Epidermolysis bullosa acquisita

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Introduction and AIMS

Short Definition in Layman Terms

Epidermolysis bullosa acquisita (EBA) means acquired, not inherited, bullous loosening of the skin. The autoimmune disease is caused by antibodies against a component of the skin that attaches the upper part to the bottom part. The original cause of this autoimmune disease is unknown. Patients with EBA complain of skin blisters after minor bumping or of red spots that may appear spontaneously. There is no cure, but the disease can be kept quit with medicine that alter immunity.

Learning Objectives
After reading this chapter you know the clinical subtypes of EBA, understand the pathogenesis, and are aware how to make the diagnosis. You also can make a treatment proposition that fits with the disease subtype and the patient needs.

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Case Study: Part 1
A 36-year-old woman noticed skin blisters on her feet after jogging. Later she also developed spontaneously blisters on the shoulders and abdomen. The lesions were painful and itchy. At physical examination tense blisters were seen on normal skin on both sites of the hands and feet, and on the extensor surface of the elbows.

Didactical Questions: Cross Section of Questions to Prime the Readers Interest

Why is EBA included in the pemphigoid spectrum? What determines the clinical subtype? What is the blister level considering that the immune deposits are so low in the basement membrane zone? How do you make the diagnosis? And what options do we have for this treatment refractory disease?

Facts and Figures

Definitions and Classification

Epidermolysis bullosa acquisita (EBA) is a subepidermal autoimmune blistering disease (sAIBD) characterized by autoreactivity to type

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VII collagen located in the anchoring fibrils in the epidermal basement membrane zone (EBMZ) [1]. EBA is a clinically heterogeneous disease that may be characterized by either a mechanobullous or an inflammatory phenotype.

Epidemiology

The estimated EBA annual incidence in central European countries is about 0.25 new cases/million/year. The estimated frequency of EBA among patients with pemphigoid diseases is 5.5%. EBA may occur at any age, and occurs in both children and adults. A gender preference of females exists of 2.2. The ratio of the mechanobullous and inflammatory phenotypes of EBA is 1:2 [2].

Pathogenesis

The main autoantibody isotype in EBA is IgG, predominantly IgG1 and IgG4 subclass, but deposits of IgA, and complement may also be found along the epidermal BMZ. Most EBA patients' sera react with epitopes located within the non-collagenous (NC)-1 domain of human type VII collagen (Fig. 16.1). Binding of patient autoantibodies to the collagenous or the NC2 domain is rarely observed. No correlation is detected between antibody specificity to type VII collagen subdomains and clinical phenotype (mechanobullous/inflammatory).

Split formation is dependent on activation of neutrophils through the Fc domain of immunoglobulin. Split formation occurs in most cases at the level of the lamina lucida, and not at the level of the anchoring fibrils in the sublamina densa zone. These split formations within the lamina lucida most likely represent the intra-lamina lucida-separating effects of leukocyte-derived proteolytic enzymes, when those cells are chemoattracted to the dermo-epidermal junction by bound immunoreactants.

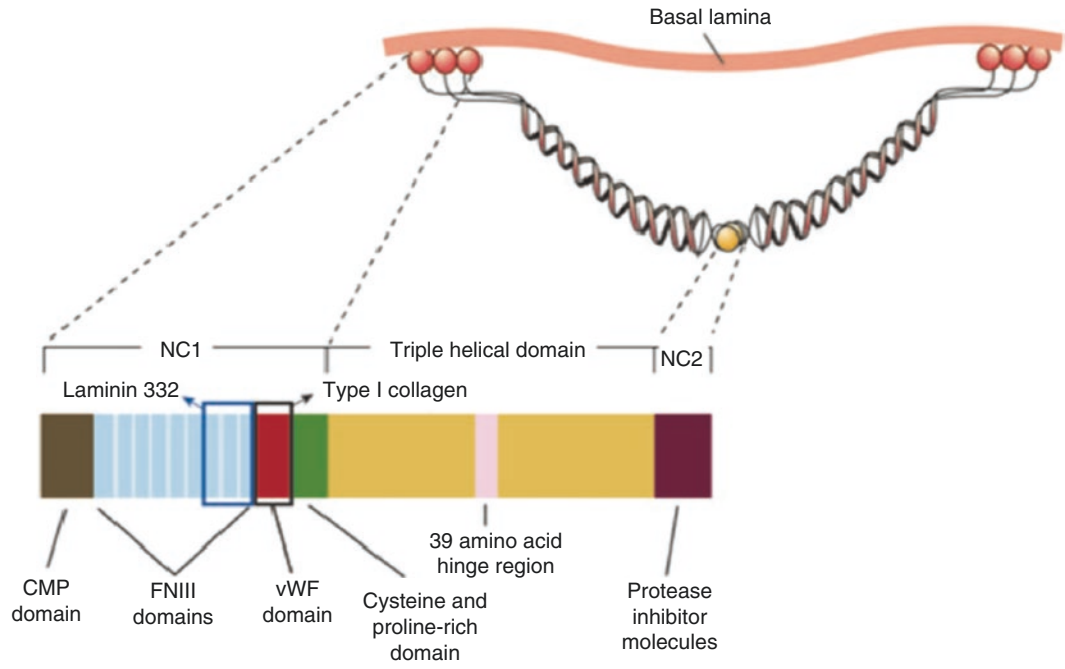

Fig. 16.1 Diagram of type VII collagen shows the immunodominant NC-1 domain. *N* aminoterminal, *C* carboxyterminal, *CMP* cartilage matrix protein, *FNIII* fibronectine-type III-like repeats, *VWFA* a domain of von Willebrand factor, *NC-1* non-collagenous aminoterminal domain, *NC-2* non-collagenous carboxy-terminal domain

