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Acquired Epidermolysis Bullosa and Linear Immunoglobulin A Bullous Dermatoses

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Abstract

Acquired epidermolysis bullosa is a rare subepidermal bullous disease characterized by autoantibodies to type VII collagen, the major component of anchoring fibrils. Although the exact pathophysiologic mechanism remains unclear, reduction or perturbation of the anchoring fibrils results subepidermal blister formation and clinical features such as skin fragility, blisters, erosions, scars, milia and nail loss. Acquired epidermolysis bullosa includes various clinical manifestations resembling genetic epidermolysis bullosa, bullous pemphigoid, cicatricial pemphigoid, Brunsting-Perry pemphigoid and linear immunoglobulin A bullous dermatosis. Numerous treatment options are available but patients are often refractory to treatment. Linear immunoglobulin A bullous dermatosis is another subepidermal bullous disease characterized by the accumulation of IgA antibodies in lamina densa or sublamina densa region of the basement membrane and neutrophil-rich infiltrates in histopathology. It can be seen both in children and adults. The form seen in children usually begins under the age of 5 and it is called chronic bullous disease of childhood. The classical presentation is annular/polycyclic plaques and papules with blistering on perioral and perineal regions, giving a “cluster of jewels” appearance. The adult form is often seen after the fourth decade and clinical features are similar to those of dermatitis herpetiformis, bullous pemphigoid or cicatricial pemphigoid.

Keywords: acquired epidermolysis bullosa, blisters, linear Ig A bullous dermatosis, subepidermal bullous diseases, linear IgA disease, chronic bullous dermatosis of childhood

1. Acquired epidermolysis bullosa

1.1. Introduction

Acquired epidermolysis bullosa (AEB) is a chronic autoimmune subepidermal blistering disease characterized by autoantibodies to type VII collagen (C7), which is the main component of anchoring fibrils (AFs) [1, 2]. AEB patients have both tissue bound and circulating immunoglobulin (Ig)G autoantibodies targeting C7 [3]. AFs participate in attachment of epidermis and its underlying basement membrane zone (BMZ) to the dermis. It is thought that destruction of AFs due to autoantibodies targeting C7 results in a clinical phenotype of skin fragility, blisters, erosions, scars, milia and nail loss resembling genetic dystrophic epidermolysis bullosa [4]. Pathogenicity of these anti-C7 IgG antibodies is proved by demonstrating AEB-like blistering disease development in immunocompetent mice when human AEB antibodies were injected to them [5]. So, AEB results from an acquired autoimmune mechanism by which AFs can be compromised rather than by a gene defect as in hereditary dystrophic forms of epidermolysis bullosa (EB) [6].

AEB includes various clinical manifestations resembling dystrophic EB, bullous pemphigoid (BP), cicatricial pemphigoid (CP), Brunsting-Perry pemphigoid and linear immunoglobulin A bullous dermatosis (LABD) [7]. The diagnosis of AEB is often challenging because of these variety of clinical presentations. Evaluating patients only on the basis of clinical presentation and routine lesional histology is generally inadequate to distinguish AEB from other autoimmune subepidermal bullous diseases. Ancillary tests such as immunofluorescence, salt-split skin immunofluorescence (SSSI), transmission electron microscopy (TEM), immune electron microscopy (IEM), Western blot analysis, enzyme linked immunosorbent assay (ELISA) and fluorescent overlay antigen mapping (FOAM) are often necessary to confirm the diagnosis [8]. AEB is a chronic disease and often refractory to treatment but there have been developments in newer treatment modalities that have achieved some therapeutic success [9].

1.2. Historical aspects

AEB was initially described by G.T. Elliott in 1895 in two patients with acquired bullous disease reminiscent of EB who had no affected family members [10]. The term of “epidermolysis bullosa acquisita” was first coined by Kablitz in 1904 [11]. AEB was placed in the category of epidermolysis bullosa approximately 100 years ago because physicians were stuck by the similarity of clinical lesions seen in AEB patients and those seen in patients with hereditary dystrophic forms of EB [12]. In 1971, Roenigk et al. reviewed the AEB world literature and suggested the first diagnostic criteria for AEB: (1) spontaneous or trauma-induced blisters resembling hereditary dystrophic EB, (2) an adult onset of the disease, (3) a negative personal or family history for blistering disorder and (4) the exclusion of all other bullous diseases [13]. In 1980s, it was shown that patients with AEB had linear IgG deposits at their dermoepidermal junction (DEJ) detected by direct immunofluorescence. By IEM, it was demonstrated that the IgG immune deposits in AEB were localized below the lamina densa differently from BP [3, 14]. After that, in 1984, Woodley et al. identified 290-kDa and 145-kDa proteins

as the target antigen of AEB using serum samples from nine patients as a source of antibodies and concluded that AEB is a specific disease that is different from other primary bullous diseases [1]. This 290-kDa protein was later understood to be C7 [15]. A growing number of case reports about clinical presentations that are reminiscent of inflammatory BP, CP and Brunsting-Perry pemphigoid had reported in time [16–18].

