

Subepidermal blistering disorder in a 16-year-old female: case report

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ABSTRACT

Subepidermal blistering disorders (SBD) are diseases associated with antibodies that attack structural proteins of the skin. Blister formation with widespread distribution is common in these diseases. The diagnosis of SBD is established through demonstration of immunoglobulin deposits in the dermoepidermal junction by direct immunofluorescence microscopy, and the presence of circulating autoantibodies by serology. Systemic corticosteroids and other immunosuppressive drugs are used to treat SBD. We present the case of a 16-year-old female with a 6-week history of intensely pruritic, erythematous plaques with generalized blister formation on the face, trunk, upper extremities, and inner thighs. We diagnosed the patient as having a subepidermal blistering disorder. We placed her on a course of prednisone and azathioprine, which successfully treated her lesions.

Keywords. autoimmune disease, bullous pemphigoid, epidermolysis bullosa acquisita, direct immunofluorescence, corticosteroids

INTRODUCTION

Subepidermal blistering disorders (SBD) are autoimmune disorders of the skin caused by the presence of autoantibodies to the structural components of the basement membrane.¹ All dermatologic conditions under this group histopathologically manifest as blister formation beneath the epidermis. SBD include the pemphigoid disorders [e.g., pemphigoid gestationis, mucous membrane cicatricial pemphigoid, bullous pemphigoid (BP)], linear IgA bullous dermatosis² epidermolysis bullosa acquisita (EBA), and anti-p200 pemphigoid.¹ These diseases share some clinical features—including the presence of pruritic, tense blisters—but their differentiation based on clinical presentation alone is difficult, hence the need for laboratory diagnostics such as direct immunofluorescence (DIF) and antibody testing.³ There are a number of therapeutic options, but steroids are the first-line treatment.⁴ Here, we report the case of a 16-year-old female who presented with vesicobullous skin lesions and was managed as having a subepidermal blistering disorder based on histopathologic and immunologic findings.

CLINICAL FEATURES

A 16-year-old female was admitted in our hospital with a six-week history of generalized, erythematous, pruritic, urticarial plaques, which gradually progressed to tense vesicles and bullae on the face, trunk, upper extremities, and inner aspects of the thighs. Two weeks prior to admission, the patient

consulted a dermatologist who prescribed the topical application of betamethasone dipropionate + mupirocin ointment twice daily on the lesions and oral intake of cetirizine 10 mg once a day for 2 weeks. There was no history of drug intake immediately prior to the onset of the lesions. She had no weight loss, easy fatigability, hair loss, photosensitivity, oral ulcers, or joint pains accompanying or preceding the lesions. No other family or household members had the same condition. Past medical history was unremarkable. She received due vaccinations until she was 1 year old. Development was at par with age. She had her menarche at 12 years old. She denied any sexual contact.

Dermatologic physical examination re-

IN ESSENCE

Subepidermal blistering disorders (SBD) are clustered autoimmune diseases characterized by severe bullae or vesicle formation.

The diagnosis of SBD is established through direct immunofluorescence microscopy and serological tests. Steroids are given as first-line treatment. Supplemental immunosuppressants can be added to the regimen in case adverse effects of long-term steroid therapy occur.

In this case report, we describe a 16-year-old female who presented with generalized blister formation on erythematous urticarial plaques. We successfully treated her with prednisone and azathioprine.





Figure 1 Multiple, erythematous, urticarial plaques and papules, and eroded plaques with purulent discharge on the right axillary area (A) and abdomen (B), topped with tense vesicles and bullae containing clear fluid.

vealed multiple, erythematous, urticarial plaques on the face, back, upper extremities and inner thighs. There were multiple, tense bullae containing serous fluid on the trunk, axillae, and extremities. The sizes of the bullae ranged from 1-3 cm in diameter. (Figures 1). Eroded plaques with purulent discharge were also noted. There were no mucosal lesions. Scarring, Nikolsky sign, and milia formation on or around the lesions were all absent. The rest of the physical examination findings were unremarkable.