Diagnosis Paths

History and Physical Examination

The classic mechanobullous phenotype mimics hereditary dystrophic epidermolysis bullosa, while mild cases may look like acral blistering of porphyria cutanea tarda that heal with atrophic scarring, milia and hypo- or hyperpigmentation (Fig. 16.2). Scalp, neck and shoulders involvement occurs in 20% and leads to extensive non-healing erosions with scarring, similar to clinical features of Brunsting-Perry pemphigoid (Fig. 16.3).

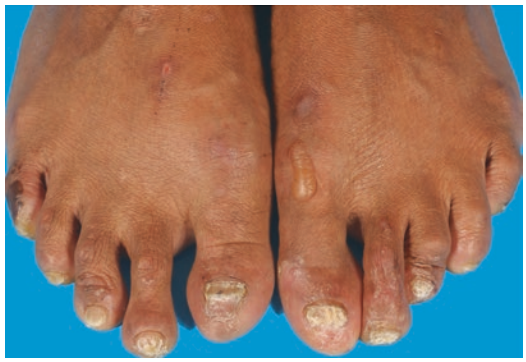

Fig. 16.2 Mechanobullous EBA in a young female showing bullae and crusts, and nail dystrophy on the feet

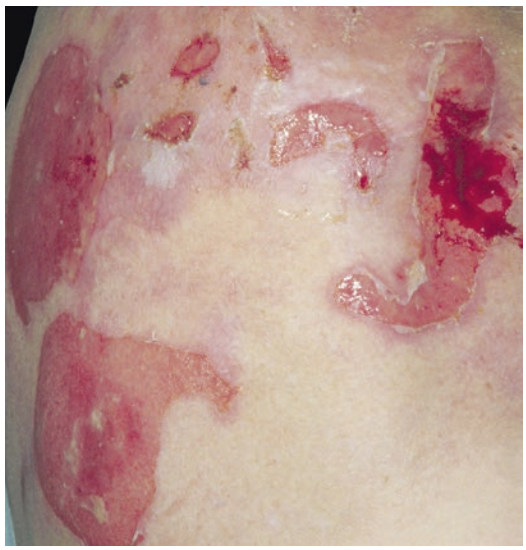

Fig. 16.3 Mechanobullous EBA similar to Brunsting-Perry pemphigoid in a female with scarring lesions affecting the neck and scalp

The inflammatory phenotype presents with widespread vesicles and bullae involving intertriginous and flexural areas, that heal with no or few milia without scarring (Fig. 16.4). This phenotype may appear similar to bullous pemphigoid or non-bullous pemphigoid, and a presentation with predominantly mucosal involvement similar to of mucous membrane pemphigoid with scarring on the mucosal surfaces (Fig. 16.5). EBA is associated with SLE and inflammatory bowel disease.

General Diagnostics

Transition from mechanobullous to inflammatory phenotype or vice versa is sometimes found. In a

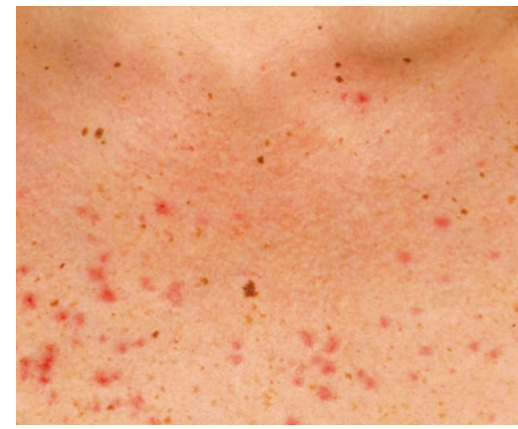

Fig. 16.4 Inflammatory EBA in a 37-y-old female showing lenticular erythematous papules with erosive top on the chest

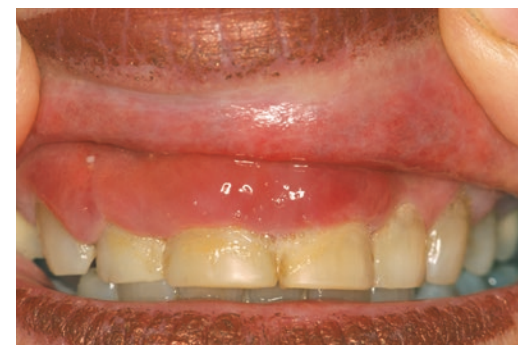

Fig. 16.5 Mucous membrane pemphigoid with antibodies against type VII collagen in a female with hypertrophic gingiva

