CASE ESSAY 2

44-Year-Old Man with a Bullous Skin Disorder

A 44-year-old man was referred because of a progressive bullous skin disease. He was well until 2 weeks ago when he developed herpes simplex on the upper lip. The patient was treated for several days with oral Acyclovir and after a couple of days developed erythematous and bullous rash on the buttocks, thighs, genitalia, palms and soles. There were no lesions on oral mucosa.

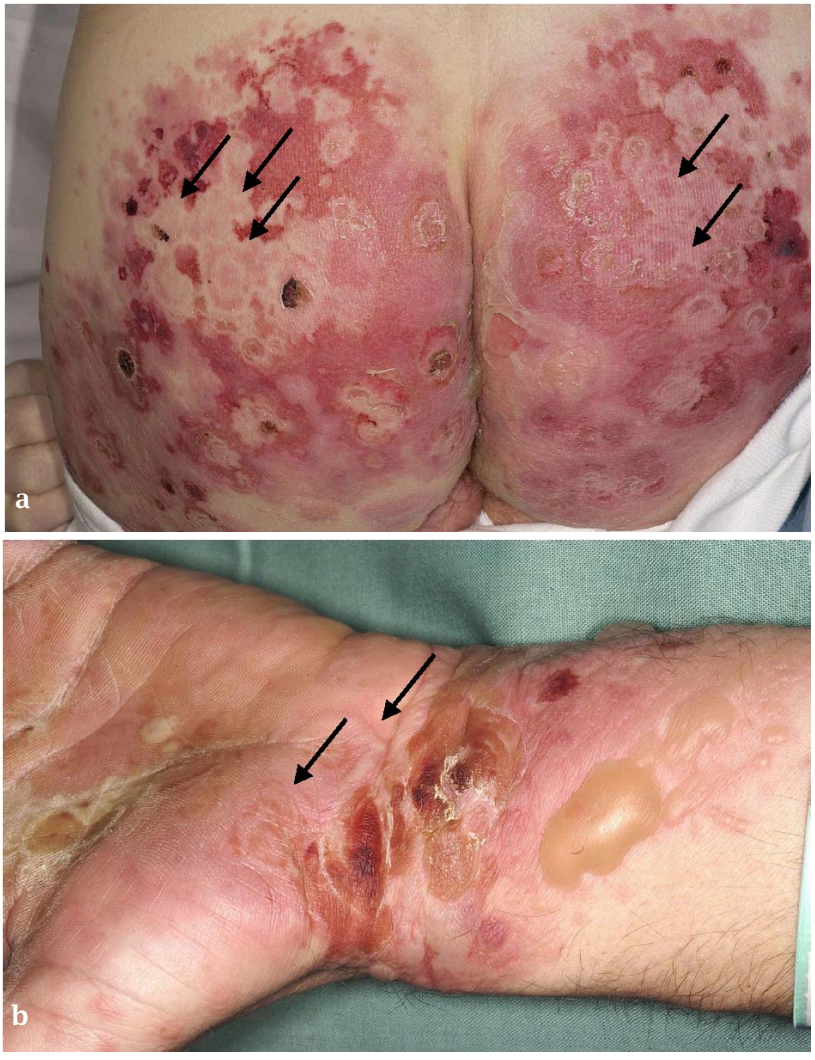

Fig. 1. Bullous and erythematous rash on the buttocks (a) and hands (b). Note annular lesions resembling target lesions of erythema multiforme (arrows).

The history of herpes labialis followed by a bullous skin disease with a predilection for hands and feet is typical for ERYTHEMA MULTIFORME BULLOSUM**. Erythema multiforme has three major clinical forms: the minor (Hebra) form, the major form and the Stevens-Johnson syndrome. The common denominator of the minor and major forms is the presence of typical target lesions consisting of two concentric erythematous rings and the fact that they can be precipitated by infections, most notably herpes simplex. The target lesions are typically localized acrally on the dorsal aspects of hands. Blistering is more common in the major form which usually is accompanied by mucosal lesions. Skin lesions in this patient comprised diffuse erythema, skin infiltration and annular lesions (Fig 1, arrows). Blisters were tense and present both in the areas of erythema and on clinically uninvolved skin. A diagnostic biopsy was taken.**

Routine histology showed a subepidermal blister with eosinophilic and neutrophilic inflammation. Electron microscopy showed a subepidermal split in the lamina lucida. Treatment with local and systemic steroids was initated but the disease progressed.