DIAGNOSTIC APPROACHES

The patient's complete blood counts showed leukocytosis ($20.09 \times 10^3/\mu\text{L}$) and eosinophilia (differential count: 20%). Erythrocyte sedimentation rate was normal. ANA and anti-dsDNA levels were negative. Chest x-ray findings were within normal limits. Pregnancy test was negative. Culture and sensitivity of wound discharge showed no growth of organisms after five days.

Histopathologic examination of a vesicle located on the volar aspect of the left forearm revealed a subepidermal split with neutrophilic infiltrates (Figure 2), consistent with SBD. We sent a sample of perilesional skin from the trunk for (DIF). Results showed linear deposits of IgG and C3 on the basement membrane zone, consistent with pemphigoid disorders or epidermolysis bullosa acquisita. (Figure 3). The patient's

anti-BP180 IgG was elevated at 82.43 U/mL (normal value: < 9 U/mL).

Considering the clinical presentation of the patient, the DIF findings of linear deposits of IgG and C3 at the dermoepidermal junction, and the presence of autoantibodies against BP180, we managed the patient as having a subepidermal blistering disorder.

THERAPEUTIC APPROACHES AND OUTCOMES

Upon admission, we gave the patient intravenous clindamycin 300 mg every 6 hours and gentamicin 80 mg once a day, both for one week, to cover the infection. Topical steroid application was continued while awaiting the final biopsy results. After establishing the diagnosis of SBD through DIF, we started the patient on prednisone 50 mg/day (1 mg/kg/day based on the patient's weight of 50 kg). After the third day of prednisone, the old lesions did not improve, and new lesions appeared, so we increased the dose to 70 mg/day (1.4 mg/kg/day). After the dose increase, no new vesicles appeared, and the old lesions healed, leaving only hypopigmented patches. We discharged the patient two weeks after admission with instructions to return for regular follow-up consultations.

Starting on the third week of steroid use, we attempted to titrate down the patient's prednisone. However, on the 9th week, when

the prednisone dose was 20 mg/day, the patient developed Cushingoid facies. We added azathioprine starting at 50 mg/day with the aim to down-titrate the steroid over the next few weeks. On the 16th week, when the prednisone dose was 10 mg/day, the Cushingoid facies resolved but the patient developed new vesicles, so we increased the azathioprine dose to 75 mg/day. The patient did not return for follow-up for a year, but we came to know upon her return that, within the year, she eventually discontinued taking azathioprine, and intermittently took prednisone 10 mg whenever new vesicles would appear. She returned for follow-up because she developed new urticarial plaques and vesicles with generalized distribution. We restarted the patient on prednisone 10 mg/day and azathioprine 25 mg/day. When the vesicles started to diminish in number, we tapered the prednisone dose over 24 weeks and discontinued azathioprine on the 16th week. In the course of tapering the doses, there was one episode of appearance of new vesicles, which we were able to control by increasing the steroid dose to 25 mg and the azathioprine dose to 50 mg for 2 months. By the time we discontinued the prednisone, the patient's urticarial plaques and vesicles disappeared, and no new lesions developed.

DISCUSSION

SBD are characterized by distinctive blister formation due to autoantibodies that target the structural components of the skin's basement membrane.¹ The presence of autoantibodies against collagen XVII (BP180), which is a transmembrane protein structural component of the dermoepidermal anchoring complex,² clinically manifests as multiple tense blisters with sizes ranging from a few millimeters to 3 cm in diameter, as in our patient.

We narrowed down the diagnosis for our patient's condition based on her clinical features and laboratory results. We ruled out pemphigoid gestationis since it is a pregnancy-associated autoimmune skin disorder, and we have established at the outset that our patient was not pregnant.⁵ We also ruled out cicatricial pemphigoid since the disorder presents with blisters on mucous membranes, which were not observed in our patient.⁶ Likewise, we ruled out linear IgA bullous dermatitis because its characteristic appearance of urticarial plaques and papules surrounded by "string-of-pearls" blisters was not present in our patient.⁷ We focused on BP and EBA, since both conditions have similar clinical, histologic, and routine immunohistologic features.⁸