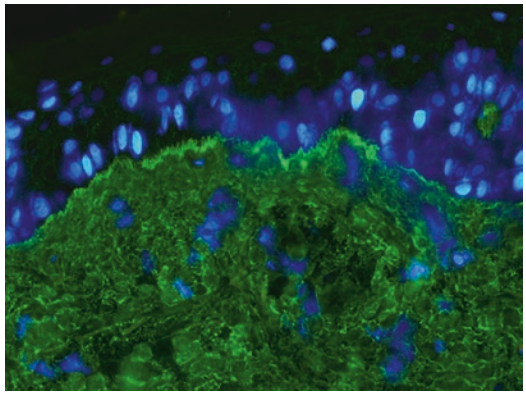

Fig. 16.6 U-serrated linear immunodeposition (IgG) along the EBMZ diagnostic for EBA or BSLE

minority of patients a temporary flare of widespread inflammatory bullae may occur in the mechanobullous phenotype during an exacerbartion. In contrast, the development of extensive milia and scarring is not observed in pathients with the inflammatory phenotype.

Specific Diagnostics

Diagnosis of EBA can be confirmed using DIF on a perilesional skin biopsy and serration pattern analysis, revealing linear u-serrated immunodepositions of IgG and/or IgA along the epidermal BMZ (Fig. 16.6) [3, 4]. Serration pattern analysis is explained in Chap. 4 Direct Immunofluorescence Microscopy. Only in approximately 50% of patients with EBA circulating autoantibodies can be detected, therefore DIF is essential for diagnosis of EBA. In serological negative cases direct immuno-electron microscopy, or DIF on sodium chloride-separated skin biopsy might reveal the diagnosis, but at risk of damaging the biopsy specimen [5]. Indirect immunofluorescence microscopy (IIF) performed on 1 M NaCl-split skin (SSS) substrate shows binding of antibodies to the dermal site (floor) of the blister, while immunoblot analysis may reveal immunoglobulin binding to the 290 kDa antigen. Autoantibody detection by type VII ELISA has a rather low sensitivity of 45%. Combining IIF SSS and ELISA reaches a sensitivity of 50% [6]. Sophisticated serological methods may aid in diagnosis of EBA, such as IIF on skin deficient of type VII collagen of patients with hereditary dystrophic epidermolysis bullosa.

Case Study: Part 2

Skin biopsy for direct IF revealed linear depositions of IgG 4+, IgA 3+, and C3c 1+ in a u-serrated pattern along the EBMZ. Examination of the serum by indirect IF was positive for IgG 2+ and IgA 1+ in the floor of salt-split skin. IIF on knockout skin was negative on type VII collagen deficient skin, whereas positive on laminin-332 deficient skin. The type VII collagen ELISA index of IgG was 137 (positive). A diagnosis was made of epidermolysis bullosa acquisita, mechanobullous type.

Treatment Tricks

Initial Treatment and Therapeutic Ladder

EBA is a chronic disease that is often refractory to many treatment modalities. The 1st line therapy for EBA is a combination of low dose corticosteroids, colchicine or dapsone. Colchicine is used at a dose of 0.5–1 mg/day and has a low incidence of serious side-effects. Dapsone can be prescribed at a dose of 25 mg/day that is gradually increased to 100 mg/day. Treatment with oral corticosteroid follows the recommendations for bullous pemphigoid. Other adjuvant immunosuppressive drugs may be considered; such as mycophenolate mofetil, azathioprine, methotrexate, and cyclophosphamide. In refractory cases of mechanobullous EBA intravenous immunoglobulin (IVIG) or rituximab treatment might be considered.

Follow-Up and Tapering

The median time to remission of patients with EBA is estimated 9 months. The long-term prognoses of patients with EBA has proven excellent, but continuous low-dose of immunosuppressive drugs can be necessary.

Case Study: Part 3
First line therapy with prednisolone 30 mg and azathioprine 150 mg was insufficient. Subsequently, she was treated with human intravenous immunoglobulin 2 g/kg/month for 1 year. The blister frequency reduced. A maintenance therapy consisted of prednisolone 7.5 mg and azathioprine 150 mg for several years.

Review Questions

1. The most frequent clinical phenotype of EBA is
   (a) Mechanobullous
   (b) Inflammatory
   (c) a and b are equally frequent
2. Which disease or syndrome is associated with EBA?
   (a) Atopic syndrome
   (b) Neoplasia
   (c) Inflammatory bowel disease
3. In which domain are the immunodominant epitopes of type VII collagen located?
   (a) NC1 domain
   (b) Collagenous domain
   (c) NC2 domain
4. What is the most essential routine diagnostic test for EBA?
   (a) Direct immune-electron microscopy
   (b) Type VII collagen ELISA
   (c) Direct immunofluorescence with u-serrated pattern
   (d) Histopathology
5. Treatment response of EBA compared to bullous pemphigoid is
   (a) Similar
   (b) Often more treatment refractory
   (c) More favourable

Answers

1. b
2. c
3. a
4. c
5. b

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