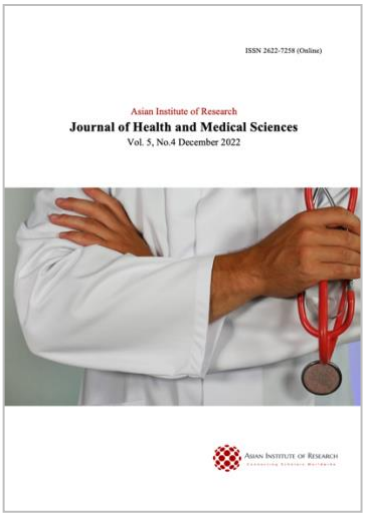

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Bullous Pemphigoid in a 37-Year Old Female: A Case Report and Literature Review

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Abstract
Bullous pemphigoid is a blistering disorder which mainly affects the geriatric population predominantly older than 70 years. It is caused by an autoimmune reaction to the hemidesmosomal proteins in basal keratinocytes, causing an inflammatory cascade and subsequent bullae formation. It is rarely encountered in infants, children, and middle-aged adults. Herein, a case of Bullous pemphigoid in a 37-year old female patient is reported. The patient presented with a three-month history of multiple serous fluid-filled tense blisters on the face, neck, trunk, flexor and extensor surfaces of the extremities up to the lower thigh, with areas of excoriation, peeling, erosion and crusting. No involvement of the mucous membranes noted. The lesions were associated with intense pruritus and pain upon rupture. Patient had no other subjective complaints and had an unremarkable past medical history. Patient was initially treated with antibiotics but noted no improvement in her condition. Histologic evaluation of the skin was done and revealed a subepidermal vesicular dermatitis with prominent neutrophilic infiltrates. No hyphae or spores were seen. With these findings, patient was admitted and treated with systemic steroids, antibiotics, and antipruritic medications. Direct Immunofluorescence was done and yielded findings consistent with the diagnosis of Bullous Pemphigoid. The overall response of the patient to therapy was satisfactory. The differentiation of Bullous pemphigoid from other subepidermal bullous diseases is important due to the potential of systemic manifestations and complications of the other diseases. The importance of clinical, histopathologic and immunologic findings in confirming the diagnosis of Bullous Pemphigoid is highlighted in this case report.

Keywords: Bullous Pemphigoid, Female, Case Report

1. Introduction

Bullous pemphigoid (BP), an autoimmune subepidermal dermatosis, predominantly affects people older than 60 years of age, with a peak incidence in the 70s (Kang et al., 2019; Kridin & Ludwig, 2018; Miyamoto et al., 2019; Rawson et al., 2018; Zanella et al., 2011). There is no known ethnic, racial or gender predilection (Miyamoto et al., 2019; Sravyasruthi et al., 2020; Zanella, 2011). The estimated annual incidence in the general population is between 2.4 and 23 cases per million (Bourdon-Lanoy et al., 2005). Reported cases of BP in individuals younger

than 50 years are rarely encountered with incidence rates usually lower than 0.5 cases per million population (Kridin & Ludwig, 2018).

BP is mediated by autoantibodies against the dermo-epidermal junction of the skin and adjacent mucous membrane. Deposition of these antibodies initiate an immunologic response by activation of an inflammatory process which subsequently activates the complement system, releasing products that cause degradation of the extracellular membrane ultimately leading to blister formation. The classic form manifests with large, tense blisters arising on normal skin or on an erythematous or urticarial base on the trunk and extremities accompanied by intense pruritus (Kang et al., 2019). Diagnosis relies on clinical assessment of the characteristic lesion described above, histologic demonstration of subepidermal blister, immunologic detection of IgG and/or C3 deposition at the basement membrane zone of the skin, and quantification of circulating autoantibodies against hemidesmosomal proteins (Miyamoto et al., 2019).

This report emphasizes the importance of considering the possibility of a diagnosis of BP in adults younger than 50 years of old. Furthermore, discussion of the clinical characteristics of the disease in a younger patient is highlighted in this report, comparing it with the usual manifestations seen in geriatric patients. Differentiaton from other subepidermal bullous disorders which closely mimics BP in clinical presentation is also highlighted.

