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Pemphigus Vulgaris Combination Adjuvant Therapy of Systemic Corticosteroid with Sparing Agent Sodium Mycophenolate

Nopriyati[1], Cayadi Sidarta Antonius[1]*, Susanti Budiamal[1], Inda Astri Aryani[1]

[1]Department of Dermatology and Venereology, Facultyof Medicine, Universitas Sriwijaya, Palembang, Indonesia

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Corresponding author:
Cayadi Sidarta Antonius

E-mail address: *:*
cayadi_a@yahoo.com

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ABSTRACT

Pemphigus Vulgaris (PV) is an autoimmune disease characterized by vesicles and bullae on the skin and mucosa resulting from an autoantibody reaction to desmosomal adhesion molecules desmoglein (Dsg) 1 and 3, which function as strong adhesions between keratinocytes. Pemphigus vulgaris is more common in the fifth and sixth decades of age. The lesions are fragile blisters on the mucosa and skin. Diagnosing PV requires anamnesis, physical examination, and investigations such as histopathologic examination and direct immunofluorescence. Therapy generally uses steroids. Adjuvant treatment is given to reduce the side effects of corticosteroids. We reported a male, 59 years old, was treated with blisters that break easily into blisters on the head, face, chest, back, groin and buttocks accompanied by burning and itching. In the scalp, facial, anterior et posterior trunk, inguinal, and gluteal regions, multiple erythematous macules were found with lenticular-plaque shape; it was partially confluent with thick brown crusts which were challenging to remove. The histopathologic examination found the presence of suprabasal bullae with lymphocyte inflammation cells. The patient was diagnosed with PV and treated with corticosteroids with the sparing agent mycophenolate sodium and showed clinical improvement. The first-line treatment for pemphigus vulgaris is systemic corticosteroids. Adjuvant sparing agent therapy is given to reduce the side effects of corticosteroids. Sodium mycophenolate sparing agent was selected because of its minimum side effects. In systemic management, the dose of corticosteroid and sparing agent mycophenolate sodium was gradually decreased. The patient experienced initial remission after treatment

1. Introduction

Pemphigus Vulgaris (PV) is an autoimmune disease characterized with vesicles and bullae on the skin and mucosa due to an autoantibody reaction to desmosomal adhesion molecules desmoglein (Dsg) 1 and 3, strong adhesion between keratinocyte.[1] On histopathological examination, intra-epidermal bullae due to acantholysis was found. There are four types of pemphigus, such as pemphigus Vulgaris, pemphigus foliaceous, paraneoplastic pemphigus, and immunoglobulin (Ig) A pemphigus.[2,3]

The most common variant of pemphigus is pemphigus vulgaris (PV). The incidence of PV between women and men is similar. Mostly occurs in the fifth and sixth decades, rarely in young ages.[4] In Asia and Southeast Asia, the prevalence rate in cannot be found. However, a study by Whardana et al.found that the ratio between men and women is 2:1.[4] Based on medical record data of outpatient and inpatient from Dermatology and Venereology Department in RSMH

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Palembang, there were 63 cases of PV in 2018-2019, 41 are male, the other is women

Four theories are explaining the pathogenesis of PV, such as desmoglein compensation theory, multiple hits hypothesis, apoptosis induced by antibodies and basal cell shrinkage hypothesis, and apoptosistheory.[5] Major clinical finding in PV are lesions on skin and mucosa. Oral lesion involvement was found in 50-70% cases. The other mucosa can be involved, such as the conjunctiva, nasopharynx, larynx, oesophagus, urethra, vulva, and cervix. The most lesion was found generally spread throughout the body but can also be localized. The predilection sites are the head, face, neck, upper chest, and back. The lesion is bullae or vesicles. Pain and erosion can be found due to rupture of bullae.[6]

The diagnosis of PV was made based in anamnesis, dermatologic examination, histopathology, and immunofluorescence examination. Histopathological examination shows the presence of suprabasal bullae and acantholysis. The most accurate assessment for PV is direct immunofluorescence to find the IgG and complement-3 on the keratinocytes surface.[2,6]

Current treatment of choice for PV is to suppress the autoimmunity, mostly with a systemic corticosteroid, prednisone <2 mg/kg/day for 2 to 3 weeks. The concern of long-term use of corticosteroid is due to the adverse effect. Based on that, the use of sparing agent as adjuvant therapy is employed. Some of the sparing agent used in PV are azathioprine, mycophenolate mofetil/mycophenolate sodium, cyclosporine, methotrexate, and rituximab.[7]

We reported a male, 59 years old with PV. The patient was treated with systemic corticosteroid and mycophenolate sodium as sparing agent adjuvant therapy. Mycophenolate sodium is still not widely used. We aimto report the effectiveness of the combination of systemic corticosteroid and mycophenolate sodium.

