Case Series

Childhood Bullous Pemphigoid with Atypical Immunopathology: A Case Series

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Abstract

Bullous pemphigoid (BP) is a rare autoimmune blistering disorder primarily affecting older adults, with limited occurrences in children. BP in children typically manifests as large, tense blisters on the skin, often on flexural areas. It also more often affects the oromucosal areas and the face in children than in adults. Diagnosis involves histopathological examination revealing eosinophilic spongiosis or subepidermal split, immunofluorescence tests highlighting immunoglobulin G (IgG) and C3 depositions, and immunological assays detecting BP180 and BP230 IgG autoantibodies. This report presents two cases of childhood BP (CBP) with atypical immunopathological findings. Clinically, the two cases had generalized plaques and bullae, including the face. The first case exhibited the characteristic linear deposits of IgG and C3 on the basement membrane through direct immunofluorescence (DIF) and revealed negative anti-BP180 antibodies on enzyme-linked immunosorbent assay (ELISA). In contrast, the second case showed negative DIF results, despite clinical suspicion, but had positive anti-BP180 IgG antibodies on ELISA. It is, therefore, crucial to consider the complete clinical presentation of the patient, in conjunction with the histological findings and immunopathologic assessments to diagnose CBP.

Keywords: *Bullous disease,* bullous pemphigoid 180, bullous pemphigoid, childhood bullous pemphigoid, direct immunofluorescence, enzyme-linked immunoabsorbent assay

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Introduction

Bullous pemphigoid (BP) is an acquired autoimmune subepidermal blistering disorder that most frequently occurs in older adults and is rare in infants and children.[1] Childhood BP (CBP) has an incidence of 2.36 cases per 100,000 infants annually in Israel and a prevalence of 4.9 cases per 1 million children each year in Germany.[2] In the Philippines, there were 50 newly diagnosed cases of CBP in the years 2011–2019, according to the Philippine Dermatological Society Health Information System.[3] Clinically, CBP classically presents as large, tense bullae either on an erythematous, urticarial base or normal skin. They are usually found on the flexural areas such as the groin, axilla, abdomen, and inner thighs.[1] Histopathologic features include a subepidermal split with a superficial perivascular inflammatory infiltrate of mostly eosinophils, spongiosis, and superficial dermal infiltrates of eosinophils. Direct immunofluorescence (DIF) would also show linear

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deposition of immunoglobulin (Ig) G and C3 at the basement membrane. Indirect immunofluorescence (IIF) may show IgG antibodies on the epidermal side, whereas immunological assays demonstrate anti-BP180 or anti-BP230 antibodies.[4] We report two cases of CBP showing atypical DIF and enzyme-linked immunosorbent assay (ELISA) BP180 results.

Case Reports

Patient 1

A 10-year-old Filipino male was initially seen in the dermatology clinic with a 1-month history of multiple, pruritic, erythematous urticarial plaques evolving into tense bullae and vesicles, predominantly on the trunk and extremities. The patient was previously seen and managed as a case of severe atopic dermatitis by a pediatrician and was prescribed prednisone 10 mg/mL syrup, 15 mL/day, and betamethasone ointment with noted improvement; however, recurrence prompted a consult at our institution. Clinical examination revealed multiple, irregularly-shaped, erythematous vesicles, and plaques with hemorrhagic crusts on the face, trunk, and extremities. No lesions were found on the orogenital mucosa [Figure 1].

A skin punch biopsy was performed, revealing prominent spongiosis of the epidermis and mild superficial perivascular infiltrate with eosinophils in the dermis. DIF of perilesional skin revealed linear deposits of IgG (+) and C3 (++) on the basement membrane zone (BMZ), whereas ELISA revealed negative anti-BP180 [Figure 2]. Despite the negative ELISA, the patient was still diagnosed as CBP and was given oral prednisone 0.5 mg/kg/day and topical steroids with rapid improvement of the vesicles and plaques, with cessation of new blister formation within several days.