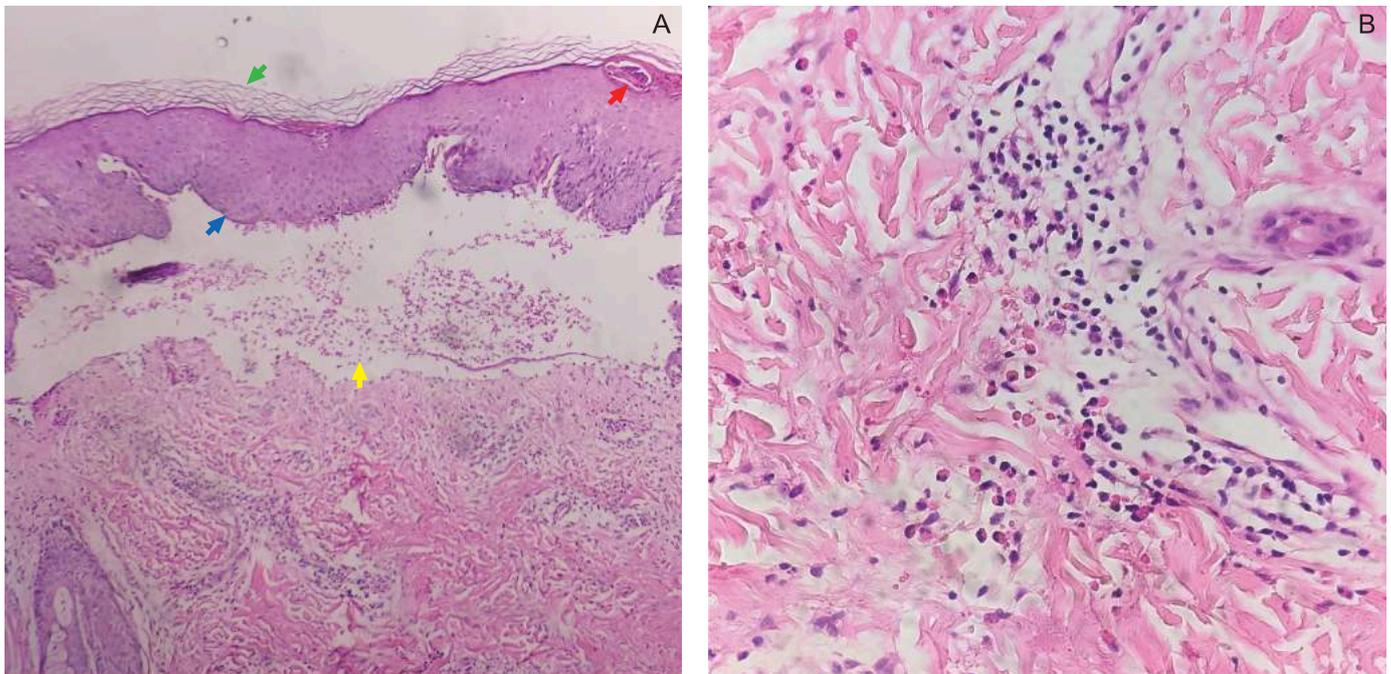


Figure 2 Histopathology of the skin showing basket-weave stratum corneum (A: green arrow) overlying an acanthotic epidermis, with focal intraepidermal collections of neutrophils (A: red arrow). A subepidermal split filled with neutrophils and red blood cells is also noted (A: yellow arrow). The dermis has superficial edema, with moderately dense perivascular inflammatory infiltrates composed of neutrophils, lymphocytes and eosinophils (hematoxylin-eosin stain, A: x10 and B: x40).

