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# Baclofen-Induced Dyshidrosiform Bullous Pemphigoid in a Paraplegic Patient Complicated by Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Urinary Infection

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**ABSTRACT** Bullous pemphigoid (BP) is an autoimmune disorder which is usually chronic, with blistering that predominantly affects the skin and occasionally the mucosa, and which includes several different types. One of them is a very rare dyshidrosiform type which is localized on the hands and feet with small or large blisters on the palmoplantar surfaces. BP resulting from a drug reaction is a relatively rare occurrence, and so far more than 50 different medications have been identified as triggers. The aim of this article was to present the case of a paraplegic patient who developed this rare dyshidrosiform type of BP while he was being neurologically treated with baclofen. In spite of therapy with systemic and topical corticosteroids and other measures, successful treatment was achieved only after eliminating baclofen from the patient's regimen. His general state of health was seriously endangered due to nasal and skin methicillin-resistant *Staphylococcus aureus* (MRSA), urinary infection, and oral mycosis (soor), and he was at high risk of sepsis and a fatal outcome. Through our efforts, however, we managed to achieve an excellent outcome. According to our knowledge, this was the first case of baclofen-induced dyshidrosiform BP.

**KEY WORDS:** bullous pemphigoid, baclofen, dyshidrosiform pemphigoid, neurological disorder, MRSA, urinary infection, complications

## INTRODUCTION

Bullous pemphigoid (BP) is a usually chronic autoimmune disorder with blistering that predominantly affects the skin and sometimes the mucosa (1-3). There are several variants, including the rarer dyshidrosiform type. It can clinically resemble common dyshidrosiform dermatitis, manifesting as small or large blisters on palmoplantar surfaces. These subepidermal blisters appear as a result of IgG autoantibodies binding to transmembrane hemidezmosomes via a 230 kDa plakin molecule (1-4). Currently, there is

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little data on etiological factors of this very rare type of BP.

The diagnosis of BP is based on clinical and histologic findings, immunofluorescent characteristics, serum antibodies, etc. (1,3,5-10). There are a few related diseases observed in patients with BP such as neurological disorders and internal malignancies. Previous research has reported a greater frequency of BP among patients with neurological disorders such as Parkinson's disease, epilepsy, multiple sclerosis, cerebrovascular disease, dementia, dyskinesia, etc. (4,6-8).

We present the case of a paraplegic patient who developed the rare dyshidrosiform type of BP while he was being treated with baclofen, a medication with spasmolytic effects on the central nervous system. To our knowledge, there is no previously recorded case of a connection between dyshidrosiform pemphigoid and baclofen.

## CASE REPORT

A white 49-year-old male paraplegic patient was admitted to our clinic due to skin lesions – various-sized blisters on the erythematous surfaces of the palms and soles of the feet and mild oral lesions (Figure 1, Figure 2) which he had noticed ten days before being admitted. Prior to his arrival he had been treated by his local dermatologist with parenteral systemic corticosteroids, peroral antibiotics (amoxicillin and clavulanic acid) and topical antiseptics, but without success.

Over the previous 4 years, the patient had been suffering paraplegia of the distal extremities and urinary incontinence as a result of spinal cord lesions (ischemic transversal myelitis with a possible inflammatory etiology). His neurologist prescribed baclofen tablets, which the patient started taking two years before admission to our clinic. Additionally, before we saw him, the patient had undergone urologic ileocystoplasty a year earlier and had since been practicing intermittent self-catheterization through a cystostomy.

Extensive workup was performed during hospitalization, including a lesional skin biopsy which showed histologic characteristics of BP (Figure 3), while direct immunofluorescence (DIF) showed linear deposits of IgG and C3 in the basement membrane zone. Serum tests were also performed: the BP180 antigen was positive (149.0 U), BP230 was negative, and DSG-1 and DSG-3 were also negative (ELISA).

