Bullous Pemphigoid Associated with Ischemic Cerebrovascular Accident and Dementia: Exclusive Blistering Lesions on the Upper Hemiparetic Limb

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ABSTRACT Bullous pemphigoid (BP) has been associated with neurological disorders (NDs), which has led to the hypothesis that molecular mimicry exists between hemidesmosomal proteins and neuronal peptides. A 79-year-old hemiparetic woman presented with tense bullae affecting exclusively her right paretic upper limb for three months. Histopathology, taken from the perilesional area, revealed an inflammatory infiltrate with predominant eosinophils. IIF evidenced linear IgG deposition in the epidermal side of the cleavage. ELISA detected circulating anti-BP180 and anti-BP230 autoantibodies. Immunoblotting exhibited unspecific reactivity against the 190-kDa periplakin in normal human epidermal extract. The immunocompromised cutaneous district concept may explain the possible mechanism for the exclusive involvement of the autoimmune blistering disease in lymphedematous hemiparetic upper limb.

KEY WORDS: bullous pemphigoid, stroke, vascular dementia, hemiplegia.

INTRODUCTION Bullous pemphigoid (BP) is caused by autoantibodies that act against the BP180 (XVII collagen) and BP230 (dystonin) hemidesmosomal proteins (1). BP has been reported to be associated with neurological disorders (NDs) – the homology between the BP antigens in the skin and the neuronal peptides in the central nervous system has been proposed as a possible cause for the association between BP and NDs (2, 3). Dementia and cerebrovascular accident are the main NDs associated with BP (4).

In 1992, Long et al. (5) reported on the first case of unilateral BP involvement in a patient with hemiparesis. The pathogenesis of preferential bullous formation on the hemiparetic side remains unclear, but Piccolo et al. (6) have proposed the explanation of this relation with a novel immunocompromised cutaneous district concept.

This report describes a BP patient with exclusive involvement of the paretic upper limb, developed after ischemic cerebrovascular accident followed by
vascular dementia, who responded well to treatment with Dapsone.

**CASE REPORT**

A 79-year-old hemiparetic female wheelchair user presented with tense bullae that had developed three months previously and exclusively affected the right paretic upper limb. She had a history of three ischemic cerebrovascular accidents due to bilateral carotid stenosis. The last event had occurred three years previously and resulted in right hemiparesis, aphasia, and seizure events, besides diagnosis of vascular dementia stage 3 as determined by Clinical Dementia Rating during geriatric evaluation. She also presented hypertension, dyslipidemia, glucose intolerance, and gastrointestinal bleeding episodes due to gastric angiodysplasia. At the onset of the blistering lesions, there had been no particular change in the regular medications used to treat her comorbidities, namely atenolol 100 mg, phenytoin 100 mg twice a day, aspirin 100 mg, atorvastatin 20 mg, furosemide 40 mg, and ranitidine 40 mg.

Physical examination revealed multiple tense bullae with hyaline or purulent content as well as erosions and crusts on the right upper limb, particularly on the forearm and on the hand dorsum and palm. Inflammatory signs with pronounced erythema and swelling resembling streptococcal erysipelas were also detected. Interestingly, the bullous lesions only affected the paretic upper limb (Figure 1, A). The lesion did not involve mucosal surfaces. A swab of the blistering lesion evidenced *Staphylococcus aureus* and *Staphylococcus epidermidis*. Based on the antibiogram, the patient was prescribed cephalexin 500 mg.

Figure 1. (A) Multiple tense bullae with hyaline or purulent content, erosions and hematic crusts, and erythema and intense swelling in the paretic right upper limb. (B) Histopathology of the skin revealed an inflammatory infiltrate where eosinophils predominated in the upper dermis and eosinophilic spongiosis emerged in the epidermis (Hematoxylin-eosin, ×400). (C) Indirect immunofluorescence using human skin as substrate (NaCl-salt split skin) and serum dilution 1:20 evidenced linear IgG fluorescence in the epidermal side of the cleavage (×400). The slide was counter-colored with Evan’s blue (red color). (D) Immunoblotting using normal human epidermal extract showed an unspecific reactivity against the 190-kDa periplakin. (E) Right upper limb four months after treatment with dapsone was discontinued; the residual lymphedema can be attributed to hemiparesis.
every six hours, followed by sulfamethoxazole-and-trimethoprim 800/160 mg twice a day for 14 days while the laboratorial tests were being processed.

