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CASE REPORT

Childhood bullous pemphigoid: A case report

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ABSTRACT

INTRODUCTION Bullous pemphigoid (BP) is an acquired autoimmune subepidermal bullous disease characterized by linear deposition of IgG and C3 along the basement membrane. It rarely occurs in childhood, especially in adolescence, with only 14 cases identified in literature. Treatment of choice is systemic corticosteroids but other treatment options such as anti-inflammatory antibacterials and methotrexate are available.

CASE REPORT A 16-year-old Filipino girl presented with a three-month history of generalized vesicles and bullae. Nikolsky and Asboe-Hansen signs were negative. Histopathology and direct immunofluorescence were consistent with BP. ELISA to BP180 autoantibody levels was elevated at 135 IU (normal <9 IU). Complete blood count showed leukocytosis with increase in neutrophils. Chest x-ray revealed pulmonary tuberculosis. The patient was given quadruple anti-Koch's medication (pyrazinamide, rifampicin, ethambutol, isoniazid), prednisone, oral erythromycin and topical clobetasol propionate. Complete remission was attained at 10 months and is sustained at the time of writing.

CONCLUSION To establish a definitive diagnosis and appropriate management, BP requires clinical, histopathologic, and immunological correlation. Childhood BP has good prognosis and rapid treatment response, with rare relapses.

KEYWORDS Bullous pemphigoid, immunodermatology, pediatric dermatology

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INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disease with predominant eosinophil infiltration of the blister cavity.[1] Autoantibodies, mainly IgG, are directed against the basement membrane.[2] BP is commonly seen in the elderly.1 It rarely affects the pediatric population and there are less than 100 cases reported in literature up to 2015.[3] Majority of cases are in infancy, followed by the next peak among elementary students.[4] Locally, there are a total of 50 newly diagnosed cases of childhood BP obtained from the Philippine Dermatological Society Health Information System (PDS HIS) from 2011 to 2019.[5] In the adolescent age group, which ranges from 10 to 21 years,6 BP has an even rarer occurrence with only 14 cases identified in literature from 1970 to 2015,[6] with a female to male ratio of 2:1.[4]

CASE REPORT

A 16-year-old Filipino female presented with a three-month history of generalized vesicles and bullae. Five months prior to consultation, she noted spontaneous appearance of severely pruritic, erythematous macules on her left volar wrist, rapidly evolving into vesicles within the day. Involvement of the neck was noted the following day. Prior to lesion onset there was no trauma, vaccinations, nor new medications. Initial assessment by another physician was herpes infection. She was given prednisone 15 mg daily for one week tapered to 10 mg daily for another week and unrecalled creams resulting to complete resolution. Two months later, pruritic erythematous macules evolving into vesicles and bullae developed on both arms and the entire upper trunk for which similar treatment was unsuccessful. One month later, the lesions spread to the entire body, prompting consult at our institution.

Past medical history revealed varicella infection at age 10. There was no family history of autoimmune blistering nor autoinflammatory disease. Immunization history including BCG vaccination was unrecalled. Physical examination showed generalized tense vesicles and bullae filled with clear-yellowish fluid on normal and erythematous skin. There were yellow,

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crusted erythematous patches with annular configuration on the arms and back (Figure 1). Superficial erosions were noted on the lower lip mucosa and ventral aspect of tongue. There was no ocular nor genital involvement. Nikolsky and Asboe-Hansen signs were negative. Review of other systems was unremarkable except for grade 1 bipedal pitting edema. Initial impression was childhood BP versus linear IgA bullous dermatosis (LAD).

Skin tissue biopsy taken from the forearm showed eosinophilic infiltrates filling the subepidermal blister cavity (Figure 2). Direct immunofluorescence (DIF) of the perilesional skin showed linear deposits of IgG (+1) (Figure 3A), C3 (+2) (Figure 3B), and IgM (+3) on the basement membrane. Enzyme-linked immunosorbent assay (ELISA) to BP180 antigen was elevated at 135 IU (normal <9 IU). Complete blood count revealed increased white blood cell count with neutrophilia. Gram stain of vesicular fluid revealed eosinophils without organisms. Clinicopathologic findings led to a final diagnosis of BP in childhood. Chest X-ray done prior to giving systemic corticosteroid revealed pulmonary tuberculosis on the left upper lung.