Patient 2

A 4-year-old Filipino female was initially seen at the emergency room with a 3-month history of few, erythematous pruritic vesicles on the bilateral lower extremities. The lesions evolved into multiple, annular tense blisters coalescing into plaques, later involving the upper extremities, trunk, face, oral, and genital mucosa, associated with dysuria. The patient was initially treated by a private dermatologist with clobetasol propionate 0.05% ointment, mupirocin ointment, and cefalexin 250 mg/5 mL TID × 7 days with no improvement. Physical examination revealed annular hypopigmented to erythematous plaques and vesicles, with erosions on the face, neck, extremities, trunk, lips, and genital and perianal area [Figure 3].

Skin biopsy sample revealed spongiosis with exocytosis of eosinophils and superficial dermal infiltrates of numerous eosinophils, lymphocytes, and histiocytes. DIF revealed negative deposits of antibodies [Figure 4], whereas ELISA showed positive anti-BP180 with a ratio of 5.971. Due to the patient's clinical, histological, and ELISA findings, the patient was diagnosed with BP and initiated with oral prednisone 0.5 mg/kg/day, clindamycin 10 mg/kg/day, and topical steroids with noted improvement and progressive disappearance of the annular erythematous plaques and erosions.

Discussion

CBP presents similarly to the adult manifestations of the disease.[5] The age of onset was observed to range from 2.5 months to 16 years.[6] Nemeth *et al*. proposed diagnostic criteria for CBP: (1) age below 18 years, (2) clinical presentation of tense bullae and histopathologic finding of subepidermal bulla with eosinophils, and (3) DIF showing linear deposition of IgG or C3 at the BMZ or IIF demonstrating circulating IgG autoantibodies at the anti-BMZ.[7]

In children, the clinical presentation of BP may involve a more generalized pattern, frequently in an annular distribution of blisters. Involvement of the mucous membranes, such as the oral mucosa and genital area, may be prevalent in up to 50% of cases, more commonly presenting in children than in adults,[6] whereas genital

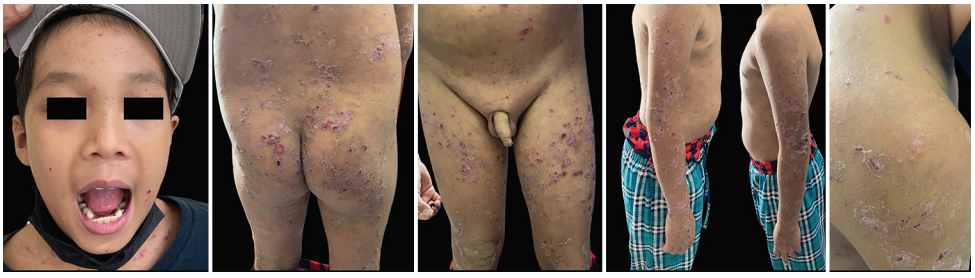

Figure 1: Physical examination of patient one showed few vesicles and multiple plaques with hemorrhagic crusts that are widespread in distribution, sparing the oral (first photo from the left) and genital mucosa (third photo from the left)

