Epidermolysis bullosa acquisita: current diagnosis and therapy

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Abstract

Epidermolysis bullosa acquisita (EBA) is an acquired, autoimmune subepidermal blistering disease with an approximate prevalence of 0,2/million people. The hallmark of EBA is the presence of autoantibodies (mainly IgG class) to anchoring fibril collagen (type VII collagen) located at the dermal-epidermal junction. Clinically EBA is subdivided into the inflammatory and the non-inflammatory phenotypes, depending on the level of the cleavage in the basal membrane. A recent addition to the diagnostic techniques is the analysis of the serration pattern of the autoantibody deposits at the basal membrane in the direct immunofluorescence. EBA and the closely related bullous systemic lupus erythematosus are the only diseases presenting with the so-called u-serration pattern which distinguishes them from many other autoimmune subepidermal blistering diseases. We also discuss the recent advances in therapy, including the experience with Rituximab.

Clinical features

Epidermolysis bullosa acquisita (EBA) was described for a century ago by Ellliot.[1] It is a rare disease with an approximate prevalence of 0.2/million people.[2] EBA is an acquired, autoimmune cutaneous subepidermal blistering disease that primarily involves the skin, and sometimes mucous membranes. There is no racial or gender predilection. EBA often presents in the fourth to fifth decades of life. The hallmark of EBA is the presence of autoantibodies (mainly IgG class) to type VII collagen, a major component of anchoring fibrils at the dermal-epidermal junction. The disease occurs in approximately 5% of unselected patients with basement membrane zone antibodies.[3] The blister-inducing potential of autoantibodies to type VII collagen have been shown by demonstrating their capacity to trigger an Fcγ-dependent inflammation leading to split formation in cryosections of human skin.[4] Clinically EBA is subdivided into two clinical types: the inflammatory and the non-inflammatory phenotype.[5] Patients with the non-inflammatory form of EBA (the classical EBA type) have increased skin fragility with subse-quent formation of blisters or erosions on the trauma-prone areas of the skin, such as extensor surfaces of elbows, knees, ankles, and buttocks. Tense vesicles and bullae appear on non-inflamed skin or scarred skin. Nail dystrophy and scarring alopecia have been observed in some patients with the classical EBA. The inflammatory form of EBA can mimic almost all other chronic bullous diseases, and its clinical differentiation from bullous pemphigoid, mucous membrane pemphigoid and linear IgA bullous dermatosis may be difficult.[6] It presents with widespread, tense vesicles and bullae and is not localized to trauma-prone sites and generally heals with minimal scarring and milia formation. Progressive and recurrent disease in the mucosal tissues can result in irreversible complications similar to those seen in mucous membrane pemphigoid (MMP) including blindness and oesophageal strictures.[7] By electron microscopy, the cleavage plane can be seen within the lamina lucida or sub-lamina densa regions of the dermal-epidermal junction. If the cleavage is within the lamina lucida, it is associated with the presence of an inflammatory infiltrate rich in polymorphonuclear neutrophils.[8] The deeper level of split in the non-inflammatory EBA type may explain why it usually heals with significant scar and milia formation, which is only rarely observed in the inflammatory type (Table 1).

Diagnostic techniques

The first diagnostic criteria for EBA were established in the early 1970s by Roenigk and associates. They were i) spontaneous or trauma-induced blisters resembling hereditary dystrophic EB, ii) adult onset, iii) a negative family history for EB, and iv) the exclusion of all other bullous diseases.[17] However, since then at least 33 verified cases of childhood EBA have been reported in the literature, mainly of the inflammatory subtype.[18] In addition a diagnosis of EBA cannot be done reliably solely by clinical findings, because of the variable clinical and histological presentations.