The patient was managed by a multidisciplinary team composed of an immunodermatologist, a pediatrician, an oto-

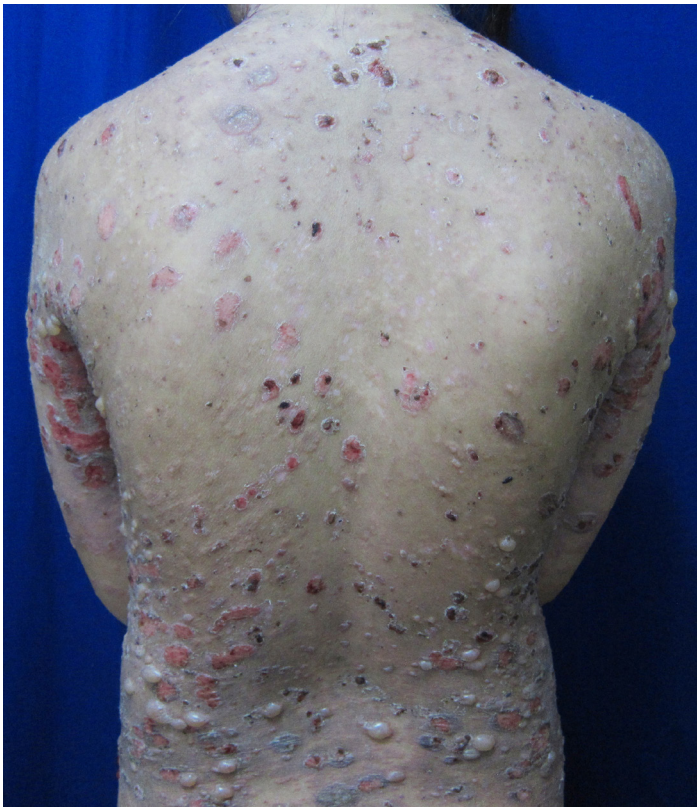

Figure 1. Generalized tense vesicles and bullae filled with clear-yellowish fluid on normal and erythematous skin. There were erythematous patches topped with yellowish crusts, some grouped into annular configuration.

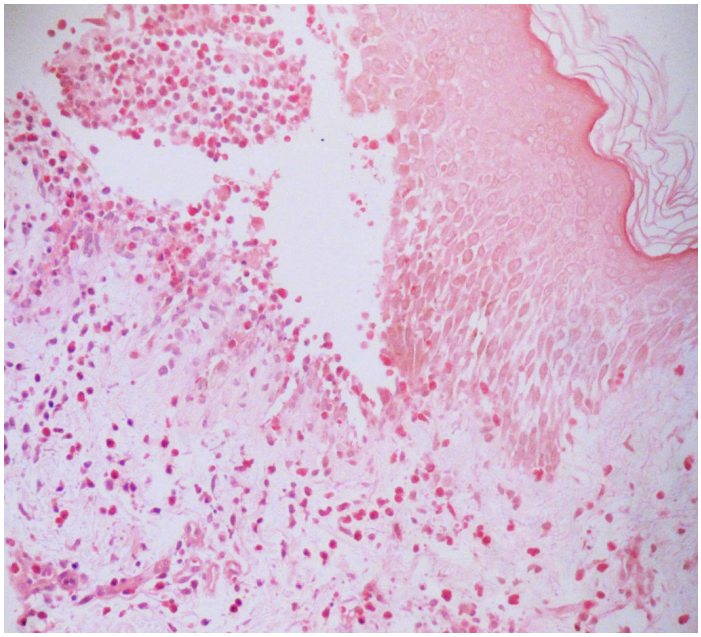

Figure 2. Histopathology shows eosinophilic infiltrates filling the subepidermal blister cavity. (hematoxylin and eosin stain, 10x).

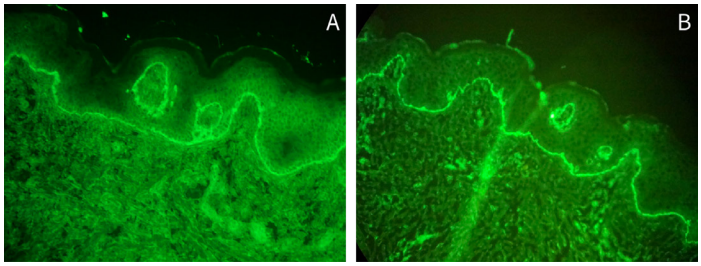

Figure 3. Direct immunofluorescence (IF) of the perilesional skin showed linear deposits of (A) IgG (+1), (B) C3 (+2) on the basement membrane zone.