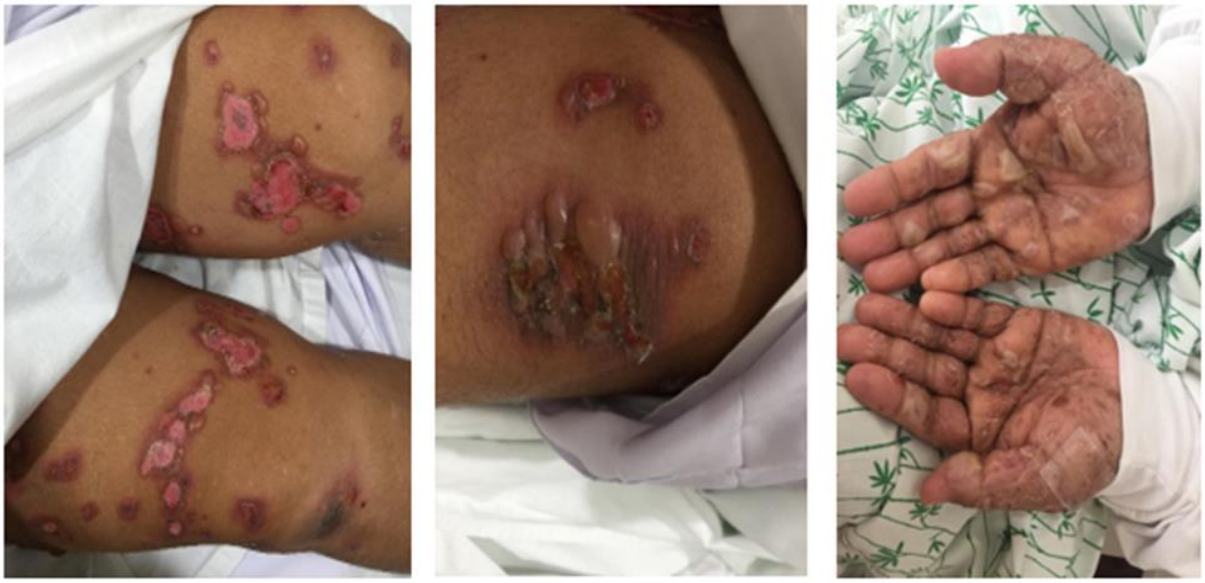
2. Case Report

A 37-year-old Filipino female presented with a three-month history of vesicular lesions and tense blisters associated with severe pruritus and pain upon rupture of the lesions. The lesions were noted initially on the face and neck but gradually spread to the trunk and extremities, up to the lower thigh. There was no history of insect bites, trauma, fever, cough, coryza, myalgias or arthralgias. She previously sought consult and was prescribed with Mupirocin 2% ointment, however lesions persisted. Skin punch biopsy on the abdominal area was done as out-patient and revealed whole epidermal necrosis in the center of the specimen with subepidermal split infiltrated with numerous neutrophils and nuclear dust. In the dermis were superficial perivascular infiltrates of lymphohistiocytes, neutrophils and few eosinophils. No hyphae or spores seen. Patient was prescribed with oral methylprednisolone and Clindamycin but advised admission for further work-up.

She is a known hypertensive maintained on Amlodipine 5mg tablet once daily. No past history suggestive of diabetes, asthma, seizure or any other illnesses. Patient is a non-smoker and non-alcoholic beverage drinker with no history of illicit drug use. Heredofamilial diseases include hypertension on the maternal side and an uncharacterized skin blistering disorder on the paternal side as claimed.

On physical examination, vital signs were within the normal limits. Inspection of the skin revealed multiple serous fluid-filled tense blisters on the face, neck, trunk, flexor and extensor surfaces of the extremities up to the lower thigh, with areas of excoriation, peeling, erosion and crusting (Figures 1a, 1b and 1c). No involvement of the mucous membranes was noted. The rest of the physical examination findings were unremarkable.

A provisional diagnosis of Bullous Pemphigoid was considered. Laboratory work up revealed increased C-reactive protein (18.06, NV: 0-5 mg/L), decreased total protein (5.5, NV: 6.0-8.4 g/dL), decreased A/G ratio (0.7, NV: 1.3-3.0), increased WBC count (11.4, NV: 4.8-10.8 10^3/uL), eosinophilia (10%, NV: 0-7%), increased SGPT (137, NV: 5-50 U/L), normal C3 and C4 levels, negative Anti-nuclear antibody (IF), negative Rheumatoid Factor and clear lung fields with minimal left lower pleural thickening on chest x-ray.