Laboratory tests showed hypertriglyceridemia (240 mg/dL; normal <150 mg/dL) and slightly increased carinoembryonic antigen (2.79 ng/mL; normal <2.5 ng/mL). Blood counts, renal function, electrolytes, blood calcium, total cholesterol, and glycermic levels were within the normal range. Serology for hepatitis B and C, HIV, and VDRL were negative. The results obtained for the G6PD test, blood proteins, and cancer antigen-125 were within the normal range. Transvaginal ultrasound, colonoscopy, chest X-ray, and mammography did not reveal any abnormality.

A skin biopsy was taken from the perilesional area. Histopathology evidenced an inflammatory infiltrate where eosinophils predominated in the upper dermis, and eosinophilic spongiosis emerged in the epidermis (Figure 1, B). Linear IgG in the basal membrane zone (BMZ) was documented by direct immunofluorescence. Indirect immunofluorescence (IIF) based on 1M-NaCl-split normal human skin as a substrate showed linear IgG fluorescence in the epidermal side of the cleavage (Figure 1, C). Complement IIF, detected using anti C3 secondary antibody, was negative at the titer of 1:20. Immunoblotting of normal human epidermal extract exhibited an unspecific reactivity against the 190-kDa periplakin (Figure 1, D). No positive reactivity arose during immunoblotting using other antigen sources, including recombinant proteins of NC16a and C-terminal domains of BP180, concentrated culture supernatant of HaCaT cells, and purified human laminin 332 (laminin 5) (data not shown). ELISA (MBL, Nagoya, Japan) resulted in positive serology for both BP230 (index 37.3U/L, cut off 9) and BP180 (index 18.0U/L, cut off 9), but negativity for both desmoglein (Dsg) 1 and Dsg 3 (index 0.845U/L and 0.443U/L, respectively; cut off 12).

The antibiotics improved the clinical course but bullae recurred later. Therefore, the patient was prescribed Dapsone 50 mg per day. Remission of BP lesions was achieved four months after the treatment, so the Dapsone dose was reduced to 50 mg on alternate days and suspended four months after the last active lesion was detected. Stable remission continued three years after the drug was discontinued (Figure 1, E).

This study was approved by the local Research Ethics Committee approved this study (#051174/2015), and the patient provided the informed consent.

**DISCUSSION**

This case report involves topics that deserve discussion: exclusive localization of the BP blistering lesions on the hemiparetic limb, association between BP and NDs, and the immunocompromised cutaneous district concept.

Remarkably, the blistering lesions were distributed exclusively in the upper hemiparetic limb. To our knowledge, this is the eighth case that has shown this distribution form (5, 7-9). Decreased blood flow, impaired nerve function, muscle contraction, adverse effects of ND medications, immobility, and scratching of the affected area are factors that may explain the unilateral compromise of BP in hemiparetic patients (7).

This patient presented blistering BP lesions three years after the third ischemic cerebrovascular accident, associated with vascular dementia. Association between BP and NDs has been increasingly reported (4). Both the expression of BP180 in the human brain tissue and the presence of a neural BPAG1n type, favor a possible molecular mimicry between BP antigens and neuronal peptides (2, 3).

In contrast to the case reported by Tsuruta et al. (7), who reported minimum inflammatory cells, the histopathological findings obtained for our patient showed that an eosinophilic inflammatory infiltrate predominated in the upper dermis, allied to eosinophilic spongiosis in the epidermis. Despite oral or topical corticosteroids as a therapeutic option in this case, due to local damage and residual lesions by previous infection it was decided to initiate Dapsone, which has been successfully used in the treatment of BP (10).

Finally, the immunocompromised cutaneous district concept proposed by Ruocco et al. (2009) (11) considers that an injured cutaneous site, such as the lymphedematous paretic limb in this case, may become a privileged location for opportunistic infections, tumors, and immune reactions.

**CONCLUSION**

BP is characterized clinically by tense bullae, mainly distributed on the extremities and the trunk. In this case we described a very unusual condition where BP lesions appeared exclusively in a hemiparetic limb and nowhere else. The pathological mechanisms involved in this condition have not been fully elucidated. The immunocompromised cutaneous district concept considered that chronic lymphedema might
generate local immune reactions and/or molecular aggressions to hemidesmossomal proteins, which may trigger BP exclusively in the lymphedematous hemiparetic upper limb.

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