rhinolaryngologist, and an ophthalmologist. She was started on quadruple anti-Koch's regimen (pyrazinamide, rifampicin, ethambutol, isoniazid) three tablets per day, prednisone 0.75 mg/kg/day, chlorphenamine maleate 4 mg tablet thrice a day, and clobetasol propionate cream twice a day. Improvement was noted on the 4th week with 10-12 new vesicles appearing every 3-4 days subsequently crusting in 2-3 days and resolving to hypopigmented and hyperpigmented macules and patches. Prednisone was tapered to 0.5 mg/kg/day. Doxycycline 100 mg/cap two capsules once a day was started for its immunomodulating properties.[2] Other medications were maintained. One of the first-line treatments for BP,[7] methotrexate, a folic acid analog, with anti-inflammatory and cytotoxic properties,[2] was not given since our patient had active pulmonary tuberculosis which is an absolute contraindication.[7]

On the 7th week of prednisone, only 3-4 vesicles appeared every 2-3 days. Generalized hypopigmented and hyperpigment-

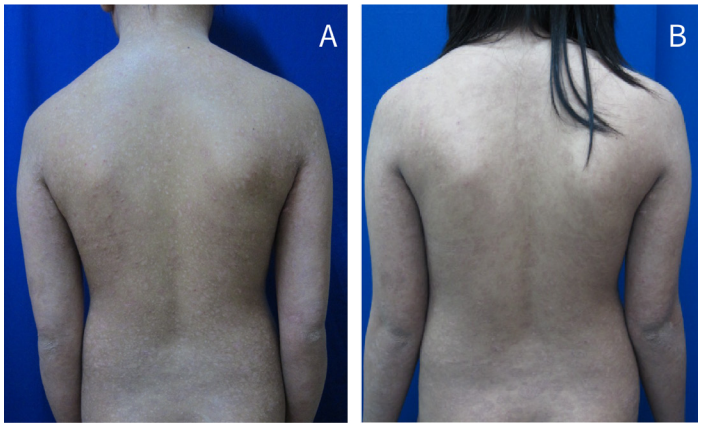

Figure 4. Follow-up photos of patient (A) on the 12th week of prednisone with diminished generalized hypopigmented and hyperpigmented macules and patches (Image alteration through cropping of sensitive area (buttocks) of patient using macOS Preview version 11.0 (999.4) Copyright 2002-2019 Apple Inc.) (B) on the 39th week with further diminution of hypopigmented and hyperpigmented macules and patches.

ed macules and patches with decreased crusting were noted. Prednisone was tapered to 0.41 mg/kg/day. Doxycycline was discontinued due to gastrointestinal complaints and shifted to erythromycin, an anti-inflammatory antibacterial at 250 mg/capsule four times a day for two weeks.[2]

On the 9th week, while maintained on prednisone 0.41 mg/kg/day and clobetasol propionate cream, disease was controlled with cessation of vesicle formation and resolution of pruritus.[7] Prednisone was tapered to 0.36 mg/kg/day.

On the 12th week, hypopigmentation and hyperpigmentation diminished (Figure 4A). Clobetasol propionate cream was discontinued and prednisone was continually tapered to 0.28 then 0.23 mg/kg/day every 2 weeks.

On the 22nd week, occasional pruritic papules appeared on both arms which resolved within the day. Prednisone was further tapered to 0.17 mg/kg/day. Erythromycin 250mg/capsule four times a day was resumed for two weeks. Monitoring of ELISA to BP180 antigen was not done due to financial constraints. Patient subsequently followed up 17 weeks after. During the interim period, she remained lesion-free with further diminution of hypopigmentation and hyperpigmentation (Figure 4B). Complete remission was achieved by our patient at 10 months and is sustained at the time of writing.

During the disease course, the patient's quality of life was unfavorably affected. Pruritic lesions prevented her from doing her daily tasks, post-inflammatory dyspigmentation limited her choice of clothes and she was unable to go to school.

