Management of a bullous pemphigoid hospitalized patient with an oral involvement (case report)

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Abstrak
Pemphigoid Bulosa (PB) adalah penyakit sub epiderma bulosa otoimun kronik dengan otoantibodi yang menyerang komponen zona membrana dasar kulit dan terkadang pada membrana mukosa mulut. Kortikosteroid, antibiotik dan agen supresi imun digunakan untuk terapi PB. Laporan kasus ini membahas penatalaksanaan oral pasien laki-laki usia 57 tahun yang didiagnosis PB dengan riwayat hipertensi dan stroke. Pasien menjalani rawat inap dibawah koordinasi bagian Kulit Kelamin RSCM. Pasien diterapi dengan metil prednisolon (MP) dengan penurunan dosis seiring perbaikan kondisi dan mycophenolate mofetil (MM) sebagai terapi adjuvan. Bagian Penyakit Mulut dilibatkan dalam penanganan pasien tersebut karena ditemukannya erosi di mukosa labial, bukal, palatum dan krusta pada bibir. Krim fluosinolon acetonid dan vaseline album diberikan untuk bula dan krusta bibir serta obat kumur povidone iodine 1% untuk lesi rongga mulut. Sebulan menjalani perawatan inap, tidak ada lesi baru, tetapi seminggu setelah rawat jalan, pasien alami eksaserbasi, ditemukan krusta bibir, deskuamasi gusi, pengelupasan mukosa, kandidiasis oral; pasien dirawat inap dan diterapi kembali dengan MP, MM dan obat lainnya serta diberikan obat kumur klorhexidin diglukonat 0,2% dan obat tetes Nystatin. Hasilnya adalah kondisi pasien membaik tanpa lepuhan baru.
Kata kunci: pemphigoid bulosa, metil prednisolon, mycophenolate mofetil

Abstract
Bullous pemphigoid (BP) is a chronic autoimmune subepidermal bullous disease with autoantibodies directed against component of the basement membrane zone of the skin and rarely on oral. Corticosteroid, antibiotic and other immunosupressive agents were used to treat BP. In this case report, we discuss a 57-year-old male patient with history of hypertension and stroke, was being hospitalized and diagnosed by dermatologist as BP with oral involvement. He was treated with methyl prednisolone (MP) and gradually tapered down corresponding to the improvement of patient's condition and mycophenolate mofetil (MM) as an adjuvant therapy. Departement of oral medicine was involved in the management of this patient because the presence of erosion on labial, bucal, palatum mucosa and crust on lips. Fluocinolone acetonide cream and vaseline album were given to treat the perioral lesions and 1% povidone iodine to treat oral erosion. There is no new lesion after one month of hospitalization, but one week after ambulatory treatment, he had an exacerbation with crust on lips, gingival desquamation, mucosal sloughing and oral candidiasis. He was hospitalized and treated again with MP, MM, other drugs, 0.2% chlorhexidine digluconate and nystatin drops. The result was the improvement of the patient's condition with no new blisters.
Key word: bullous pemphigoid, methyl prednisolone, mycophenolate mofetil

INTRODUCTION

Subepithelial vesicobullous disorders are consisted of mucous membrane pemphigoid, bullous pemphigoid, pemphigoid gestationis, anti- P 200, anti- P105, anti- P450 pemphigoid, dermatitis herpetiform, linear IgA disease, bullous systemic lupus erythematosus and paraneoplastic pemphigus as stated by Verdolini and Cerio. Pemphigoid is a group of dermatological diseases, characterized by fluid filled blisters which the autoantibody damage the hemidesmosome associated proteins and lead to subephitelial vesiculation resulting in the various clinical and histopathological subtypes of pemphigoid.[1]

Bullous pemphigoid (BP) is a chronic acquired autoimmune subepidermal bullous disease defined immunologically by the existence of autoantibodies directed against component of the basement membrane zone of the skin. Oral and ocular mucosa involvement rarely occurs in BP. BP is characterized by linear immune deposition of IgG and/or C3 at the basement membrane zone.[2] Involvement of mucous membrane lesions are rare, occur in about 10-30 percent of patients,[2,3] with mainly affecting the buccal mucosa in about 10-20% of the cases.[3]