Based on these findings (histopathology, DIF, BPAGs), we established the diagnosis of BP and concluded it was specifically dyshidrosiform BP due to the appearance of dyshidrosiform skin lesions. Being the probable trigger, baclofen was gradually discontinued in consultation with a clinical pharmacologist and neurologist. Perioral low-dose diazepam was thus introduced instead.

Nasal and skin swabs were taken as part of our workup, and methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated in both samples, showing heavy bacterial growth. Since it was mupirocine-resistant, a topical skin treatment with chlorhexidine solution was used. Octenidine was used for nasal decolonization over 5 days. The patient was treated under special conditions and in isolation. After topical treatment, control swabs showed eradication of MRSA. Urine cultures revealed *Pseudomonas aeruginosa* ($\geq 10^6$ CFU/mL), which we treated with ceftazidime and cefepime. In a second urine culture, *Enterococcus spp.* ($\geq 10^6$ CFU/mL) was isolated and consequently treated (amoxicillin and nitrofurantoin).

The patient was also treated parenterally and perorally with systemic corticosteroids (40 mg of

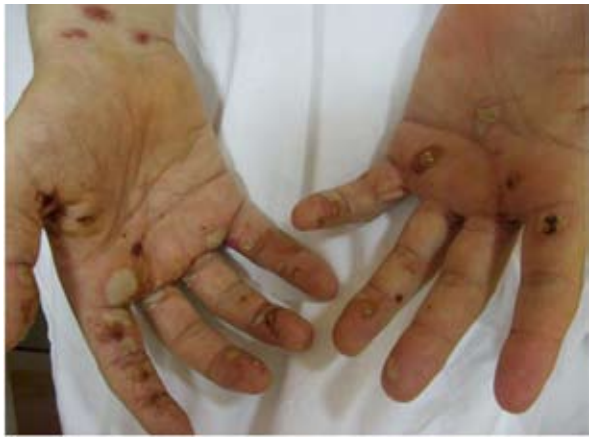

**Figure 1.** Blisters, erosions, and crusts on the hands.

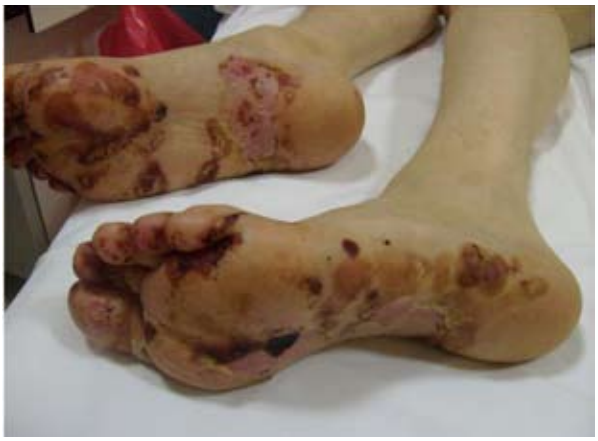

**Figure 2.** Blisters, erosions, and crusts on the feet.

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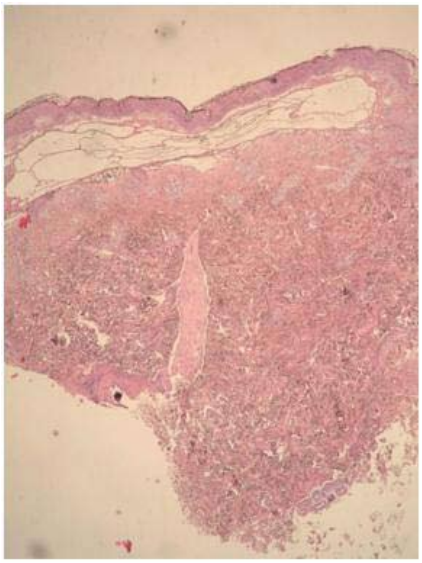

**Figure 3.** A biopsy specimen from the left hand showed focal spongiosis in the epidermis (thin arrow; hematoxylin and eosin ×40).