1.3. Epidemiology and etiology

AEB is known as one of the rarest autoimmune blistering diseases with a incidence of approximately 0.17–0.5 per million people, per year and a prevalence of 2.84/million inhabitants [19–21]. The disease occurs at all ages but an epidemiological study of 30 Korean patients with AEB demonstrated the average age of onset of disease to be 44 years [22]. Children can also be affected [23]. No gender predisposition is known [21, 22]. AEB was found significantly more frequent in black patients in France. In the same study, there was a significant human leucocyte antigen (HLA)-DRB1*15:03 association with black patients from sub-Saharan Africa, suggesting a genetic predisposition to AEB in black patients of African origin [24].

The etiology of AEB is still unknown, but because the disease features IgG autoantibodies directed against C7, it is hypothesized that AEB may have an autoimmune pathogenesis [1, 2]. AEB is genetically associated with HLA-DR2; that is, HLA-DRB1*15 in black patients and HLA-DRB1*13 in Koreans [24–26]. HLA-DR2 phenotype has already been associated with hyperimmunity, which suggests an autoimmune etiology for AEB [25]. UV-radiation, vancomycin and contact allergy to metals have been reported as triggering factors of AEB in the literature [27, 28].

1.4. Pathophysiology

AEB is characterized by IgG autoantibodies directly attacking C7 within AFs [1, 2]. Although the precise role of autoantibodies against C7 in the pathogenesis of AEB is unclear, some clinical evidences support pathogenic role of antibodies to C7 in AEB. Blister formation in neonate of an AEB mother suggests that autoantibodies transferring from mother play a pathogenic role in inducing neonatal AEB [29].

Exact pathophysiological mechanism is unclear but it is very likely that AFs are essential for adherence of the epidermal layer of skin to the dermal layer. Because, the patients who are born with a defect in the gene that encodes for C7 exhibit skin fragility and skin blisters just like AEB patients due to the paucity of normal AFs [30].

AFs are specialized attachment complexes localized to the epithelium-mesenchyme interface in several tissues. AFs extend from the lower portion of dermoepidermal basement membrane to the underlying papillary dermis. They attach at both ends to the lamina densa, allowing entrapment of interstitial collagen fibers into U-shaped structures [31]. Ultrastructural studies of AEB skin have demonstrated a paucity of AFs [3, 14].

C7 is composed of three identical polypeptide alpha chains, coiled around each other to form triple helix configuration. Each alpha chain has 145-kDa central collagenous domain, characterized

by repeating Gly-X-Y amino acid sequences and a 39-amino acid non collagenous hinge region. The central domain is flanked by a large 145-kDa amino-terminal noncollagenous domain (NC1) and a smaller 34-kDa carboxyl-terminal noncollagenous domain (NC2) [32].

The amino-terminal (NC1) domain is approximately 145 kDa in size and consists of submodules with homology to adhesive proteins. NC1 includes a segment with homology to cartilage matrix protein (CMP), nine consecutive fibronectin type III-like repeats (FNIII), a segment with homology to the A domain of von Willebrand factor (VWF) and a short cysteine and proline-rich region [33, 34]. At the other end of the alpha chain, the carboxyl terminus, there is a much smaller non-collagenous globular domain called NC2, which is only 34 kDa [32]. The NC2 domain has a similar structure to the Kunitz protease inhibitor molecule [35].

Within the extracellular space, two C7 molecules align into antiparallel, tail-to-tail dimers. The carboxyl-terminal domains overlap between two C7 molecules, and the amino terminal domains present at the both ends of the molecule. Assembly of two C7 molecules is accompanied by proteolytic removal of a portion of the carboxy-terminal ends of both C7 molecules and stabilization by intermolecular disulfide bonding. Then, dimers aggregate laterally to form AFs, which are seen as semicircular loops in electron microscopy [36, 37].