The aim of the treatments is to suppress the inflammatory process and the production of the pathogenic antibodies, to eliminate pathogenic antibodies and inflammatory mediators by plasmapheresis and to modulate immune system by intravenous immunoglobulins. All of these drugs are corticosteroids,

antibiotics (e.g. tetracyclines, sulphones); azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil and cyclosporin.[4]

Mycophenolate mofetil is an immunosupressive agent in the prevention of graft rejection, treatment of psoriasis and now used by dermatologist as an adjunct to oral methyl prednisolone in treatment of BP.[5,6] In this report, a fifty seven year old male with BP and oral and ocular mucosa involvement treated by dermatologist with methyl prednisolone for 3 weeks and azathioprine for 3 days. Then the patient treated with methyl prednisolone and mycophenolate mofetil as an adjunct agent but BP was relapsed after 3 days later. Departement of oral medicine was also involved in the management of this patient because the presence of erosion on labial, bucal, palatum mucosa and crust on lips. Fluocinolone acetonide cream and vaseline album were given to treat the perioral lesions and 1% povidone iodine to treat oral erosion.

CASE

A 57-year-old male first presented with blisters and erosion on all over his body of 3 weeks duration. They were associated with itching. The blisters were noticed first on the left arm and spread to other parts of the body. The patient reported oral ulcers with pain and difficulty in swallowing. The patient had a stroke 2 years ago and uncontrolled hypertension. He used traditional medicine to treat his hypertension. He worked as a contractor.

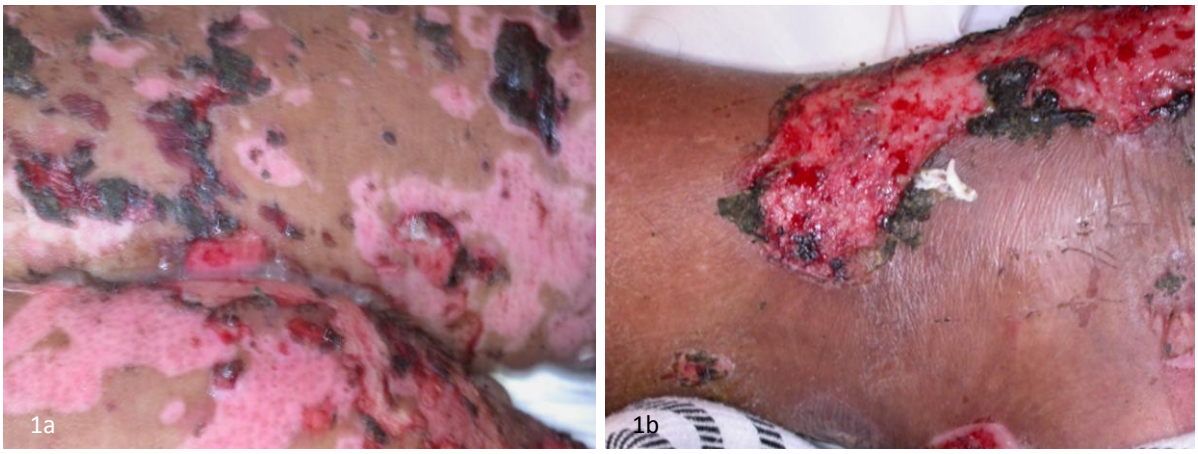

Figure 1 Multiple superficial ulcerations with purulence and crusting on trunk (a), lower limbs (b).

