ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Clinical Challenges in the Diagnosis of Bullous Pemphigoid and the Role of Direct Immunofluorescence: A Case Study.

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ABSTRACT

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease of the skin. It is a chronic disease, with spontaneous exacerbations and remissions, which may be accompanied by significant morbidity and mortality. BP is associated with tissue-bound and circulating autoantibodies directed against hemidesmosomes that promote dermo-epidermal cohesion. The cutaneous manifestations of BP can be extremely polymorphic, posing a clinical challenge in its diagnosis. It may mimic or co-exist with a host of inflammatory dermatoses. Here, we report a case of bullous pemphigoid that clinically impersonated with features of lichen planus. However, a subtle clue in patient history, histopathological examination and direct immunofluorescence helped in diagnosing an atypical variant of BP. Appropriate treatment with systemic corticosteroids induced remission in this patient. A thorough understanding of pathophysiology of the disease can help develop specific targeted therapies for BP.

Keywords: Bullous pemphigoid, Lichen planus, direct immunofluorescence, clinical challenge

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ISSN: 0975-8585

INTRODUCTION

Bullous pemphigoid (BP) is a subepidermal autoimmune blistering disease characterized by the presence autoantibodies directed against two components of hemidesmosomes (a part of the basement membrane that attaches the epidermis to the dermis), BP180 (also called BP antigen 2 [BPAG2] or type XVII collagen) and BP230 (BPAG1-e) [1]. The annual incidence has been estimated to be at least 6–7 new cases per million population, with significant mortality in the first year following the diagnosis of BP ranging from 10 to 40% [2]. BP ppredominantly affects the elderly population, with onset after the age of 60 years being common, and has increased risk for mortality as well as long term morbidity. Its' incidence increases with age, contrary to almost all of the autoimmune disorders [3].

Triggers implicated in the causation of BP are burns, trauma, UV radiation and drugs like aldosterone antagonists, loop diuretics and neuroleptics [4, 5].

BP has a polymorphic clinical presentation. It is characterized by the formation of large, tense bullae either over normal or urticarial, or erythematous bases. Blisters are tight, with variable size, usually symmetrical and ungrouped, with serous and / or hemorrhagic contents [3]. The lesions tend to localize in the flexural areas such as inner aspects of thighs, flexor surface of forearms, axillae, groin and lower abdomen. Itching is characteristic feature of BP and Nikolsky sign is negative. The clinical presentation, however, may be with 'nonspecific' symptoms such as severe pruritus, accompanied by eczematous, papular, urticarial, excoriated and or prurigo lesions [1]. A variety of other inflammatory dermatoses, e.g. dermatitis, toxic drug reactions, ectoparasitoses, fixed urticaria or prurigo, may mimic the features of BP. 'Lichen planus pemphigoides' is described as coexistence of BP and lichen planus, in which the affected patients are usually younger compared to the typical elderly BP patients and their disease is limited and less aggressive.

The diagnosis of BP is particularly challenging in all instances in which either obvious blistering is lacking or blisters and erosions remain localized.

Here, with the aid of a case of bullous pemphigoid, we report a not so typical bullous presentation of BP, posing as a diagnostic challenge for this most common autoimmune blistering disease.

Case Presentation

A 65-yr-old male patient, palm oil harvester by occupation, visited the dermatology OPD in Hospital Sunghoi Buloh with complaints of recurrent dryness and itching of skin over the face, trunk, limbs and scalp since one year. He was a known case of type 2 diabetes, hypertension and dyslipidemia, on treatment. He had a positive family history of atopy. On examination, the lesions on the thighs, forearms and trunk were scaly and hyperpigmented papules [Figure 1a, 1b]. Dry and scaly patches were visible on the scalp. Drug allergy was ruled out. At this point in time, the most likely diagnosis was papular eczema. He was prescribed cetrimide shampoo, topical hydrocortisone for face and flexures and betamethasone valerate cream 0.1% for local application. Hydroxyzine 10mg daily was advised to control the itching.