2. Case Presentation

Male, 59 years old, came with a main complain of a flaccid blister on the head, face, armpits, groin and buttocks with itching and pain for three weeks before admission.

About three weeks before admission patient found a flaccid bulla with redness and clear fluid as significant as an ear of corn to Rp 100 coins on the face, armpits, and buttocks. He also complained of itching. The patient was treated in Dermatology and Venereology RSMH with 19 mg methylprednisolone every 24 hours for two weeks. However, the patient did not revisit the hospital when the drugs were run out. The patient also consumes 10 mg amlodipine regularly.

About one week before admission, the patients found a flaccid bulla with redness and clear fluid as significant as corn to Rp 100 coins on the face, armpits and buttocks and start to spread to the back. The patient also complained of itching, pain, and tenderness. There were also mouth sores on the lips,but the patient did not seek treatment.

One day before admission, the lesions increased and began spread to the chest. Patients also complained of itching and burning sensation in the blister area. There was no dysfunction in daily activities. Later, the patient complained sorely about the lips. The patient went to RSMH Dermatology dan Venereology Clinic and was advised to be hospitalized.

There has been a history of similar complain five months before admission. The patient complained flaccid blister sized of corn to Rp 100 coins with itching sensation on the buttocks. The patient also complained about sorely in the mouth. The patient went to a private hospital and diagnosed with pemphigus Vulgaris and received 16 mg of methylprednisolone every 24 hours. The complaints were reduced with no new lesion. The blisters dry up, and the itching was reduced. There is no history of red patches with tension blisters on the face, back, chest, groin, and buttocks. There is no record of similar complaints in the family.

The patient is overweight (BMI: 29.15 kg/m^2). Abnormalities were not found in general physical examination. On dermatology examination, we found multiple erythematous, from macular to patch, lenticular to nummular; it was spread discretely and partially confluent. We also found multiple erosion and

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excoriation wound covered with a thick brown crust that was hard to remove on the face and scalp.

In dermatology examination, we found erythematous to hyperpigmented macules to patch, multiple, lenticular to plaque in size, discrete, partly confluent and covered with a thick brown crust that was hard to remove. We also found various lenticulars to nummular erosion-excoriation, discrete partially confluent, covered with thick brown hardly removed crust in the anterior et posterior trunk, inguinal and gluteal region. The Nikolsky's sign and Asboe-Hansen sign showed acantholysis.

Blood analysis showed hematocrit 33%, ESR 44 mm/hour; neutrophils 71, lymphocytes 18, albumin 3.1 g/dL, creatine 1.15 mg/dL, chloride 109 meq/L, and calcium 8 mg/dL. Radiological examination showed dilatation of aorta. Histopathology examination found clefting and blister formation in suprabasal due to acantholytic process. The vesiculobullous blister also contains perivascular lymphocytes infiltration.

Histopathologic examination of the epidermis shows cleftingand blister formation in suprabasal due to acantholytic process. The vesiculobullous blister also contains perivascular lymphocytes infiltration.

The patient was diagnosed with pemphigus vulgaris and hypertension. Patient was treated with normal saline compress with three layers gauze for 10 minutes and intrasite ® gel every 12 hours on the lesions. The patient also treated with cetirizine 10 mg per oral per 12 hours, candesartan 8 mg per oral per 24 hours, and amlodipine 10 mg per oral per 24 hours. On the 4th day, the patient was given ceftriaxone injection 1 gram per 12 hours, 64 mg methylprednisolone tablet in (32-32-0) dose as an additional treatment. On the 7thday after further treatment, the methylprednisolone was reduced to 48 mg per day in (32-16-0) dose. The patient also treated with 1440 mg Myfortic® (mycophenolate sodium) in (720-720-0) dose.

After being treated for 11 days, the patient was discharged. The treatment was being continued at home with some modification. The patient has treated with cefixime 100 mg per 12 hours as an antibiotic. The patient also was given methylprednisolone lowered into 40 mg (24-16-0) dose. The Myfortic ® was continued with 1440 mg. Later, the methylprednisolone was reduced become 32 mg (16-16-0), and Myfortic® reduced become 720 mg (360-360-0).