methylprednisolone daily with gradual dose tapering), systemic antihistamines, and azathioprine (100 mg daily). Topical corticosteroid and antibiotic treatments were also applied to skin lesions. He also received anticoagulation therapy (low-molecular warfarin) due to paraplegia and a pulmonary embolism incident 4 years earlier. The patient was also under neurological and urological supervision, and gastroenterological and proctologic workups were performed because of gastrointestinal discomfort. The patient was also examined by an oral pathologist who observed desquamative gingivitis. Because of oral mycosis (soor), confirmed by isolation of *Candida spp.* from a tongue swab, an antimycotic treatment and antiseptic oral solution were recommended.

When therapy resulted in regression of skin lesions and epithelization at sites of erosion, the patient was discharged and continued therapy at home (24 mg of peroral methylprednisolone daily with subsequent gradual dose tapering; 100 mg of azathioprine daily as a topical therapy).

Five years later, the patient reported feeling well with no signs of relapse.

## DISCUSSION

Apart from typical BP presentation, there are a number of clinically distinct BP variants (gestational, infantile, vegetans, nodularis, vesicular, papular, eczematous, erythrodermic, lichen planus pemphigoid, purpuric, and dyshidrosiform) (1,3,11-13). Dyshidrosiform pemphigoid is rare, but this subtype should be specifically identified when it does occur (14-16).

However, all BP types are based on the basic pathophysiological mechanism of autoantibodies binding to hemidesmosomal proteins of the dermoepidermal junction: BP antigen 180 (BPAg2 or type XVII collagen) and BP antigen 230 (BPAg1e). Although BP is mostly a disease of the elderly (onset usually occurs after age 60), it can also appear at a somewhat earlier age, as was the case with our patient (1,13). The association of BP with medical conditions such as neurological diseases is probably due to a patient's advanced age rather than to BP itself (3,4). It should be noted that there is a similarity between BP230 (dystonin) and BPAg1 which may cause autoantibodies to react similarly, thus possibly explaining the connection between neuroautoimmunity and the autoimmune response in the pemphigoid group (17). Furthermore, special variants of BP230 are also expressed throughout the central and peripheral nervous system (3). Although the association between BP and neurologic diseases has been well documented, their exact pathogenic relationship is yet to be elucidated (4,7,8).

BP as a result of a drug reaction is a relatively rare occurrence. However, more than 50 different medications have been described as triggers so far, with the number rising further (18,19). Since testing our patient was not possible, we still do not have diagnostic confirmation that baclofen was the trigger for disease development; however, the patient was previously treated with systemic corticosteroids, and only after discontinuation of baclofen did we observe long-term lesion resolution, confirming that baclofen was the trigger. Testing can result in false negatives even when it is performed, and adverse reactions sometimes have etiologies which cannot be discovered by tests but only by discontinuing a medication or by process of elimination.

As of this writing, no reports of similar cases were found in which baclofen was the possible trigger of BP, as described in our case study. Furthermore, according to the PubMed/MEDLINE database, the total number of published articles retrieved with the key words "dyshidrosiform pemphigoid" does not exceed 26.

Fatal outcomes are common in patients with severe general skin conditions such as BP, as described by other authors (12,20). A crucial factor for achieving a good outcome is the exclusion of the causative agent – in this case a drug, supported by administration of systemic and topical corticosteroids or other immunosuppressive therapies such as azathioprine or even dapsone (1,13). However, special caution is needed with patients receiving a high dosage or long-term immunosuppressive therapy because of the high risk

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of sepsis or other complications. Therefore, adequate recognition and treatment of infection, including potentially life-threatening pathogens such as MRSA, is essential, as is the prevention of other complications (e.g. thrombosis). It is especially important to achieve a long-term stable condition for the patient, and they can only be declared disease-free after a longer period of monitoring.

## CONCLUSION

Given that the dyshidrosiform variant of pemphigoid is a rare occurrence within the pemphigoid group, more research is needed to establish an association between it and various factors, including medications such as baclofen.

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