DISCUSSION

Bullous pemphigoid in childhood is rare especially in adolescence.[6] Literature search by Patsatsi A. et al., identified only 14 cases from 1970 to 2015.[6] Of these, nine were in early adolescence (10-13 years) and five in middle adolescence (14-17 years).[6] All cases satisfied the Nemeth et al. criteria.[6,8] Limited data were obtained for late adolescence (18-21 years) which are recorded in adult registries.[6]

With seeming rarity in this group, we report a mid-adolescent 16-year-old female with a 3-month history of pruritic, generalized tense vesicles and bullae with annular configuration on the arms and back, with mucosal involvement. Given this clinical picture, LAD versus childhood BP were considered,[1] the former being the most common acquired autoimmune blistering disease in children.[3] Distribution of tense blister formation in childhood BP can be acral, or flexural involving the extremities, lower abdomen and groin, or anogenital involving the vulva.[1] It can be generalized and oral mucosal erosions are common,[1] as observed in our patient. Ocular mucous membrane involvement is common to both childhood BP and LAD[1] but was absent in our patient. Both are non-scarring and heal with post-inflammatory hypo- or hyperpigmentation.[1]

Our patient satisfied the criteria for childhood BP proposed by Nemeth et al.,[8] specifically, (a) Age 18 years or less with tense blister formation, and subepidermal bullae with eosinophils on histopathology, and (b) Linear IgG or C3 deposition at the basement membrane on DIF or reactive IgG antibodies to the basement membrane on IIF, and therefore our final diagnosis was childhood BP.

Given its rarity, there are no randomized controlled trials on childhood BP.[2] Hence, treatment recommendations are the same as adult BP but are administered with caution, taking into consideration their safety profile.[2] Since childhood BP generally has good prognosis, less toxic medications are recommended.[2,7]

For the management of widespread disease in children, first line is prednisone or prednisolone at 0.5-2 mg/kg/day, depending on disease severity.[2] Dose is gradually tapered according to clinical course.[7] Anti-inflammatory antibacterial medications, which suppress blister formation are often added to topical or oral corticosteroids,[2] are another option for mild to moderate disease.[7] Doxycycline which inhibits chemotaxis of eosinophils and neutrophils[2] has a better safety profile compared to systemic corticosteroids but are contraindicated in <12 years old since it interferes with tooth and bone development.[2] Therapeutic benefit can be attained at one to four weeks2 and our patient noted decrease in new vesicle formation after three weeks. Erythromycin is recommended in pediatric cases for its low adverse effects.[7] It has shown to be effective in childhood BP,[9] with its anti-inflammatory effect obtained in one to four weeks,[2] our patient showed cessation of new lesions in 2 weeks. In two cases of childhood BP, resolution of lesions was noted when erythromycin was given in combination with niacinamide and dapsone, and in another with an addition of topical steroid.[9]

An immunosuppressant, methotrexate, is a treatment option for mild to severe disease.[7] Adverse effects are myelosuppression and hepatotoxicity, hence, adequate patient screening

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for any contraindications, proper instruction to weekly dosing and ctompliance to regular monitoring should be emphasized.[7] In childhood BP, methotrexate 15 mg/week combined with prednisolone was shown to elicit a favorable response after three months, undetectable BP180 antibodies after six months, and sustained remission after one year of disease onset.[10]

For disease unresponsive to treatment or relapse with very high doses of corticosteroids, other immunosuppressants such as azathioprine or chemotherapeutic agents such as dapsone can be used alone or added to existing treatment.[2] An anti-IgE monoclonal antibody, omalizumab, has been shown to be another effective treatment with a steroid-sparing effect in a case of recalcitrant infantile BP.[11]

Control of disease defined as cessation of new lesions and healing of existing ones[6] is achieved from two to ten weeks,[4] and was attained by our patient within nine weeks. Complete remission or absence of lesions off treatment for two months[6] is attained at an average of 12 months or can reach five years,[4] and was achieved by our patient at 10 months. Relapses are uncommon as was seen in our patient.[9]

Long term monitoring is recommended until complete remission is achieved and all treatment is discontinued to ensure symptom control without overtreatment and adverse effects managed.[12]

Due to the disease burden of BP, quality of life assessment should be included in future cases for comprehensive management inclusive of psychosocial care.[13]

CONCLUSION

BP in childhood is rare especially in adolescents. To establish a definitive diagnosis and appropriate management, clinical, histopathologic, and immunologic analysis and correlation is necessary. Prognosis of childhood BP is good. Relapses rarely occur and treatment response is rapid from weeks to a few months. Treatment of choice is systemic corticosteroids. Long term monitoring and quality of life assessment is recommended to ensure treatment evaluation and psychosocial care.

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