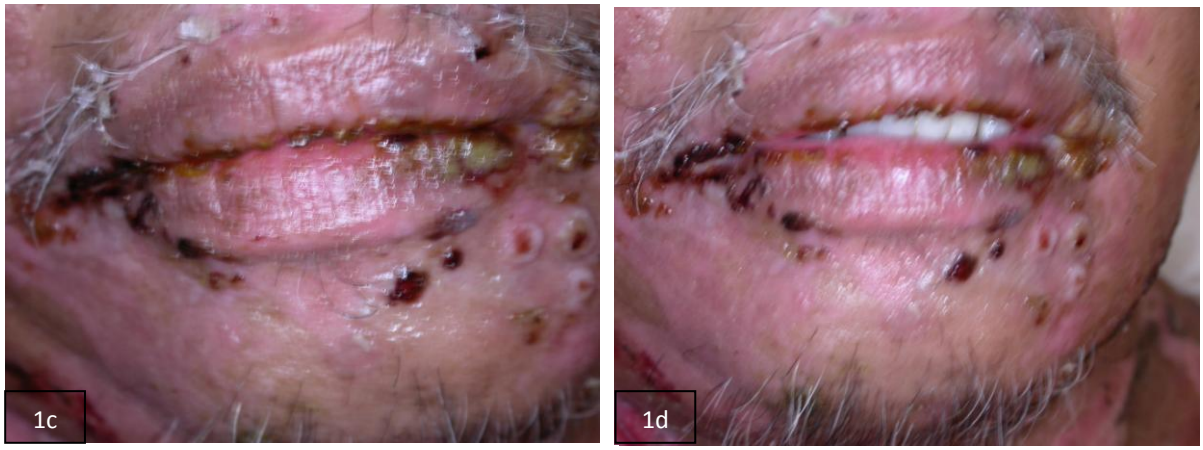

Figure 1c, 1d Erosion, bullae and crust on the lip

Cutaneous examination by dermatologist revealed multiple superficial ulcerations with purulence and crusting on the face, trunk, upper and lower limbs (fig 1a and 1b). Nikolsky's signs were negative. We examined his oral cavity and showed erosions on labial, buccal and palatal mucosa and bullae and crust on the lip (fig 1c and 1d). Dental examination showed radix on 18,17,16,15,22,25,38,37,36,48. Biopsy of a fresh blister shows a subepidermal cleft containing eosinophils, hyperkeratosis, mild acanthosis. Direct immunofluorescence showed a bullae with deposition of IgG low intensity at the intercelullar bridge (fig 2a and 2b)

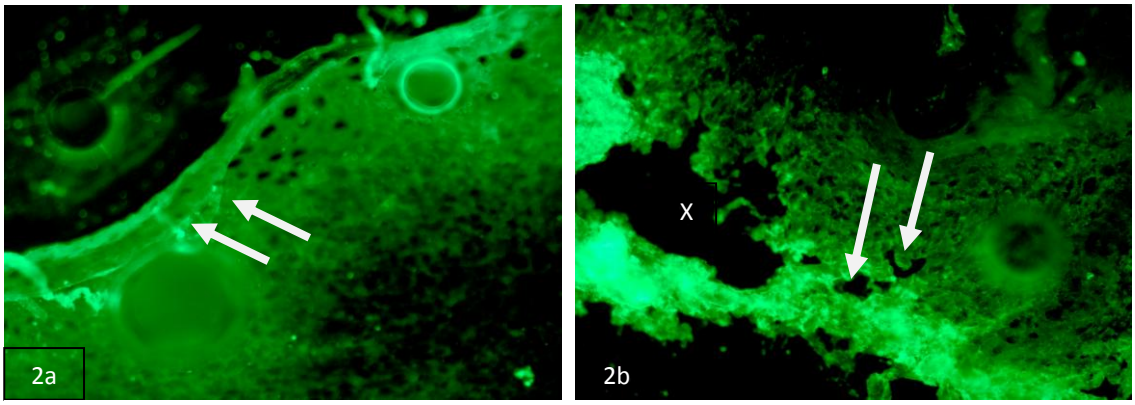

Figure 2a, 2b Direct immunofluorescence showed a bullae (X) with deposition of IgG low intensity at the intercelullar bridge.(arrows).

