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"Half-half" blisters in bullous pemphigoid successfully treated with adjuvant high-dose intravenous immunoglobulin

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Abstract

Bullous pemphigoid is a rare, autoimmune blistering disease. Its clinical presentation is tense blisters that may arise on normal-appearing or erythematous skin. Bullous pemphigoid refractory to systemic corticosteroids in combination with immunosuppressants such as azathioprine and mycophenolate mofetil may benefit from adjuvant high-dose intravenous immunoglobulin (IVIg). We describe a particular case with an unusual clinical presentation unresponsive to systemic corticosteroids plus azathioprine, in which the addition of high-dose IVIg was successful. The combined therapy of systemic corticosteroids and azathioprine plus high-dose IVIg can be an option in refractory cases due to its efficiency and tolerability.

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Introduction

Bullous pemphigoid (BP) is a chronic, autoimmune, blistering skin disease that rarely affects mucous membranes. The onset of presentation is usually after the sixth decade. A similar incidence has been reported between genders, with no ethnic or racial preponderance.

BP may be preceded by an urticarial or eczematiform eruption that may persist for several weeks or months. In the next stage of BP, the development of vesicles and bullae is the hallmark, usually associated with mild or severe pruritus. These blisters could arise in normal or erythematous skin and once formed are large and tense, assuming a round or oval shape, which soon rupture, leaving simple or crusted erosions. BP involves the mucosa in up to 10 to 25% of patients. Rarely, "half-half" blisters, characterized by purulent fluid accumulated in the lower half of the blister or vesicles, may be observed in BP (2).

Corticosteroids with or without the addition of adjuvant conventional immunosuppressive therapies are the mainstay in the treatment of moderate to severe BP (3, 4). Alternative therapeutic interventions such as rituximab or high-dose intravenous immunoglobulin (IVIg) have been adopted for unresponsive forms to conventional therapy (5).

We present a severe case of BP refractory to systemic corticosteroids associated with the immunosuppressant drug azathioprine that responded to IVIg as an adjuvant combined therapy.

Case report

A 51-year-old Caucasian male was admitted for a widespread polymorphous skin eruption, with erythematous patches, wheals, and tense blisters, some of them half-filled with purulent fluid showing a hypopyon like-appearance, with a month's evolution (Fig. 1a, Fig. 1b). The patient's personal and pharmacology history was irrelevant.

Laboratory tests: hemoglobin 15.4 g/dL (RV = 13–17.5), erythrocyte sedimentation rate at 1st hour 9 mm (RV < 30), eosinophils 3.19 × 109/L (RV = 0.0–0.5), lactate dehydrogenase 386 U/L (RV = 208–378), total IgE 562 U/ml (RV < 87), and bacteriology swabs of the blisters negative.

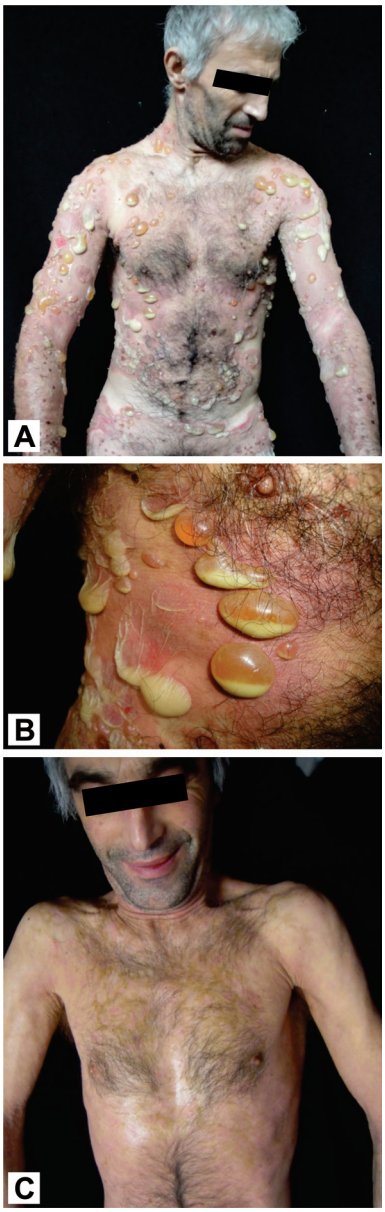

Figure 1 | (A) Clinical features on hospital admission (B) "Half-half" blisters in a serpiginous arrangement (C) Complete remission after intravenous immunoglobulin.