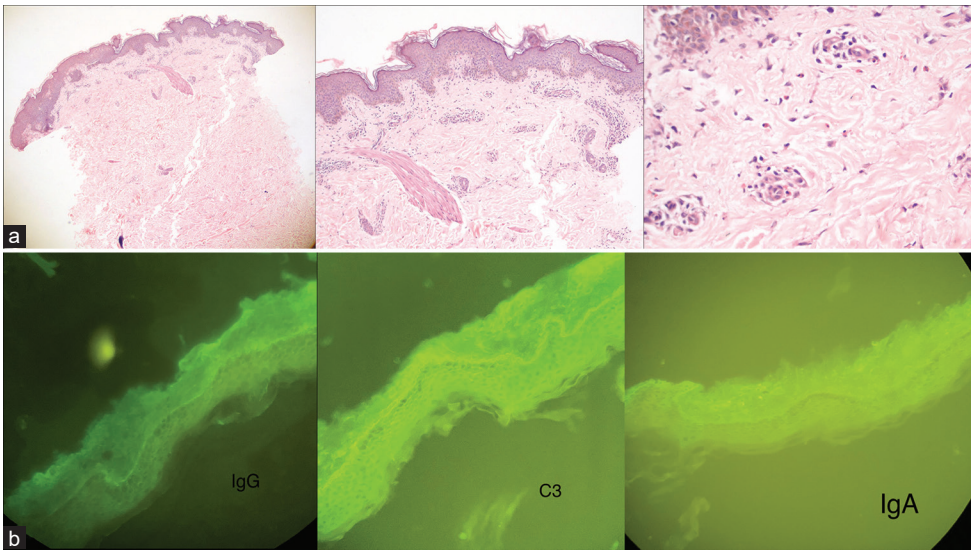

Figure 2: (a) Hematoxylin and eosin stain showing prominent spongiosis of the epidermis, with dermis revealing superficial perivascular infiltrate with eosinophils. From left to right: Scanning objective (4x), lower power magnification (10x), high power magnification (40x). (b) Direct Immunofluorescence shows fluorescence of IgA and C3 on the basement membrane zone. IgA: Immunoglobulin A, IgG: Immunoglobulin G

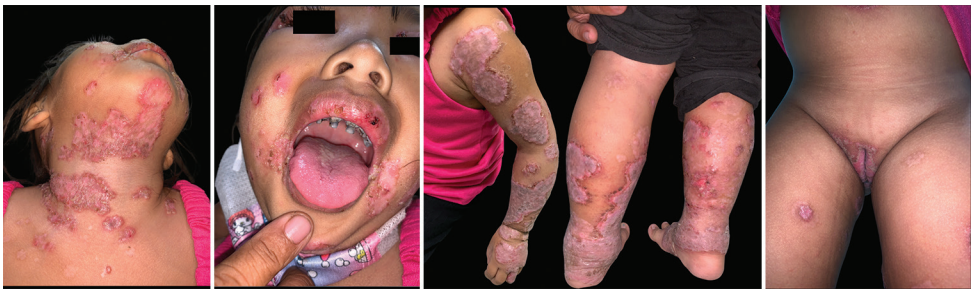

Figure 3: Physical examination of patient two showed multiple, annular plaques on the body with widespread involvement

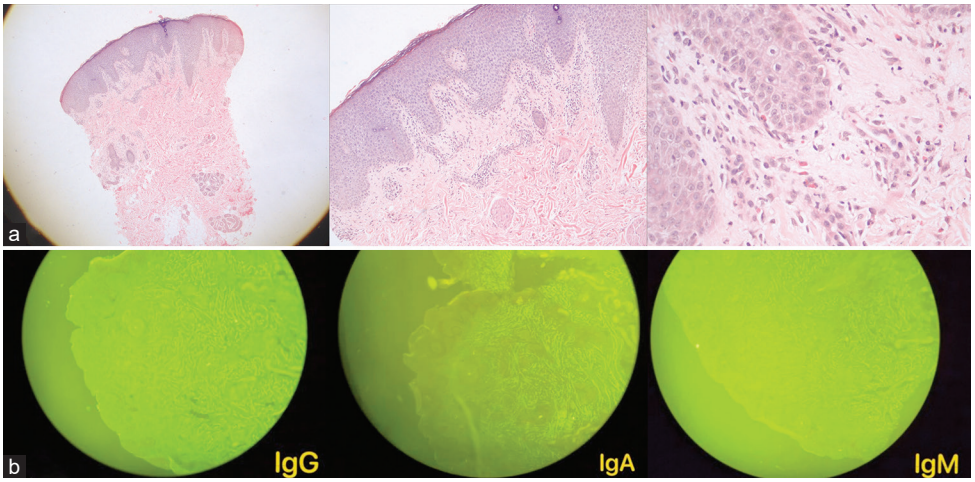

Figure 4: (a) Hematoxylin and Eosin stain showing spongiosis with exocytosis of eosinophils. The dermis reveals superficial infiltrates of numerous eosinophils and some lymphocytes. From left to right: Scanning objective (4x), lower power magnification (10x), high power magnification (40x). (b) Direct immunofluorescence showing negative fluorescence of immunoglobulin G, immunoglobulin A, and immunoglobulin M. IgA: Immunoglobulin A, IgG: Immunoglobulin G, IgM: Immunoglobulin M

involvement would occur more often in girls.[8] Similarly, both of our cases presented in a generalized pattern, including the face, while our second patient presented with orogenital lesions.

