HYPERKERATOTIC BULLOUS PEMPHIGOID: A NEW CLINICAL VARIANT

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Introduction

Bullous pemphigoid (BP) is a rare chronic autoimmune blistering disease.¹ Classically, BP presents with a pruritic eruption, characterized by vesicles and bullae, sometimes associated with eczematous, urticarial plaques or infiltrated papules.¹ Lesions are often symmetrical and predominate on the flexural aspects of the proximal extremities.¹ Beside the classic clinical manifestations, several variants of BP have been described, including nodularis, papular, and seborrheic BP.²

IgG autoantibodies play a main role in the pathogenesis of BP, but IgE and IgA against BP180 and BP230 are also involved.^{2,3} IgG mainly recognize the non-collagenous 16A domain (NC16A) of BP180 and, secondarily, the NH2- and COOH-termini of the cytoplasmic BP230.³

Case series

Here we describe five patients presenting a peculiar clinical variant of BP, that we named *hyperkeratotic BP (HBP)* (**Figure 1**).

Five patients were admitted in our department during the period between December 2013 and January 2017. All BP patients showed (I) diffuse hyperkeratotic cutaneous lesions, (II) palmo-plantar keratoderma, and (III) high IgE levels. The clinical and immunological features of HBP patients are reported in Table 1 (**Table 1**). All patients complained of a pruritic eruption with diffuse hyperkeratotic cutaneous lesions, in some cases associated to vesicles and blisters (*case 1,2,5*) The hyperkeratotic cutaneous lesions were associated in *case 1* with urticarial plaques on the trunk, while in *case 2* with nodular and bullous lesions on the limbs; *case 3, 4 and 5* presented eczematous and infiltrated papules pityriasis rubra pilaris (PRP)-like. On the one hand, we observed a PRP-like palmo-plantar keratoderma (case 3,4,5); on the other hand, we observed an acanthosis nigricans-like palmo-plantar keratoderma (case 1,2). Three patients were started on a combined immunosuppressive therapy (case 1, 2 and 5), while case 4 was started only on corticosteroid therapy, because she developed later a B cell lymphoma. BP is considered a polymorphic disease, because of the protean clinical features. We described a subtype of BP, that we named HBP, according to the diagnostic criteria proposed by Cozzani et al.2

We found out that most of patients showed extreme high levels of IgE (>1000 KU/L) and we detected anti-BP180 IgG in four patients, confirming the leading pathological role of IgG also in this clinical BP variant. It has to be mentioned that in case 5 were performed two skin biopsies; one on abdomen, which included hyperkeratosis lesions, and one on perilesional bullous lesion of the leg. DIF examination showed linear IgG and C3 on the basal membrane zone of both biopsies that lead to confirm the diagnosis of BP for both cutaneous lesions.

Discussion

Keratinization is a continuous process of proliferation and differentiation of all keratinocytes cells. Alteration of the cell adhesion could induce an abnormal keratinization.⁴ We can speculate, as suggested by Hamada,⁴ that in these BP patients in the context of a genetic predisposition, circulating autoantibodies against hemi-desmosomal proteins could disrupt dermal-epidermal adhesion, leading to abnormal keratinization.

From the therapeutic point of view, all patients received multiple drugs, including corticosteroid, steroid-sparing agents, and biological drugs, indicating that the HBP, at least in some cases, represents a resistant disease that required multiple systemic treatments.

Conclusion

We described five patients that shown the criteria to made a diagnosis of BP, but whose clinical aspects have not been never described beforehand. We retain that it is possible to deal with a new subtype of BP, which we have called HBP. Therefore, in case of diffuse hyperkeratotic cutaneous lesions and palmo-plantar keratoderma it should be taken into account the diagnosis of HBP, even in the absence of frank blisters.

Figure 1: *Case 1:* clinical presentation characterized by diffuse hyperkeratosis with urticarial and bullous lesions on trunk and limbs with palmo-plantar keratoderma

CASE	SEX	AGE	CLINICAL PRESENTATION	ABSI	DIAGNOSIS OF BP	Eosinophilia (10 ³ /microl)	IgE levels (kU/L)	IgG BP180 ELISA (U/ml)	IgG BP230 ELISA (U/ml)	IgE BP180 ELISA	IgE BP230 ELISA	BP THERAPY
1	F	30	Diffuse hyperkeratosis with urticarial and bullous lesions with palmo-plantar keratoderma	28	Histology: detachment at the BMZ; DIF: linear C3 on the BMZ; IFI: IgG anti-BMZ on epidermal side of SSS	1.78; 16.1%	43.960	228	neg	neg	pos	Ccs, Aza, Cs, RIT, IFN
2	F	54	Pruritic nodular and bullous eruption with hyperkeratosis lesions on limbs associated to palmo-plantar keratoderma	23	Histology: detachment at the BMZ; DIF: linear C3 on the BMZ; IIF: neg	3.91; 27.3%	3420	51.1	neg	neg	neg	Ccs, Cs, Aci, Cyc, RIT
3	F	57	Diffuse hyperkeratosis PRP-like and thick yellow palmo-plantar keratoderma	42	Histology: detachment at the BMZ; DIF: linearIgM and C1q deposits along the BMZ; IIF: neg	NA	188	neg	neg	neg	neg	Ccs
4	F	35	Diffuse hyperkeratosis PRP like and palmo-plantar keratoderma	25	Histology: psoriasiform hyperplasia of epidermis with parakeratosis and perivascular lymphohistiocytic infiltrate in the dermis DIF: finely granular C3 on the BMZ; IIF: neg	NA	8750	80.3	neg	neg	neg	Ccs
5	M	77	Diffuse hyperkeratosis PRP-like with bullous lesions on abdomen associated with palmo-plantar keratoderma	41	Histology: detachment at the BMZ; DIF: linear IgG and C3 on BMZ; IIF: IgG anti-BMZ on epidermal side of SSS	1; 14.4%	4432	240	34.5	neg	pos	Aci, Ccs, Uste

Table 1: Clinical and immunological features of five hyperkeratotic bullous pemphigoid cases

M: male; F: female; neg: negative; DIF: direct immunofluorescence; IIF: indirect immunofluorescence; SSS: salt split skin; BMZ: basament membrane zone; Ccs: corticosteroid; Aza: azathioprine; Cs: cyclosporine; RIT: rituximab; IFN: interferon-alpha; Aci: acitretin; Cyc: cyclophosphamide; Uste: ustekinumab; NA: not available; ABSIS: Autoimmune Bullous Skin Disorder Intensity Score.

References

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