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Due to the patient's age and laboratory test results, the exclusion of malignancy was imperative and some additional examinations were performed, such as full-body CT scan, upper and lower GI endoscopy, and myelogram and tumor markers: all negative, except for squamous cell carcinoma antigen (SCC) 20.1 ng/ml (RV = 0–1.5). The histological examination of a skin blister, the perilesional skin for direct immunofluorescence (DIF) (linear pattern of immunoglobulin IgG and complement C3), indirect immunofluorescence (IIF) (IgG circulating autoantibodies), and the salt-split technique (IgG on the blister roof in the epidermal side) were performed and confirmed the diagnosis of BP. Treatment with prednisone 60 mg/q.d. and azathioprine 150 mg/q.d was started for 90 days without clinical improvement. At this time, intravenous rituximab perfusion (twice with 1,000 mg 2 weeks apart; C-MabThera®, Roche) was administered as an adjuvant therapy, but was discontinued due to the appearance of hyperpyrexia and laboratory parameters of infection; blood cultures were carried out without microbial isolation and a 2 week empirical course with a broad-spectrum cilastatin-imipinem antibiotic (1,000 mg, tid) was given. Due to the worsening of the dermatosis, after effective antibiotic treatment, IVIg infusion (Sandoglobulin®, Novartis) at 2 g/kg per cycle was started, divided over 5 consecutive days. Repetition treatment cycles were given every 4 weeks (3 cycles). Due to the severity of the disease, three more additional cycles of IVIg were administered every 8 weeks. One year after the last infusion, the patient remains in complete remission and is medicated with prednisone 10 mg q.d plus azathioprine 75 mg q.d (Fig. 1c).

Discussion

BP is an autoimmune blister disorder that in some cases can be refractory to conventional therapy with systemic corticosteroids plus immunosuppressant (6, 7). Our case showed severe BP in a middle-aged man that made us think of an underlying neoplastic disorder or other more rare blistering diseases such as epidermolysis bullosa acquisita (EBA) or Sneddon-Wilkinson disease, which was excluded during the investigations.

In BP, tense blisters may arise on normal-appearing or erythematous skin (3, 8). Blistering may be widespread or occur at one site, typically a flexural location. "Half-half" blisters or vesicles are classically observed in other blistering disorders, in particular subcorneal pustular dermatosis, and in acute generalized erythematous pustulosis (2, 9). Some cases of blistering diseases with a hypopyon-like appearance are related and are rarely seen in BP. BP diagnosis is defined by major and minor criteria.

Major criteria:

1) Clinical: polymorphic skin eruption with blisters and erosions, rare mucosal involvement;
2) Histopathology: subepidermal blistering with eosinophils;
3) DIF findings: deposition of IgG and C3 along the basement membrane.

Minor criteria:

(a) IIF findings: deposition of IgG and C3 along the basement membrane;
(b) BP antigens 1 (BPAG1) or 2 (BPAG2) – ELISA;
(c) Bands at 180 or 230 kDa by Immunoblotting (1).

For a diagnosis of BP there must be three major, or two major, criteria present, one of them being DIF plus other minor criteria (1).

The differential diagnosis of BP is with EBA, in its disseminated inflammatory variant, characterized by tense vesicles and bullae not localized exclusively at trauma-prone sites. Generalized erythema, urticarial plaques, and generalized pruritus may occur in some patients. This form of EBA clinically resembles BP in 10% of the cases or linear IgA BP (10).

Our patient had some clinical events, suggesting other blistering disorders such as Sneddon-Wilkinson disease or acute generalized erythematous pustulosis, which were ruled out on the basis of histology and immunofluorescence findings. The same was true for excluding EBA diagnosis (11). Some studies have reported that indirect immunofluorescence using the salt-split technique is a simple routine and an accurate method for differentiating EBA from BP (12). In this case, the salt-split immunofluorescence method revealed IgG on the blister roof (epidermal side of split skin), which is compatible with BP.

The therapeutic strategy for the management of severe BP consists of systemic corticosteroids, alone or in combination with immunosuppressant agents such as azathioprine, mycophenolate mofetil, or tetracyclines. Immunosuppressors are usually started simultaneously, followed by gradual tapering of corticosteroids and continuation of steroid-sparing drugs until clinical remission is achieved. Methotrexate may be an alternative in patients with contraindication or intolerance to systemic corticosteroids. In unresponsive forms to these conventional therapies, treatment with the anti-CD20 chimeric antibody (rituximab) must be considered (13). IVIg has mainly been used as adjuvant treatment for patients with long-lasting BP unresponsive to conventional therapy (14). The mechanism of action of IVIg is not completely understood, but may be attributed to interaction or modulation with multiple immune pathways, such as synthesis and release of cytokines and cytokine antagonists, neutralization of circulating autoantibodies by idiotypic antibodies in IVIg, functional blockade of Fc receptors on splenic macrophages, inhibition of complement-induced damage, and blockade of Fas receptors by anti-Fas antibodies present in IVIg (14, 15). Recently, the use of IVIg and its impact on treatment in the early onset of the disease has been evaluated with positive results (16).

In severe and refractory cases of BP, adjuvant therapy with IVIg may be considered as an option due to its efficiency and good tolerability, as illustrated by this case report.

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