 et al,2016);Hammers et al, 2016) Dsg1 and 3 are found in varying amounts in the skin and mucous membrane. Dsg1 is found more in upper layer of epidermis, while Dsg3 is found in lower layer of epidermis. This causes different clinical manifestation in PV and PF. (Dimarco, 2016; Pollmann et al, 2018;Ruocco et al,2013). There are two main types of PF, which is idiopathic PF, that are found universally and appears sporadically, and fogo selvagem (FS) which is an endemic form of PF associated with several geographic areas.(James et al,2011)

IgG autoantibody of PV and PF bound NH_2 domain of Dsg ectodomain. This domain is the same area as the area that plays a role in desmoglein intercellular adhesion, which directly caused acantholysis. In addition, studies on keratinocytes show that loss of intercellular adhesion due to autoantibodies causes desmoglein internalization and degradation. (Payne et al, 2012; Pollmann et al, 2018). Pathogenic antibodies to desmoglein tend to bind to matured desmoglein on keratinocytes. (Pollmann et al, 2018). In PF, pathogenic IgG binds to Dsg1, causes phosphorylation of p-38 mitogen-activated protein kinase (MPAK) thus encouraging apoptosis in keratinocytes.(James et al,2011)

Clinical manifestation of PF and PV can resemble one another, which is superficial blisters that rupture easily causing erosions. (Pollmann et al, 2018;James et al,2011) Patients usually complain about pain and burning sensation on their skin lesions. (Payne et al, 2012;James et al,2011) It can be located on chest, face, scalp, upper back and traumatized area. (Pollmann et al, 2018) Skin lesions in PV can be found on the entire surface of the skin, but rarely on palms and feet. There are several clues that can help us distinguish PF from PV. Skin lesions of PF are initially found locally and spread on seborrheic location. This condition can expand to entire body and can be aggravated by ultraviolet light. (Payne et al, 2012) Bullae in PF is more prone to rupture than PV, therefore the clinical manifestation of PF usually are small erosions with crusts. (Hammers et al, 2016) Also, PF rarely involves the mucous membrane. (Dimarco, 2016) Both V and PF show a positive Nikolsky sign. (Hammers et al, 2016) Initially in our patient, skin lesions appeared on her left hand, which lasted for several weeks, then spreads slowly throughout her body. There are no similar lesions that were reported on mucous area, therefore we considered PF as one of differential diagnoses. However, given the similar clinical manifestation of PV and PF, we still could not eliminate PV as differential diagnosis.

Another differential diagnosis from this patient is bullous pemphigoid. It usually found in adult age more than 60 years old and caused by IgG autoantibody against antigen in dermo-epidermal junction causing subepidermal blister. Skin lesions that are usually found are tense skin blisters on normal or erythematous skin on flexors, lower thighs and abdomen. Sometimes, skin lesions can be found in the mucous membrane. Nikolsky sign is negative in patients with bullous pemphigoid. (Culton et al,2012) Our patient complained about easily rupture blisters with erosions that appeared after friction. Therefore, based on anamnesis and physical examination, we concluded that bullous pemphigoid could be excluded from differential diagnoses.

The diagnosis of pemphigus should be supported by histopathology and laboratory tests. Biopsy samples are usually taken from newly formed vesicle or edge of blister. Moreover, direct immunofluorescent should be carried out by taking biopsy at least 1 cm from blisters or inflamed skin. Enzyme-linked immunosorbent assay (ELISA) is also useful to measure IgG antibody titers against desmoglein in patient's serum. (Dimarco, 2016; Pollmann et al, 2018). In this patient, we taken biopsy sample from newly formed vesicle from her back.

Histopathologically, pemphigus shows loss of intraepidermic cell adhesion. (Pollmann et al, 2018). While in PV, histopathological examination shows suprabasal blister with acantholysis with "row of tombstones" that sign of bad prognosis. In PF, acantholysis can be found right under stratum corneum and in stratum granulosum. Other finding

include subcorneal pustules contains neutrophil. (Payne et al, 2012; Hammers et al, 2016) Old PF lesion usually shows papillomatosis, acanthosis, hyperkeratosis, parakeratosis and follicular plug. Increase pigment formation can also be found in melanocytes of basal layer and there is capillary dilatation in papilla dermis. There are also infiltrates consist of neutrophils, eosinophils, and lymphocytes. (James et al,2011) Histopathological characteristics of PF is often difficult to differentiate with bullous impetigo or staphylococcal scalded skin syndrome. (Payne et al, 2012) According to this informations, we concluded that histopathological examination of this patient support diagnosis of pemphigus foliaceus. Differential diagnosis of bullous pemphigoid could be eliminated because usually the blisters are located in subepidermis with eosinophils, neutrophils and monosit infiltrate in superficial dermis.(Culton et al,2012)

Immunofluorescence examination of pemphigus showed IgG autoantibody on the surface of keratinocytes. In patients with PV and PF, direct and indirect immunofluorescence can give similar findings, which is IgG on epidermal cell surface with netlike intraepidermal staining pattern (Payne et al, 2012; Pollmann et al, 2018). Biopsy samples for direct immunofluorescence can be taken from perilesion area and stored on Michel's transport media before examination. While in indirect immunofluorescence, patient's serum was incubated with tissues obtained from esophagus of monkey, human skin, or bladder epithelium from mice or rabbit.(Pollmann et al, 2018). We could not perform this examination on this patient because it is not available in our healthcare facilities.

Serological examination such as ELISA can be used to identify and monitor IgG antibody serum level in pemphigus. According to the type of autoantigen, such as Dsg1 and Dsg3, we can identify different type of pemphigus in patients (Pollmann et al, 2018). Unfortunately, this modalities also not yet available and routinely tested at our healthcare facilities so that this examination is not carried out in this patient.

There has been no FDA-approved therapy for pemphigus. (Payne et al, 2012) General recommendation for treatment of pemphigus remain inconclusive because of various research designs and different outcomes from previous studies. (Pollmann et al, 2018;Singh et al,2011) Initial therapy for pemphigus is high dose of systemic corticosteroid equivalent 0,5-1,5 mg/kg/day of prednisone with adjuvant immunosuppressive medication. (Pollmann et al, 2018;Singh et al,2011;Hertl et al,2015) Patients that unresponsive to initial therapy or have contraindication for high dose of corticosteroid can be given second line therapy, which is intravenous immunoglobulin 2 g/kg/cycle. Monoclonal antibody of anti CD20 is also useful in patients with refractory pemphigus (Pollmann et al, 2018 (Pollmann et al, 2018;Singh et al,2011) Pemphigus foliaceus with local skin eruption can be treated with topical corticosteroid. However, if the disease is active and widespread, we can use similar therapy as pemphigus vulgaris(Payne et al, 2012) Our patient were given NaCl 0,9% compress for 15 minutes every 4-6 hours, fucidic acid cream twice a day, methylprednisolone 32 mg every morning, and clarithromycin 500 mg once a day. After control, there were improvements in patient complaints.

4 CONCLUSION

Pemphigus is group of autoimmune disease associated with IgG to desmosome of stratified squamous epithelial skin and mucous membrane, causing acantholysis with clinical manifestation of easily rupture blisters and erosions. We reported 68 years old female patient with blisters on her face, body and extremities since 1 year ago. Differential diagnosis includes pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid. Anamnesis, physical examination and histopathological examination are important for diagnosis and in this case, we concluded patients as pemphigus foliaceus. Immunofluorescence examination is also important for diagnosis but still unavailable in our health facility. Treatment with systemic corticosteroid provides benefits for clinical improvement of patients.

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