Immunofluorescence techniques remains the cornerstone of the diagnosis of EBA and have increasingly replaced the immunoelectron microscopy (IEM) as the *gold standard*.[19] Other investigative diagnostic techniques are immunoblotting, ELISA, and immunoprecipitation. Direct Immunofluorescence (DIF) on perilesional skin demonstrates linear immune deposits of immunoreactants, mainly IgG, at the basement membrane zone. However deposits of IgA, IgM, C3, C4, or properdin may be detected as well. In EBA depositions of IgG in the absence of C3 is seen more commonly than in BP. Furthermore, deposits of multiple conjugates (including IgG, IgA, IgM, C3, C4, or properdin) are seen more frequently in the setting of EBA.[7] Indirect immunofluorescence (IIF) can detect the presence of circulating IgG autoantibodies, directed against type VII collagen in the basement membrane, it usually detects the IgG autoantibodies that binds to the dermal floor on salt split skin. Salt split skin substrate can be used to distinguish EBA and bullous pemphigoid (BP), because IgG autoantibodies from patients with bullous pemphigoid bind to the epidermal roof (upper part) of salt-split skin. If the antibody labels the dermal side of the separation, the patient usually has either EBA or bullous SLE (there are, however, other diseases with dermal staining; anti-epiligrin (lamina-5), Cicatricial pemphigoid, *Chan's disease*, *Zilliken's disease* and *Ghohestani's disease*).[19]

A breakthrough in the diagnostics was the observation of specific serration patterns in the autoantibody deposits at the basement membrane in direct immunofluorescence. Besides a true linear staining pattern, two DIF immunodeposition patterns have been described i) a u-serrated staining pattern is typical of EBA, and ii) an n-serrated staining pattern in other subepidermal immunobullous diseases.[9] The binding of autoantibodies in EBA to type VII collagen, can ultrastructurally be seen as upstanding arms between the rootlets of the basal keratinocytes, resulting in u shapes. Consequently these two distinct patterns can be applied in order to differentiate EBA from other pemphigoid variants by DIF only. The type of serration in the case of IgA and IgG is similar, however, in the case of IgA it is more easily recognized due to better fluorescence image contrast. Diseases such as IgA-mediated EBA and inflammatory EBA may look like BP, however, using the serration patterns algorithm, patients with EBA who otherwise would have been erroneously diagnosed can be detected.

Immunoelectron microscopy (IEM) documents the localization of the immune deposits within the dermal-epidermal junction of the skin of EBA patients. By direct immunoelec-

Table 1. Comparison of the clinical and immunopathological features of subepidermal blistering diseases.