3. Discussion

Pemphigus Vulgaris(PV) is a chronic vesiculobullous autoimmune disease of the skin and mucosa due to antibody reaction to desmosomal adhesion molecule, desmoglein (Dsg) 1 and 1, which function for strong adhesion between keratinocytes.[1] one of the most common pemphigus is PV. The incidence of PV,as reported by Didona *et al.*, in 2019, is about 0.76 to 16.1 per million population. Jews have a higher incidence due to the presence of HLA-BRBI*04:02 antigen. In the United States, it was found that the incidence of PV is dominantly found in women with a ratio of 5:18, while in RSMH, we found that the balance between women and men is 1:2. Our data also found that the incidence of PV is mostly in the fourth decade, as also reported by Payne et al.in 2012 that the incidence of PV in Saudi Arabia and Turkey primarily found in the fourth decade.[2] We reported a case of PV found in men, 59 years old.

In normal condition, the skin is composed of 3 layers, the epidermis, dermis and subcutis. The connection between the epidermis and dermis is called basal membrane zone (BMZ), consist of cytoskeletons, called hemidesmosome and basal keratinocytes membrane, lamina Lucida, lamina densa and sublamina densa.[9]

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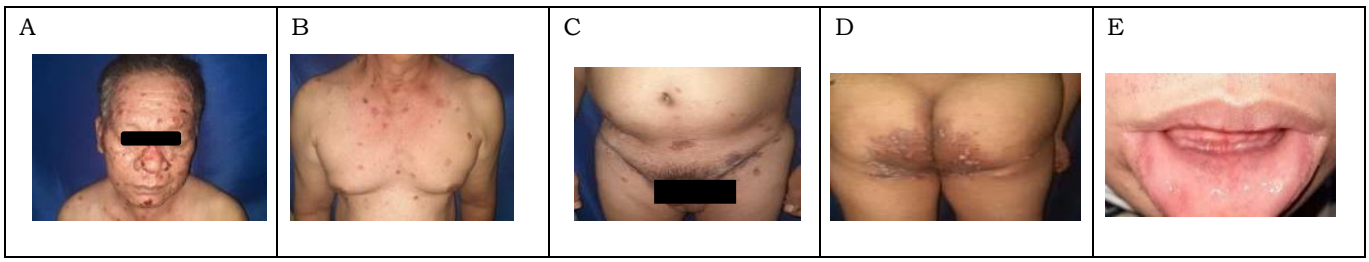

Figure 1. Clinical overview of the patient in the facial (A); anterior trunk (B); inguinal (C); gluteal (D) and lips (E). Macular to patch erythematous multiple, lenticular until nummular, discrete partially confluent; erosion to excoriation, multiple, lenticular to numeral, discrete partially confluent, covered with a thick brown crust, difficult to remove and erosive to excoriation, numerous, lenticular to nummular, partially confluent discrete, covered with a thick brown crust, difficult to remove.

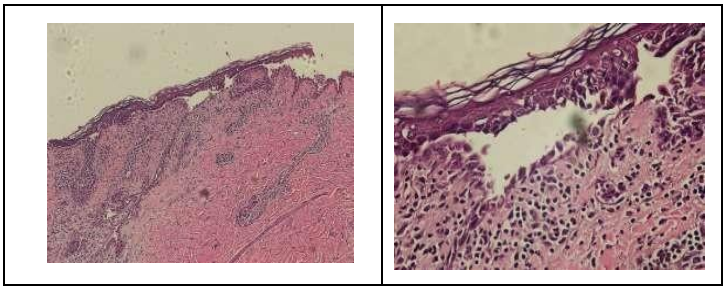

Figure 2. Histopathologic examination of the epidermis shows clefting and blister formation in suprabasal due to acantholytic process. The vesiculobullous blister also contains perivascular lymphocytes infiltration.

4. Discussion

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The blister occurred in PV is the result of autoantibody reactions against the surface molecules of keratinocytes, thus damaging the intracellular substances, resulting in the separation of keratinocytes from one another. The process is known as acantholysis. This process also resulted in the immune complex, consist of IgG, IgG, IgA and complement C3 that bound to desmosomal transmembrane proteins of keratinocytes, usually Dsg1 and Dsg3. These desmosome-forming proteins, Dsg1 and Dsg3, are involved in cell adhesion and cell shape. Both Dsg1 and Dsg3, 160 kDan and 130 kDa transmembrane glycoproteins, are engaged in PV.[9]