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Full blood counts result confirm anemia normocytic normochrom, neutrophilia, thrombocytosis, high titer of eosinophils. Diagnosis of bullous pemphigoid was made with other systemic conditions such as hyperuricaemia, hipoalbuminemia, leukocytosis, left hemipharesis, pterigium and catarac senillis.

MANAGEMENT

Patient was hospitalized and treated with methyl prednisolone, mycophenolate mofetil, antibiotic Ceftriaxone, Clindamycin, other medications such as Calcium supplement, ranitidine, antihistamine Cetirizine, antialergy and histamine hydroxyzine diHCl, pyridoxine, cyanocobalamine, folic acid, sinvastatin, nifedipine and valsartan. For cutaneous treatment, salicylic acid in fluocinolone acetonide was given by dermatologist to treat macula with minor eritema and fusidic acid twice daily for erosion. All these lesions was compressed with NaCl 0.9% 1 hour daily. Fluocinolone acetonide cream and vaseline album was first given to treat bullae and crust on the lips. Six days later, povidone iodine gargle was given. The patient's condition improved with no new blisters and mild itching, but the patient then developed acute kidney injury and steroid induced diabetes by an increased fasting blood sugar. After 29 days of hospital care, patient went home with medication and doses according the last day of his hospital treatment.

After a week of ambulatory treatment, the patient had an exacerbation of new blisters with itching on trunk, limbs, groin and abdomen. Oral examination showed desquamation of gingiva and lips with crust, oral candidiasis at dorsum of tongue and sloughing at ventral of tongue. Oral hygiene was impaired. He was hospitalized again for 9 days and treated with methyl prednisolone, mycophenolate mofetil, calcium supplement, ranitidine, cetirizine. and also clobetasole propionate cream, salicylic acid to treat cutaneous lesions. For oral lesions, we gave 0.2% chlorhexidine digluconate gargle and one hour later with nystatin drops 1 cc qid to eliminate the Candida sp.

He remained treated with methyl prednisolone with mycophenolate mofetil until the disease appeared to be under control. A month later, the patient's condition improving with no new blister, and methyl prednisolone was tapered and laboratory monitoring was performed during MM therapy to observe the adverse effect of MM and methyl prednisolone.

DISCUSSION

Bullous pemphigoid (BP) is a chronic autoimmune subepidermal bullous disease with autoantibodies directed against component of the basement membrane zone of the skin and rarely on oral causing large tense blisters with content. Lever found BP in 1953 and is the most common autoimmune blistering disease with an incidence more than 400 new cases in France and of six to seven cases per million population per year in France and Germany; forty three cases per million population per year in UK. It affects the elderly in the sixth to eighth decades of life with male predilection but no racial predilection is apparent and can also affect younger patients and children. Only 10-30% of patients have involvement of the mucous membranes, which is usually transient.[2,3] Yet, there is no definite epidemiology data in Indonesia about Bullous pemphigoid, but our patient has same representation of age, sex predilection with the data above.

Our patient consumed traditional medicine (he does not remember the name and perhaps contain certain drugs (spironolactone, bumetanide, fluoxetine, etc) to treat his hypertension and worked as

contractor with frequent UV exposure (especially UV-A irradiation) which in our suspicion can induce BP.[3] The underlying mechanisms involved in triggering the autoimmune response in BP are largely unknown.[7]

Autoreactive T cells play role in the pathogenesis of BP by recognizing BP antigen 2(BPAG2) and NC16A mostly with a T-helper (Th) 2, expressing CD4 memory T cell surface markers and increasing activity of Th1 and Th2 cytokines.[7,8] Anti-BMZ autoantibody (anti –mBP180 antibodies) trigger subepidermal blister formation and it is mediated by inflammatory cells (Eosinophils, mast cells, neutrophils). Degranulation of mast cells was found by Wintroub et al at the lesion recruited neutrophils to the target tissue and followed by complement activation. Eosinophils is important in the initiation and/or progression of BP. Infiltration of neutrophils influence the disease severity and are crucial in early stage of local tissue damage of the basement membrane.[7]