Subepidermal immunobullous disease	Clinical Characteristic features	DIF	Binding on salt split skin	Serration pattern
Bullous pemphigoid (BP)	Elderly, most common autoimmune blistering disease. Tense blisters on inflamed or non inflamed skin. Pruritus common, variable severity. More common in patients with multiple sclerosis. Predilection sites: the inner or anterior thighs, groins, flexor surfaces of the upper extremities and lower abdomen. Oral mucosal lesions are rare.	IgG and C3 or C3 alone (± weaker staining IgM, IgA) at the dermal-epidermal junction.	Epidermal (few dermal)	n-serrated[9]
Pemphigoid gestationis	During pregnancy and/or puerperium; urticarial plaques and/or tense blisters. Pruritus typically severe. Predilection sites: umbilical and periumbilical regions; trunk and extremities.	Linear deposition of C3 ± IgG at the dermal-epidermal junction.	Epidermal	As BP; n-serrated
Lichen planus pemphigoides	Usually benign, tense blisters and lesions of lichen planus (usually persistent) on top of lichen planus lesions or on clinically normal skin. Predilection sites: the extremities, trunk and oral mucosa.	Linear deposits of IgG at the dermal-epidermal junction.	Epidermal	Unknown
Mucous membrane pemphigoid	Elderly (female) patients. Tense blisters and erosions with scar formation. Predilection sites: mucosa of the mouth, eyes, nose, larynx, eosohagus or anogenital regions.	In anti-BP180 MMP and antilamin 332 MMP10: linear IgG, ±C3 occasionally IgA. In ocular MMP:[11] linear IgA ±IgG.	Epidermal in anti-BP 180 MMP and ocular MMP Dermal in antilamin 332 MMP	n-serrated[9]
Dermatitis herpetiformis	Adult patients. Erythematous papules, urticarial plaques, papulovesicles, vesicles and rarely bullae, isolated or in herpetiform grouping often healing with scar formation. Intensely pruritic. Predilection sites: symmetrically distributed lesions on extensor surface of the extremities, scalp, nape, shoulders, sacral region and buttocks.	Granular papillary and basement membrane IgA.	Negative	Irrelevant
Linear IgA disease	Papulovesicular eruption *in cluster of jewels* configuration. Pruritic (ranging from mild to severe). Predilection sites: trunk, extremitites, the face, abdomen and perineum. Frequent mucous membrane involvement (may induce severe complications).	Linear IgA (rarerly granular) at the dermal-epidermal junction.	Epidermal (few dermal)	n-serrated[9]
Linear IgA/IgG bullous dermatosis[12]	Resemble the lesions of BP, annular vesicobullous lesions with frequent involvement of the oral mucosa. Predilection sites: no specific	Linear IgA and IgG ± C3 at the dermal-epidermal junction.	Epidermal (few dermal or both epidermal and dermal)	Probably n-serrated
Anti-p450-pemphigoid[13]	Only one case in literature, Fujiwara *et al*[14]	Only one case in literature, Fujiwara *et al.*[14]	Epidermal[13]	Unknown
Anti-p200 pemphigoid[32]	Often resembles BP, could resemble dermatitis herpetiformis, linear IgA disease or EBA. Could involve mucous membranes. Often coexisting psoriasis. (rapid response to treatment)	Linear IgG and C3 at the dermal-epidermal junction.	Dermal	n-serrated[9]
Epidermolysis bullosa acquisita	*Classical EBA:* skin fragility, trauma- induced blisters and erosions. Predilection sites: extensor surfaces of the extremities. ± mucous membrane lesion. *Inflammatory EBA:* widespread eruptions of tense blisters on erythematous or normal appearing skin. Predilection sites: usually on flexural and/or intertriginous areas. ± mucous membrane lesions	Linear IgG (± IgA, IgM), C3 at the dermal-epidermal junction.	Dermal	u-serrated[9]
Bullous SLE	Mainly adult patients. Tense blisters on normal or erythematous skin, eruptions usually in a herpetiform arrangement in patients with SLE. Pruritus may be severe. Predilection sites: trunk and flexural surfaces. Frequently oral lesions.	Linear or granular depositions of IgG (± IgM, IgA, C3) at the dermal-epidermal junction.	Dermal (rarely epidermal or combined binding)	u-serrated[9]
Anti-p105-pemphigoid[16]	Bullae and erosions on mucous membrane and skin, resembling toxic epidermal necrolysis or pemphigus vulgaris[13]	Linear IgG and C3 deposition at the skin basement membrane zone[13]	Dermal[13]	Unknown

tron microscopy the ultrastructural localization of in vivo-bound IgG autoantibodies at the basement membrane is documented. With indirect immunoelectron microscopy the binding site of circulating IgG autoantibodies at the basement membrane is detected. IEM detects IgG autoantibodies at the lamina densa and sublamina densa areas of skin basement membrane. Bullous pemphigoid IgG autoantibodies, on the contrary, are localized to the hemidesmosome and upper lamina lucida.[20]

Immunoblotting represents a sensitive detection method for EBA.[21] EBA sera will bind to a 290-KDa band in Western blots of human skin basement membrane proteins containing type VII collagen, whereas sera from all other primary blistering diseases will not. This band corresponds to a single alpha chain of the type VII collagen homotrimer molecule.[22] Western blotting differentiates between anti-p200 pemphigoid and EBA. To distinguish between the latter two disorders, patients' sera have to be subjected to Western blotting of extract from human dermis and then react with 200 and 290 kDa proteins in antip-200 pemphigoid and EBA, respectively.[2]