Figures 1a (left), 1b (middle) and 1c (right) show the characteristic lesion of BP described as tense blister arising on an erythematous base. These lesions were located in the lower extremities (1a and 1b) and hands (1c)

As presented by the patient clinically, the lesions of Linear IgA Dermatosis can resemble those of BP, consisting of papulovesicles or larger bullae that are symmetrically distributed on extensor surfaces also associated with moderate to severe pruritus. Histologically, the distinction is made from Direct Immunofluorescence (DIF) microscopy of perilesional skin. Mucosal involvement, however is an important clinical manifestation of Linear IgA dermatosis and was absent in the patient. Dermatitis Herpetiformis (DH) is a papulovesicular skin disease characterized by lesions spread symmetrically over extensor surfaces of the body and is associated with intense pruritus. Histologic examination reveals a neutrophil-rich infiltrate within the dermal papillae. As with Linear IgA Dermatosis, DIF is required to confirm the diagnosis. Bullous Systemic Lupus Erythematosus (BSLE) is a distinctive clinical presentation of SLE that affects young adult females and involves both sun-exposed and non-exposed skin. Lesions may be similar to BP, consisting of blisters appearing on an erythematous base with a predilection for the face, upper trunk and proximal extremities. Skin biopsy findings of subepidermal neutrophilic infiltrates also support the diagnosis. The absence of a history of other systemic symptoms commonly associated with SLE flares, along with a negative ANA result and normal C3 and C4 levels makes the diagnosis of BSLE less likely.

In view of clinical and histologic criteria, the patient was managed as a case of Bullous Pemphigoid and was started on Hydrocortisone 100mg IV every six hours to decrease the inflammatory response and control active blister formation. She was also given antibiotic prophylaxis of Amoxicillin-clavulanic acid 1.2g IV every eight hours and Cetirizine 10mg tablet, one tablet orally twice a day for relief of pruritus. A sterile gauze dressing soaked in PNSS was applied on affected areas twice a day.

On the first to fourth hospital day, patient noted less pruritus in the affected areas. No subjective complaints of pain, fever or dyspnea. Vital signs remained stable. A 4mm punch biopsy of perilesional skin was taken on the abdominal area and sent for DIF studies in another institution.

On the fifth to ninth hospital day, patient noted relief of pruritus and gradual diminution and flattening of bullae. Patient had no subjective complaints and vital signs remained stable. Complete blood count showed leukocytosis (15.59, NV: 4.8-0.8 10^3/uL) with neutrophilia (78%, NV: 40-74%). An increase from baseline was noted in the patient's SGPT value (126, NV: 5-50 U/L). Patient was started on Dapsone 100mg tablet, one tablet orally once a day, Azathioprine 50mg tablet, one tablet orally once a day and L-carnitine capsule, one capsule orally thrice a day. Intravenous Hydrocortisone was gradually tapered and eventually shifted to Methylprednisolone 16mg tablet,

one tablet orally twice a day. The seven-day course of Amoxicillin-clavulanic acid was completed and patient was eventually discharged with pending DIF results. Patient was advised to continue Azathioprine, Methylprednisolone, Cetirizine, L-carnitine and Mupirocin ointment as take home medications.
Patient returned for follow-up one week after discharge and reported flattening of blisters associated with relief of pruritus. Results of DIF studies revealed linear deposition of fibrinogen, IgA, IgM, and IgG along the basement membrane zone. The strongest fluorescence was seen with C3 and IgG, findings consistent with the diagnosis of Bullous Pemphigoid. Methylprednisolone was tapered to one 16mg tablet once a day and the rest of the take home medications were continued.

3. Discussion

BP is the most common subepidermal immunobullous disease chiefly affecting adults older than 60 years of age rarely in individuals younger than 50 years of age (Baroero et al., 2017; Kang et al., 2019; Kridin & Ludwig, 2018, Rawson et al., 2018; Zanella et al., 2011). Two key hemidesmosomal proteins strongly linked to BP have been identified namely BPAg1, also called BP230, and BPAg2, otherwise known as BP180 (Lee et al., 2014; Parellada et al., 2018; Sravyasruthi et al., 2020; Zanella et al., 2011). Autoantibodies (i.e anti-BP 180) directed to these antigens causes subsequent activation of the classical complement pathway, recruitment of inflammatory cells (mainly eosinophils and neutrophils) and formation of subepidermal bulla (Kang et al., 2019).