BP diagnosis is confirmed by clinical, histological, and immunofluorescence (direct and/or indirect IF) examinations.[2,3] Clinical examination on skin showed blister, multiple superficial ulcerations with purulence and crusting on the face, trunk, upper and lower limbs with negative point of Nikolsky's sign. The lesions ulcerate become pustular or rupture become crusted lesions.[2] All these clinical lesions of BP were presented in our patient. Oral lesions were involved and consist of erosions and located on the labial, buccal and palatal mucosa; bullae and crust on the lip.[3]

DIF is used to detect immunoglobulins and other components within biopsy specimens.[9] DIF of perilesional skin shows linear, wavy, tubular and granular deposits of Immunoglobulin G and /or C3 at the BMZ (with other type of immunoglobulin).[4] Dermatologist performed direct immunofluorescence after treatment had been started and showed a bullae with deposition of IgG in a low intensity at the intercelullar bridge (reduced number of positive IF). Deposition of IgG in a low intensity might be caused by overtime treatment[4] and partial or complete degradation of immune deposits in inflamed and blister skin.[9] The best location for biopsy specimens for BP is performed using perilesional skin. Biopsy of a fresh blister shows a subepidermal cleft containing eosinophils, hyperkeratosis, mild acanthosis.[4]

The circulating IgG autoantibodies in BP were against two major hemidesmosomal antigens of 230 kDa (BP230/BPAG1) and 180 kDa (BP180, BPAG2/type XVII collagen).[1,5] In DIF using salt split specimens, deposition in BP is within the outer site next to basal cell membrane (lamina lucida) related in location of the extracellular domain of BP180 antigen that was recognized by BP antibodies.[9]

The aim of the treatment is to control and suppress the clinical signs and the formation of new blister, urticarial lesions and pruritus including on the oral lesions.[4] Consideration of treatment is also needed although BP is self limiting and usually remits within 5 years because of multiple therapies, high risk of adverse drug reactions and side effects which can impair general health of the patient. Our patient is an elderly and represent generalized BP with oral involvement and other systemic diseases such as hypertension and history of stroke. Therefore topical and systemic corticosteroids (Prednisone is the most common glucocorticosteroid) along with other immunosuppresive medications are the main therapy for BP.[2,10] MM as immunosuppresive agent was used when dose of Prednisone was reduced/tapered for maintenance therapy and to reduce side effects of glucocorticosteroid.[2] Departement of oral medicine was involved in the management of this patient because of oral involvement.

The efficacy of systemic corticosteroid depends on severity of disease with doses between 40 and 80 mg daily, usually 60 mg daily. Systemic corticosteroid therapy seems the best established initial treatment for BP. The occasional urticated lesion or blister is acceptable, and indicates that the patient is not being over-treated.[4] Then corticosteroid dose is tapered by relatively large portions (10 mg) initially and smaller portions (2.5-5 mg) later.When the daily dose is 30-40 mg, as shift to every other day is attempted to decrease the potential for long term glucocorticosteroid side effects. This shift is usually accomplished with a decrease in the second day dose by 5-10 mg every 1-2 week. Once the second day dose is nil, the first dose may be tapered slowly. If a disease flare develops during the tapering phase, the dose may be increase by 10-20 mg for 2-3 weeks and then tapered more slowly.[10]

A very potent topical corticosteroid as 0,05% Clobetasol Propionate cream or 0.025–0.1% fluocinolone acetonide are also used as adjuvant to systemic treatment especially for the treatment of clinically severe diseases.[10] In this case, fluocinolone acetonide cream and vaseline album were given on first hospitalization to treat the crust and 1% povidone iodine as an antiseptic to overcome opportunistic infections especially on oral erosion. The patient at the second hospitalization was treated with 0.2% chlorhexidine digluconate and nystatin drops to overcome candidiasis as a result of side effects of corticosteroid and MM medications.