ELISA (Enzyme-linked immunosorbent assay) documents the specific basement membrane antigen recognized by the patient's IgG circulating autoantibodies. The ELISA method identifies non-denaturated, nonreduced proteins and is more sensitive than immunoblotting, which only detects denatured, reduced proteins.[7]

Treatment

Compared with other autoimmune blistering diseases, EBA has a decreased responsiveness to therapy. Inflammatory EBA, EBA presenting in children and IgA-EBA, respond more favourably to the conventional treatment approach of high-dose corticosteroids and corticosteroid sparing agents. In most cases of IgA-EBA, the skin lesions respond to therapy with dapsone alone.

Dapsone and low-dose prednisone are usually effective in treating childhood EBA.[18] However, high doses of corticosteroids are not recommended as maintenance therapies as the adverse effects of corticosteroids are both time and dose dependent.

Non-inflammatory (classical) EBA is often refractory to systemic corticosteroids, azathioprine, methotrexate, and cyclophosphamide.[23] Therapeutic options that have proven effective in retrospective observations include extracorporeal photochemotherapy (ECP), i.v. immunoglobulin (IVIG), and Rituximab.

The treatment of EBA patients with IVIG has shown encouraging results. In one retrospective analysis two patients with severe EBA were treated with monthly cycles of IVIG. One of the patients had a complete response, defined as absence of lesions for more than 4 weeks without any treatment. The other patient responded to the treatment, however, due to metastatic lung cancer the treatment was discontinued.[24] Another case describes a patient treated with 6 cycles of IVIG at a dose of 400 mg/kg per day for 5 consecutive days (repeating the cycle every 4 weeks). After the second cycle, most of the erosions had healed and marked remission was observed during the 6-month follow-up period. The patient did not experience any negative side effects.[25]

Patients that have had unsatisfactory response to steroid, immunosuppressive agents and IVIG may benefit from the therapy with rituximab. This monoclonal antibody reacting against CD20 depletes mature, autoreactive B-cells. Of the reported cases of EBA patients treated with rituximab, either complete remission or very good partial remissions have been reported. In one retrospective analysis the patient, a 58-year old woman, had to be hospitalized due to the severity of EBA. She had extensive cutaneous and oral ulceration, cellulitis and a deep vein thrombosis secondary to immobility.

After four rituximab infusions at a dose of 375 mg m^{-2}, she experienced complete remission.[26] Another patient, a 54-year-old woman experienced a partial remission within a month after the onset of rituximab. After twelve rituximab infusions at a dose of 375 mg m^{-2}, she experienced almost complete cutaneous clearance with improved oral intake and mobility.[27] Rituximab can safely be combined with high-dose IVIG, which may exert a synergistic effect and simultaneously protect against serious infection-related adverse events.[28,29]

Long-term ECP has been reported to induce remission in three patients with drug resistant, aggressive cases of EBA.[30] ECP is based on separation of a leukocyte/lymphocyte-enriched cell fraction from the peripheral blood, extracorporeal treatment of the cells with 8-MOP/UVA, and subsequent reinfusion of the cells in the patient. The main effects in EBA seem to consist in inhibition of pathogenetic autoantibody production by B lymphocytes and generation of regulatory T cells.

When treating a patient with EBA, it is important to be aware of coexisting systemic diseases that might influence the choice of therapy.

Among the systemic diseases reported in association with EBA, are malignancies and autoimmune diseases.[23] Inflammatory bowel disease (IBD) is one of the more common systemic illnesses associated with EBA; 25% of EBA patients have IBD.[31]

There are a few cases of EBA patients with coexisting psoriasis.[32] Ultraviolet radiation is not a treatment option in this case as it has been demonstrated that it can induce blistering in patients with EBA.[33]

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