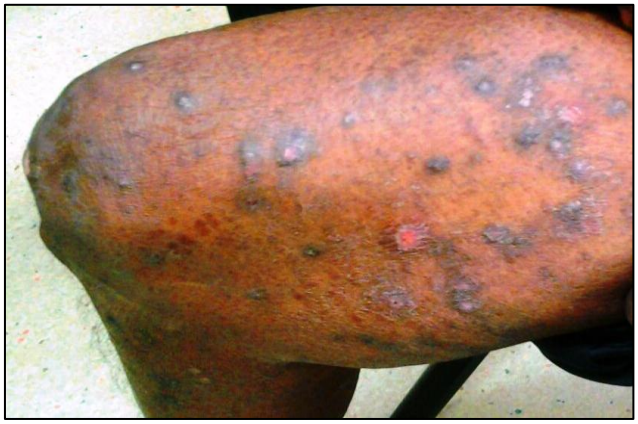

Figure 1a: Scaly and hyperpigmented papular lesions on the thigh

ISSN: 0975-8585

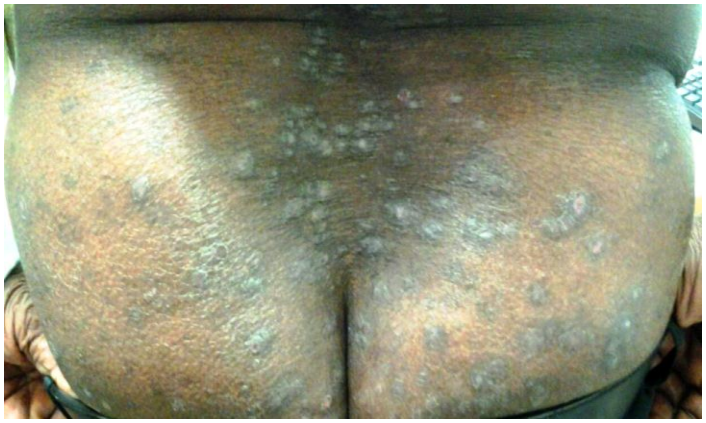

Figure 1b: Scaly and hyperpigmented papular lesions on lower back region

On follow-up examination, two months later, multiple excoriated papules and plaques were seen on the trunk and limbs. The patient mentioned that the lesions would appear as blisters that would itch and excoriate subsequently. However, on examination, bullous lesions were conspicuous by their absence. Scaly papules were present on the scalp. Whitish streaks were seen on the oral mucosa akin to Wickham's striae. The treatment was continued and skin biopsy was advised. Clinically a diagnosis of Lichen planus was thought of, with Prurigo nodularis and Papular eczema being the differentials. The patient, however, was not responding satisfactorily to Betamethasone valerate cream 0.1%, as evident by the generalized papules and excoriated lesions. A week later, skin biopsy was taken from the right thigh and the specimen was sent for histopathology examination and for direct immunofluorescence microscopy (with salt-split skin technique).

The following findings were recorded on skin biopsy:

- Presence of unilocular subepidermal blisters.
- Lumen with scanty neutrophils and rare eosinophils. There was sparse dermal eosinophilic infiltrate – 'cell poor'.
- Presence of few lymphocytes and monocytes.
- Mild pigmentary incontinence and perivascular lymphoplasmocytic infiltration seen.
- Linear homogenous deposition of Ig G and C3 along the basement membrane zone of the skin seen.
- No basal cell damage, basal vacuolar change or interphase dermatitis seen.
- No granuloma/ malignancy reported.

Histopathology and direct immunofluorescence examination (DIF) was suggestive of 'Bullous Pemphigoid' (cell poor type). The patient was prescribed oral prednisolone 15mg three times a day and clobetasol propionate for local application, to which he responded well and a remission was achieved. He had sustained remission and no recurrence of the lesions 3 months later at which point his prednisone was tapered off.

Besides absence of frank blisters, another interesting aspect of the reported case is the development oral mucosal lesions, which are reported in less than 15% of cases of BP. Thus, what appeared like a case of papular eczema and/ or lichen planus clinically, was confirmed as BP with the help of DIF. However, infants with BP show a preferential involvement of palmoplantar regions, oral and genital mucosae and face [3].

DISCUSSION

Diagnosis of BP is not always easy and straightforward. Diagnosis is based on a combination of clinical, histopathological and immunopathological features, particularly direct IF microscopy findings. However, immunopathological findings may remain negative, making the diagnosis suggestive, but not conclusive. Classification of patients carries utmost significance for the initiation of appropriate treatment and development of consistent reporting of outcomes [1].

French scientists [6, 7] have suggested that the diagnosis of BP can be made with high specificity and sensitivity in patients with linear IgG and/or C3 deposits along the dermoepidermal junction when three of four clinical criteria are present:

i. age >70 years
ii. absence of atrophic scars
iii. absence of mucosal involvement and
iv. absence of predominant bullous lesions on the neck and head.

This set of criteria seems sufficient to make the diagnosis of BP with a sensitivity of 90%, a specificity of 83% and a high positive-predictive value.

In this case, however, the criteria related to age and mucosal involvement was not met. This reinforces on the protean presentation of BP and the importance of immunopathological criteria, especially direct immunofluorescence in its diagnosis.

Immunofluorescence is a valuable auxiliary diagnostic tool for bullous pemphigoid and other autoimmune bullous diseases, as their clinical and histopathological findings may sometimes be inconclusive. Treatment for BP aims only to alleviate symptoms and shorten the duration of illness. An in-depth knowledge on the pathophysiology of BP can incite the development of new immunomodulatory specific target treatments.

CONCLUSION

Bullous pemphigoid may present clinically in an atypical fashion, which poses as a clinical diagnostic challenge. Immunopathological studies like direct immunofluorescence and ELISA are not only conclusive, but also help to determine the type of anti-hemidesmosome antibody involved. This case confirmed most of the characteristics reviewed in the literature and had an excellent response to conventional therapy, achieving remission within the usual time frame. Due to the varied presentation of bullous pemphigoid, this link can help providers make diagnostic decisions based on the immunopathological investigative armamentarium.

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