The histological findings do not support the diagnosis of erythema multiforme. Established lesions of erythema multiforme show lichenoid (interface) reaction pattern with apoptosis of the basal

keratinocytes. Extensive death of basal keratinocytes leads to microvesiculation which can coalesce into bullae. In the biopsy from this patient the basal keratinocytes were intact and the bullous reaction was caused by the split within the basal membrane. In view of this, one should think of an autoimmune subepidermal blistering disease, such as BULLOUS PEMPHIGOID (BP) or EPIDERMOLYSIS BULLOSA ACQUISITA (EBA). A biopsy for immunofluorescence should be obtained.

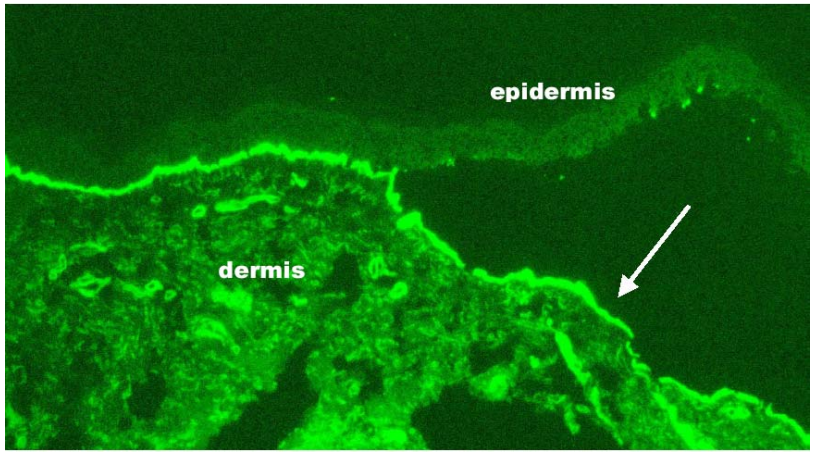

Fig. 2. Direct immunofluorescence diagnosis with anti-IgG antibodies on salt split skin. Note the presence of IgG depositions on the dermal side of the split (arrow).

Immunofluorescence showed the presence of linear deposits of IgG and C3 complement component along the basal membrane of involved and clinically normal skin.

Immunofluorescence findings heavily support the diagnosis of BP or EBA. Although basement membrane deposits of immunoglobulins and C3 can sometimes be seen in erythema multiforme, the presence of such unspecific deposits in the clinically uninvolved skin would be highly unusual. However, on second thought, the clinical picture is not typical for erythema multiforme either. The annular lesions on hands and buttocks are not classic target lesions and may simply represent sequel after blister disruption. The localization of the lesions is unspecific for erythema multiforme (palms instead of dorsal hands, buttock lesions). Atypical targetoid lesions may occur in Stevens-Johnson syndrome, but lack of mucosal involvement renders this diagnosis unlikely. The temporal relationship to herpes infection could be a coincidence. At this point I would abandon the diagnosis of erythema multiforme and pursue the concept of the autoimmune blistering disease. I would take a third biopsy for the immunofluorescence study on split skin.

A biopsy from the clinically uninvolved skin was obtained and incubated in 1M NaCl for 24 h to produce dermal-epidermal split. Direct immunofluorescence showed the presence of IgG deposits on the dermal side of the split (Fig. 2).

Split skin is a relatively easy investigational tool allowing for the differentiation between BP and EBA. In classic BP the deposits of IgG and C3 are localized on the epidermal site of the split (or sometimes on both epidermal and dermal). EBA is an autoimmune blistering disease associated with the presence of IgG against collagen VII. Since collagen VII remains on the dermal site of the split, the immunofluorescence produces the dermal floor-staining pattern. The diagnosis of EBA was made.

The patient was treated with a higher dose of prednisone (75 mg) in combination with 100 mg azathioprine daily. Unfortunately an attempt to taper prednisone resulted in a quick relapse of skin blistering. Remission was obtained after cyclosporine had been added (150 mg daily). At the time of writing, the patient is in full remission on the prednisone dose of 45 mg daily.