Chlorhexidine digluconate is effective against gram-positive organisms, gram-negative organisms, aerobes, facultative anaerobes, and yeast.[11]

Mycophenolate mofetil is the 2-morpholinoethyl mofetil ester of mycophenolic acid. MM is a prodrug that is rapidly hydrolyzed to the active drug mycophenolic acid (MPA), a selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), an important enzyme in the *de novo* pathway of guanine nucleotide synthesis. B and T lymphocytes are highly dependent on this pathway for cell proliferation, while other cell types can use salvage pathways; MPA therefore selectively inhibits lymphocyte proliferation and functions, including antibody formation, cellular adhesion, and migration. The effects of MPA on lymphocytes can be reversed by adding guanosine or deoxyguanosine to the cells.[13] It has been used successfully at doses of 0,5–1 g twice daily as an adjunct therapy to oral prednisolone and it was used at doses 720 mg daily.[4]

MM is generally a welll tolerated immunosuppressive agent with a preferred side effect profile compared to other immunosuppressives because MM has less nephrotoxic, hepatotoxic, and neurotoxic effects. The most common side effects are GI and are dose dependent,occuring up to 20% of patients at dose of 2 g daily.[12]

Patients mostly complain of diarrhea, nausea, vomiting, abdominal pain, anal tenderness, soft stools, frequent stools and constipation that are usually mild and rarely severe enough to result in discontinuation of therapy. Other side effects are hematologic, occuring in less than 5% of patients. The most common side effects include anemia, leucopenia and thrombocytopenia that are usually mild, dose related, and reversible with discontinuation of therapy or dose reduction. Leukopenia occurs in up to 34.5% of patients at dose of 3 g daily.[12]

Uncommon cutaneous side effects include generalized urticaria, dishyfrotic eczema, blistering hand dermatitis and onycholysis. MM also induced elevated hepatic transaminases and hyperbilirubinemia. Other uncommon side effects include reversible erythroid aplasia, lymphopenia, respiratory failure, pulmonary fibrosis, acute inflammatory syndrome and myalgia. Incidence of opportunistic infections has been reported in patients treated with MM, especially when exceeding doses of 2 g daily.**[12]**

After 3 weeks of hospitalization, this patient had steroid induced diabetes and in DM patients treated with MM, may develop complications included Mycobacterium xenopi abscess, bronchopulmonary legionella and pulmonary blastomycosis. Other fungal infections that have been associated with MMF include cryptococosis, candidiasis, mucormycosis, and pneumocystis jirovecci.[12]

The use of MM for various dermatologic diseases in off label with no published dosing recomendations. However, in review the published literature on the use MM for dermatologic disease, effective dermatologic doses are similar to those recomended in transplant patients. The starting dose typically depends on the disease being treated. Typical starting doses range from 1 to 2 g daily, usually in twice daily dosing. If there is no improvement after 1 month of therapy, doses are typically increased in 500 mg increment up to doses of 3 g per day. Dossage adjustment is recommended for patients with chronic renal insufficiency such that doses no higher than 1 g twice daily with a glomerular infiltration rate les than 25 ml/minute.[12]

Laboratory monitoring during MM therapy reflects the adverse effect and recommend a baseline complete blood cell count (CBC) with differential and platelet count, chemistry profile, liver function test with only CBC with differential continued weekly for the first month, bi weekly for the second and third month and then monthly through the first year of treatment. When patients experienced moderate to significant responses, satisfactory control of disease and minimal side effects or adverse effects.**[12]**

CONCLUSION

The result was the improvement of the patient's condition with no new blisters. Patient with BP usually has a favorable prognosis, with spontaneous resolution noted in a small percentage of patients within months to years of initial presentation and need to be followed until in complete remission and off all treatment. MM is an effective sparing agent with corticosteroid. This patient is prone to have pre-existing illnesses, therefore it is very important to appreciate the different types of steroid sparing agents available with toxic side effects that affect different organs with laboratory monitoring and other medication to reduce the side effects. This will allow for the most appropriate choice of adjuvant therapy in each patient.

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