The acantholysis process in PV occurs just above the basal cell layer. The intraepithelial separation sometimes appears in the stratum spinosum. There are two types of acantholysis, namely primary and secondary. Primary acantholysis is the disintegration of desmosome resulting in separation or breakdown of keratinocytes due to direct disruption of the desmosome or hereditary defects in the development and formation process. Meanwhile, the secondary acantholysis is because of the changes or damage to keratinocytes structure due to various factor. Primary acantholysis is seen in multiple conditions such as pemphigus, Darier's disease, and Staphylococcus Scalded Skin Syndrome (SSSS). Secondary acantholysis is seen in diseases such as herpes simplex, herpes zoster, borderline-tuberculoid (BT) leprosy, bullous epidermolysis, basal cell carcinoma, keratoacanthoma, adenoid squamous cell carcinoma, and psoriasis. Some factor can trigger acantholysis such as autoimmunity, medication, infection, heat, burns, sweating, friction, trauma, contact dermatitis, and ultraviolet B (UVB).[10] In this case, report, we found primary acantholysis in by manual examination of Nikolsky's sign and Asboe-Hansen sign.

The typical clinical symptoms of PV are pruritus and pain due to erosions. The primary lesion of PV is flaccid blisters that can appear on all parts of the body, both skin and mucosa, except on the palms and soles. Blisters can appear over average or redness skin.[2] According to Yoshida et al.in 2005 in Japan, they found there are rare cases in PV can be found only on the skin lesions.[11] In this case, the lesions were found both on the mucosa and predominantly on the skin in the anterior and posterior of trunks, inguinal and gluteal.

The site selection for obtaining biopsy specimens is a necessary process. If the lesion is small, all blisters can be removed and collected as a specimen for histology examination. If the lesion is expansive, the selected lesions are new lesion and inflamed lesion. For direct immunofluorescence (DIF), the chosen site is perilesion skin. The typical histological examination of PV is the formation of intraepidermal blister due to the loss of adhesion of keratinocytes (acantholysis) without keratinocyte necrosis. The keratinocyte and epidermal cells also appeared in the blister cavity. The basal cell loses its desmosome interface and maintains its attachment to the basement membrane via the hemidesmosome, shown row of tombstones appearance. The blisters contain inflammatory cells, particularly eosinophils. It also shows that in the dermis, there is the infiltration of mononuclear cells and eosinophils perivascular.[12]

In the DIF examination on PV, IgG is found to bond to the surface of keratinocytes cell in peri lesion skin. In this case, the sample was taken from the lesion and the surrounding area. The result of DIF is that the sample does not contain IgG, IgA, IgM, C1q, and fibrinogen in the intracellular epidermis and basement membrane. Buch et al., in 2014 found that several errors can result in false-negative results of DIF examination, such as technical errors due to lack of epidermis in the biopsy, exposure to light, wrong place on skin biopsy and too long exposure to normal saline.[13]

The differential diagnosis of PV is pemphigus foliaceus (PF) and bullous pemphigoid (PB). In PF, the easily broken bullae are found on the skin, while the histopathology examination shows the gaps in the subcorneal. In PV, the bullae are found in skin and mucosa, and the histopathology examination offered the bullae is found in suprabasal due to acantholysis process. In the PB, there are tense bullae on the skin.[14]

The pathology specimen for this case was taken from the base of detached bullae on suprabasal due to acantholysis. We found many inflammatory cells,

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especially lymphocytes. The superficial examination also found perivascular infiltration by lymphocytes. This finding is consistent with pemphigus Vulgaris.

Primary goals of PV treatment are to repair the skin and to reduce the antibodies with the lowest dose of therapy, or even without treatment. The management of PV consists of 2 main phases, that is the induction of remission and maintaining the remission. The first process should be the primary concern of the doctor because of the high rate of relapse. The relapse rate reaches to 47% after the treatment was stopped. the first choice of treatment in moderate to severe cases is systemic corticosteroids with adjuvant immunosuppressants. Clinical response should be seen within a few days after the treatment, although the cessation of new bullae may take several weeks. Complete remission should be seen in 6-8weeks after the beginning of treatment.[15] In this case, the remission was marked by no new bullae forming and the repair of old lesions after the administration of systemic corticosteroids.

There are two primary modalities for PV treatment, namely systemic corticosteroids, and immunosuppression. European Academy Dermatology and Venereology and British Association of Dermatologists suggested azathioprine (AZA) and mycophenolate mofetil (MMF) as the first choice of 8adjuvant immunosuppressant.[8] The first choice of corticosteroid is prednisolone, combined with AZA and MMF. The recommended dose of prednisolone is 1-1,5mg/kg/day. A higher amount (more than 1,5 mg/kg/day) can be used if the lesions are uncontrollable in 3 weeks. After the disease is controlled, the dose is reduced by about 25% every week, but if there is a relapse, the dosage was doubled, two times the previous dose. If the patient needs more the 100 mg/day of prednisolone, they should be given in a pulse dose to reduce the side effects.