Classic forms typically start as pruritic, erythematous lesions and progress into the formation of large tense blisters where intact epidermis forms the roof (Lee et al., 2014). These lesions may occur anywhere but most frequently seen on flexural surfaces, the lower abdomen, and the thighs. Bullae are filled with serous or hemorrhagic fluid and typically, Nikolsky and Asboe-Hansen signs are negative (Kang et al., 2019). The disease is usually widespread, however, localized forms presenting as tense blister to localized areas of involvement have been reported.

The diagnosis of BP fulfills at least 3 of these criteria: (1) clinical findings consistent with BP that is, tense blisters arising from normal, erythematous or urticarial lesional skin affecting the trunk and extremities, (2) histologic evaluation findings suggestive of subepidermal blister with a superficial dermal infiltrate consisting of neutrophils, eosinophils, lymphocytes, and monocytes and macrophages, (3) DIF studies revealing linear deposition of IgG and or complement on the dermo-epidermal junction, and (4) positive anti-BP180NC16AIg antibodies on ELISA determination (Tan & Tay, 2018). These criteria may be used to rule out other subepidermal dermatoses, such as linear IgA dermatosis, dermatitis herpetiformis, inflammatory epidermolysis bullosa acquisita and bullous systemic lupus erythematosus.

In this case, the patient's clinical course was consistent with BP, presenting with tense blisters arising from an erythematous base which initially started on the face and neck progressing to the trunk and limbs. Skin punch biopsy showing a subepidermal vesicular dermatitis and DIF studies revealing IgG and C3 deposition on the skin epithelial basement membrane confirm the diagnosis of BP. Detection of characteristic antibodies by ELISA determination was not done.

The risk of BP increases with advanced age, certain HLA associations, exposure to some drugs (captopril, enalapril, furosemide, spironolactone, amiodarone, losartan, beta-blocker, ibuprofen, fluoxetine, sulfasalazine, chloroquine, D-penicillamine, ampicillin, cephalexin, ciprofloxacin, nalidixic acid, gabapentin and PUVA), and comorbidities such as neurological disease (eg, stroke, dementia, Parkinson's disease), psoriasis, cancer, and skin infection (Kridin & Ludwig, 2018; Lee et al., 2014; Miyamoto et al., 2019). Moreover, the viruses (CMV, EBV, HHV-6, HHV-8, HBV, and HCV), Helicobacter pylori and Toxoplasma gondii, and stress may also induce BP (Sravyasruthi et al., 2020). However, there were no identified triggers nor risk factors associated with the patient in this case.

Treatment is tailored according to the patient comorbidities and disease severity. Current mainstay of therapy includes high potency topical steroids and systemic steroids (Kang et al., 2019). Localized disease may be treated with topical corticosteroids such as clobetasol. In more extensive disease, patients usually respond favorably to

prednisone (0.75-1 mg/kg per day). Immunosuppressive agents, such as azathioprine or mycophenolate, are often used as an adjunct for their potential steroid-sparing effects. Poor prognostic factors include age, comorbidities, low albumin, and high doses of steroids (Bourdon-Lanoy et al., 2005; Lee et al., 2014). Treatment options should halt new blister formation, promote healing of existing lesions, and improve quality of life.

The disease may have peculiarities in the population under the age of 70 years. Studies show an increased expression of anti-BP 180 autoantibodies in younger age groups. Cases in which BP is more widespread are common, with involvement of the head and neck as seen in the index case. Treatment resistance is also commonly encountered, with varying responses to systemic steroids, dapsone or intravenous immunoglobulin in severe cases (Zanella et al., 2011). These are factors that must be considered in the diagnosis and treatment of adolescents and middle-aged adults presenting with blistering diseases.

3. Conclusion

Bullous Pemphigoid, although a disease that primarily affects the elderly, can also manifest in younger patients. A high index of suspicion must be maintained and BP should be included in the differential diagnosis of blistering diseases that present in adolescents and middle-aged adults. The distinction of BP from other subepidermal blistering diseases should be done by DIF studies of perilesional skin, and possibly antibody determination, due to differences in management and response to treatment modalities. The response of BP to steroids is often satisfactory, however the route of administration must be tailored to disease extent, severity and variation especially in younger patients. Adjuncts may be considered if treatment goals are not met.

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