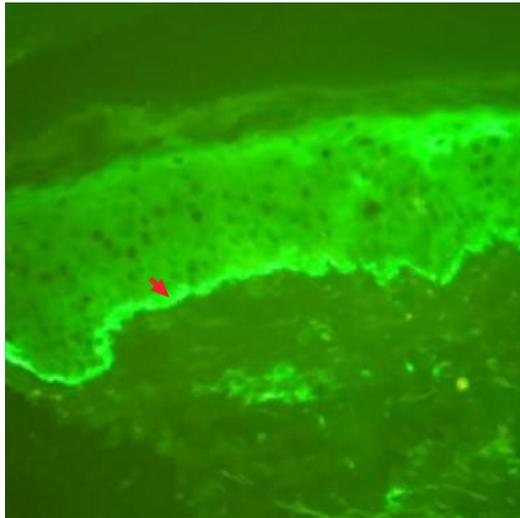


Figure 3 Direct immunofluorescence of perilesional skin (x40) showing linear deposits of IgG and C3 at the basement membrane zone (red arrow).

Both BP and EBA have female predominance and adult age of onset.⁹⁻¹⁰ BP, which mostly affects the elderly with mean age of onset around 80 years, accounts for 80% of SBD.⁵⁻¹¹ It is characterized by generalized formation of tense blisters and pruritus.³ EBA, on the other hand, is divided into two types: inflammatory and mechanobullous.¹² The mechanobullous type is seen in 0.33% of the patients and is characterized by multiple blisters on trauma-prone areas, such as the extensor surfaces of the extremities, along with milia formation and scarring.¹³ The inflammatory type more closely resembles BP, as it is also characterized by pruritus and generalized vesiculobullous lesions that affect the trunk, extremities, and skin folds.¹²⁻¹³

For our patient's diagnosis, the presence of linear deposits of IgG and C3 on the basement membrane zone on DIF and elevation of anti-BP180 pointed towards BP, but we also strongly considered the inflammatory type EBA because of its clinical similarities with BP.

In salt-split skin test, the skin biopsy specimen is incubated for 24-72 hours in 1 mol/L NaCl solution and then split at the level of the lamina lucida by teasing the epidermis from the dermis.¹⁴⁻¹⁷ This procedure differentiates EBA from BP by determining the location where antibodies bind to in the split skin.¹⁸ In BP, the antibodies bind to the epidermal side of the split skin, while in EBA, antibodies bind to

the dermal side.¹⁸ However, this examination was not performed in our patient.

Patients with SBD are commonly treated with glucocorticoids and immunosuppressants.¹⁹ Antihistamines may also be given to symptomatically treat pruritus. We started our patient initially on steroids, which produced only minimal improvement of the lesions. When we increased the steroid dose, the lesions healed significantly, but when we eventually tapered the dose, the lesions recurred. When our patient developed Cushingoid facies, which is a known adverse effect of long-term steroid use, we gave azathioprine and gradually reduced the steroid dose. This led to the complete resolution of the patient's skin lesions and Cushingoid facies.

Cytotoxic drugs, commonly used as antineoplastic agents, are also known to suppress the immune system and have been noted to be effective in the treatment of autoimmune diseases.²⁰ Cyclophosphamide, a cytotoxic chemotherapy drug, has been effectively used for BP.²¹⁻²² Methotrexate, in combination with oral or topical corticosteroids, was also reported to be effective in treating BP and EBA.¹⁹ Likewise, intravenous immunoglobulin has been used as treatment for bullous autoimmune diseases, especially EBA.²³⁻²⁴ Plasmapheresis, alone or in combination with cyclophosphamide or azathioprine, is also a viable treatment option, especially for patients who do not respond to conventional therapies.²¹

Immediate diagnosis and treatment ensure good prognosis for patients with SBD,²⁵ but there is a high recurrence rate related to down-titration or discontinuation of steroids.²⁶

Our patient presented clinically with the classic signs of SBD. Recognizing the severity of the disease, we immediately initiated an oral steroid regimen, which we later modified by adding azathioprine to minimize adverse effects of long-term steroid use. Our prompt diagnosis and use of a carefully titrated combination of prednisone and azathioprine proved to be effective in treating our patient.

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Patient consent

Obtained

Reporting guideline used

CARE Checklist

<http://www.care-statement.org/downloads/CAREchecklist-English.pdf>**Article source**

Submitted

Peer review

External

Competing interests

None declared

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