Table I. *Differential Diagnosis of the Autoimmune Subepidermal Blistering Diseases*

Entity and pathogenesis	Clinical appearance	Immunopathology
BULLOUS PEMPHIGOID IgG antibodies against antigens BP180 in lamina lucida and BP230 (plectin)	Most common auto-immune subepidermal blistering disease. Pruritic urticarial lesions and bullae both on erythematous base and clinically normal skin.	IgG and C3 deposits along the basal membrane and on the epidermal roof of the salt-split skin. Circulating IgG against BP180 or BP230 (Western blot) present in 80% cases.
ANTI-P200 PEMPHIGOID IgG antibodies against p200 protein in lower portion of lamina lucida	Similar to bullous pemphigoid.	IgG and C3 deposits along the basal membrane and on the dermal floor of the salt-split skin. Circulating IgG against p200 (Western blot).
ANTI-P105 PEMPHIGOID IgG antibodies against p105 protein in lower portion of lamina lucida	Severe bullous disease resembling toxic epidermal necrolysis	IgG deposits along the basal membrane and on the dermal floor of the salt-split skin. Circulating IgG against p105 (Western blot).
ANTI-P450 PEMPHIGOID IgG against epiplakin	Similar to bullous pemphigoid	IgG deposits along the basal membrane and on the epidermal roof of the salt-split skin. Circulating IgG against p405 (Western blot).
EPIDERMOLYSIS BULLOSA ACQUISITA IgG against collagen VII	Trauma-induced skin blisters with minimal inflammation	IgG and C3 deposits along the basal membrane and on the dermal floor of the salt-split skin. Circulating IgG against collagen VII (Western blot).
DERMATITIS HERPETIFORMIS target antigen unknown	Pruritic papulovesicles with predilection to elbows, knees and buttocks.	Granular IgA deposits in dermal papillae (most often) or granular lineas IgA deposition along the basement membrane.
LINEAR IGA DERMATOSIS IgA against BP180, BP230, type VII collagen and several other poorly characterized proteins (LABD97, LAD-1, p285)	Annular vesicular lesions and papulovesicles.	Crisp IgA and C3 deposits along the basal membrane.
BULLOUS SYSTEMIC LUPUS ERYTHEMATOSUS IgG against BP230, laminin 5, laminin 6, or type VII	Resembles bullous pem-phigoid or epidermoly-sis bullosa acquisita in the context of systemic lupus erythematosus	IgG and C3 deposits along the basement membrane and on the dermal floor of the salt-split skin
CICATRICIAL PEMPHIGOID IgG antibodies against several antigens: BP180, B4 integrin, laminin 5, laminin 6, uncein, collagen VII	Ulcerations and blisters on mucosal surfaces, healing with scarring.	Variable findings; most often IgG and/or deposits along the basal membrane and on the dermal floor of the salt-split skin. Circulating IgG present in only 30% cases.

Comment

EBA is a rare autoimmune subepidermal blistering disease caused by IgG antibodies directed against collagen VII. Onset of the disease is usually in mid-adult life but it can occur at any age including the childhood. Typically there is minimal or no skin inflammation and the bullae develop in areas subjected to minor trauma such as extensor surface of the limbs, palms and soles. This patient worked as a driver and it is conceivable that prolonged sitting aggravated the disease on the buttocks and posterior thighs. Histology shows subepidermal bullae with the split level at lamina lucida or lamina densa accompanied by minimal dermal inflammation. However, the microscopic and clinical findings are heterogenous and may resemble those of bullous pemphigoid, cicatricial pemphigoid Brunstig-Perry, or linear bullous IgA dermatosis (1). Other differential diagnoses are listed in Table I (for further review see Ref. 2). Direct immunofluorescence on the salt-split skin is the most often employed diagnostic method allowing differentiation from BP. Another method is immunoelectron microscopy showing the presence of IgG within or below lamina densa. It should be noted here that anti-p200 pemphigoid may present with clinical and immunopathologic features undistinguishable from EBA. This patient did not have circulating autoantibodies and

therefore further differentiation between EBA and anti-p200 pemfigoid could not be performed. However, I favour the diagnosis of EBA since the clinical course of anti-p200 pemphigoid is usually more favourable than seen in this case, and the disease responds readily to steroid monotherapy.

EBA is probably underdiagnosed because the salt-split immunofluorescence is not available in all dermatological centers. Treatment is difficult; the disease is often resistant to systemic steroid monotherapy and combination modalities including azathioprine, cyclosporine, dapsone, mycophenolate mofetil and intravenous immunoglobulins are required to control the disease.

Further reading

1. Hallel-Halevy D, Nadelman C, Chen M, Woodley DT. Epidermolysis bullosa acquisita: update and review. Clin Dermatol 2001: 19: 712–718.
2. Georgi M, Jainta S, Bröcker EB, Zillikens D. Autoantigene subepidermal Blasen bildender Autoimmundermatosen. Hautarzt 2001; 52: 1079–1089.

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