The histopathology of BP shows subepidermal blister formation with eosinophils. Early phases of BP before the onset of the bullae include dermal edema, perivascular lymphohistiocytic inflammation with eosinophils, and

eosinophilic spongiosis. In both of our cases, histologic examination revealed evident spongiosis of the epidermis with the dermis showing inflammatory infiltrates of eosinophils, a pattern reported in 25% of cases with BP. These suggest possible early stages of these lesions, similar to our cases.[8,9]

DIF examination revealing linear deposits of IgG and/or C3 at the BMZ remains the gold standard in diagnosing BP.[4,6] In our first case, linear deposits of IgG and C3 were appreciated on the BMZ which strongly confirms the diagnosis of BP. In contrast to this, our second case revealed negative deposits of IgG, C3, IgA, and IgM on the epidermis or basement membrane. DIF has a sensitivity ranging from 82% to 90.5% and a specificity of 98%, relatively more likely to produce false-negative results. Fudge and Crawford reviewed the DIF findings of BP patients and found that 3 out of 289 cases (1.04%) had initially negative DIF that became positive when retested. The varied biopsy results may be due to the presence of autoantibodies at levels below the detection threshold of standard DIF testing, suboptimal (e.g. lesional, lower extremities) biopsy site, varied IgG subclass, and anatomic variation of antigen expression undetectable by this test.[9] Wang *et al*. reviewed BP patients with a positive BP180 or BP230 on ELISA with a negative DIF, similar to our case. They observed that 4 of the 41 patients with a negative DIF followed up with a positive DIF upon retesting.[10] Due to the possibility of initial false-negative results, the authors suggested that if a patient presents with a strong clinical suspicion of BP, particularly when accompanied by histopathological features such as eosinophilic spongiosis, a diagnosis of BP remains highly likely, and repeating the DIF test is advisable.[9,10]

In our first case, the ELISA test did not detect any antibodies despite the positive DIF results. Research has indicated that approximately 8% to 10% of patients with BP may receive negative results in the currently available ELISA tests for BP180, which are designed to detect antibodies within the NC16A domain. This phenomenon occurs because this specific subset of patients is known to exhibit immune reactivity to regions outside of the NC16A domain.[11] Due to the relatively low sensitivity of ELISA (87%), CBP was still considered in this patient. However, ELISA anti-BP230 was requested but was not done.

The mainstay treatment in CBP includes topical corticosteroids in mild cases and potent systemic steroids (prednisone 1–2 mg/kg/day) for moderate-to-severe cases. However, alternative treatments include dapsone, sulfapyridine, combination of systemic corticosteroids, and methotrexate or erythromycin and nicotinamide. Recent reports also suggest intravenous rituximab once a week especially in severe and recalcitrant cases. CBP is associated with a favorable to excellent prognosis. Most instances of CBP exhibit an indolent nature, marked by intermittent relapses, often requiring treatment for a period of up to 2 years.[6]

The two cases presented underscore the discordance in laboratory findings, particularly in DIF and ELISA results. DIF still remains the gold standard for BP diagnosis, albeit with sensitivity limitations that can result in initial false-negative outcomes. ELISA tests may also produce negative results in a subset of patients, emphasizing the need to consider the clinical presentation of the patient along with other diagnostics such as histopathology. Repeat testing for DIF is also advised, especially if the clinical suspicion for BP is high. A comprehensive assessment of the patient's clinical symptoms, in conjunction with histological and immunopathologic assessments, is essential for arriving at a CBP diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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