Corticosteroid induced some signal transductions pathways to produce anti-inflammatory, immunosuppressive, anti-proliferative and vasoconstriction effects. The side effects of long-term use of corticosteroids are higher risk of infection, adrenal insufficiency, osteoporosis, hyperglycemia, hypertension, and subcapsular cataract. Long-term of skin side effects are purpura, telangiectasis, skin atrophy, acne and rosacea and facial edema.[8] In this case, the patients was given 64 mg methylprednisolone per oral every day, for 3 days. Later, the dose was reduced to 48% in the fourth day. Then, the dose of MP was reduced to 40 mg, 32 mg, 28 mg and 24 mg. The patient was also given myfortic® as sparing agents and to control the hypertension in the patient.

The main purpose of early treatment is to control the diseases, as the healing of old lesions and there are no new lesions. After the disease is being controlled, the next step is to achieve complete remission. This phase is achieved if 80% of all lesions have been healed and no new lesion in 2 weeks. This phase relatively in short duration, but it can be longer due to wide ulceration. Oral ulcer takes longer to heal than skin ulcer and it can be the last lesion to be healed in PV. Thus, Oral ulcer becomes the sign for reducing the dose of corticosteroid.

The aim of maintenance phase to reduce the dose and to minimize the side effect. The main goal of the treatment is to maintain the remission with low dose prednisolone (10 mg or lower). Pemphigus vulgaris is a chronic disease and about 36% of patient was treated for 10 years.[16]

Mycophenolate sodium (MS) is converted from mycophenolic acid (MPA) after oral administration. Mycophenolic acid downgrade immune system by selective downgrade of inosine-5′-monophosphate dehydrogenase, that block purine synthesis in B cell and T cell. Lymphocyte is the main target of MPA because the lymphocyte is dependent to purine biosynthesis. Due to this functions MS is relatively safer than other immunosuppressant. The recommended dose is 2 g/day divided to 2 doses. The dose needed to be adjusted in patient with kidney failure. The initial dose of MS is 720 mg/day. Latest dose of 1440 mg/day MS is given after gastrointestinal tolerance is achieved. The side effect of MS is rarely reported. Some side effect reported is nausea, vomit, and diarrhea. Other side effect reported is opportunistic infection, hematology diseases, esophagitis, and gastritis. MS is not recommended in

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pregnancy and lactation due to high risk of miscarriage and congenital malformation.[8] MS is the commonly used as first line therapy of sparing agent to corticosteroids. The patient response to treatment in 8 weeks after MS administration.[16]

Topical treatment, such as wound care is given especially to wide and deep lesions. There are four aims in wound treatment(1) prevent infection; (2) to moist the environment; (3) to cover the wound and (4) to prevent wound scar. Small blisters should be left intact, to prevent secondary infection. However, large blisters need to be aspirated with a sterile needle, to keep the roof of the bullae intact for protection against injury. Saline and antiseptic can be used twice a day to clean the wound. For most wound, the dressing should be able to absorb the exudate. If the wound is dry, the dressing should be able to moist the base of wound.

Pemphigus is marked with superficial wound, the damage usually restricted to epidermis. There are some factors to be considered to choose the type of dressing, such as the characteristic of dressing, absorbing capacity, hydration quality, adhesive quality and comfort. Hydrocolloid and hydrogel can be applied for wound care. There are 2 types of hydrocolloids: hydrocolloid sheets and gels. Both are consisted of carboxymethyl cellulose, gelatin, and pectin. Hydrocolloid has absorbent and debridement quality without causing significant pain. However, the use of hydrocolloid can induce contact dermatitis. Hydrocolloid also resulted in "gel and odor", foul-smelling yellowish gel inside the dressing. In this case, topical therapy is used for wound care with 0,9% NaCl every 12 hour and hydrocolloid Intrasite®.15,17Intrasite® consists of 2,3% polymer carbomethylcellulose, 20% propylene glycol, and 77.7% water. Carbo methyl cellulose acts as an autolytic debridement and propylene glycol increases wound penetration.

5. Conclusion

We reported one case of pemphigus vulgaris in 59 years old male. The patient was treated with systemic corticosteroids with sparing agent mycophenolate sodium, along with cetirizine as symptomatic therapy. Saline and and Intrasite® was used to compress the lesion. After 12 weeks of observation we found that the lesion was improved so the dose of corticosteroid and sparing agent mycophenolate sodium was decreased gradually.

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