NC1 interactions with several structural molecules of the BMZ such as type IV collagen, laminin-332, fibronectin and type I dermal collagen were demonstrated using recombinant NC1 expressed from human cells [35, 38, 39]. The seventh to ninth FNIII domains bind to laminin-322 [38] and vWF domain binds to type 1 collagen [40]. The NC1 domain has been shown to be the major antigenic portion of C7 in AEB using epitope mapping [41, 42]. It is suggested that autoantibodies directed against NC1 compromise the function of these adhesive proteins and lead to epidermal-dermal disadherence [6].

The results of several studies indicated that the autoimmune response is the key element in the pathogenesis of AEB. Gammon et al. demonstrated that sera from AEB patients induced leukocyte recruitment to the DEJ using a leukocyte attachment assay [43]. Sitaru et al. showed that sera from AEB patients induced dermal-epidermal separation in the cryosections of normal human skin, whereas sera from healthy controls did not [44].

Besides in vivo studies, animal models for AEB were developed. In the first successful passive AEB model, the disease could be induced in mice by injection of autoantibodies against murine C7 derived from immune rabbits [45]. In the active disease model, the clinical, histopathological and immunopathological findings in AEB patients were reproduced in mice by immunization with a recombinant fragment of the murine NC1 domain [46]. The latter served to investigate the loss of tolerance to C7. Further studies showed that complement activation and infiltration of granulocytes into the skin are essential for AEB induction in animal models [47, 48].

A number of studies have provided direct evidence that human AEB autoantibodies to NC1 domain of C7 are pathogenic and capable of inducing epidermal-dermal separation of skin. In one of them, affinity-purified anti-NC1 antibodies from AEB patients' sera were injected into adult immunocompetent hairless mice. The mice developed subepidermal bullous disease reminiscent of human AEB [5]. Woodley et al. demonstrated a small N-terminal 227 amino acids CMP homology domain as the first antigenic epitope on C7 proven to be a pathogenic target for AEB by passive transfer of autoantibodies from patients [49].

Subsequent evidences indicated the NC2 and the collagenous domains as to be minor targets for antibodies in AEB patients [50, 51]. Tissue-bound and circulating autoantibodies targeting the triple helical central domain of C7 were found in certain pediatric cases [52–54]. Minor antigenic epitopes localized to NC2 domain have also been demonstrated in recent reports [55]. AEB autoantibodies bound to NC2 domain may lead to epidermal-dermal disadherence by destabilizing AFs because of the role of NC2 and its adjacent collagenous segment in mediating antiparallel dimer formation of C7 [51]. As understood from these studies, AEB exhibits heterogeneous spectrum of autoantibody reactivities. But to date, there has been no evidence to indicate a correlation between epitope specificity of AEB autoantibodies and various clinicopathologic types [41, 56].

Analyses of the autoantibody response in AEB revealed the presence of IgG1 and IgG4 in the majority of patients [57, 58]. Complement-fixing IgG2a and IgG2b antibodies were detected in the basement membrane of AEB mouse models [46]. The Fc domains of IgG2a and IgG2b recruit neutrophils via Fc-gamma-RIV in the active mouse model. Inhibitor effect of Fc-gamma-RIIB and activator effect of Fc-gamma-RIV were demonstrated in the same study [59]. Complement factors are required for the blister formation in AEB, besides complement 5 (C5) knockout mice are resistant to blister development in a passive transfer mouse model [45]. T cells were proved to be required to produce blister-inducing antibodies in an active mouse model [60].

Development of inflammatory forms of AEB can be explained by the following sequential pathogenic scenarios: T cells stimulated by HLA-DR2 bearing antigen presenting cells that are presenting C7 subdomains. Activated T cells induce B cells and cause the production of C7 antibodies. These antibodies bind to epitopes on the NC1 domain of C7. The Fc domains of the antibodies activate complements and recruit neutrophils. C5a induces FcRIIIA upregulation and FcRIIB downregulation on neutrophils. C7 antibodies bind to Fc receptors and provide neutrophil activation. Reactive oxygen radicals, serine and metalloproteases that are produced by neutrophils mediate extracellular protein proteolysis. Blistering of mucocutaneous surfaces occurs as a consequence of the decrease in the amount of AFs [9, 35, 61, 62].

An experimental model for mechanobullous AEB has not been established yet so the pathomechanism of mechanobullous AEB is still unclear. But several possible mechanisms have been proposed [8]. It has been hypothesized that the normal interactions between NC1 and its extracellular matrix ligands such as laminin 5, fibronectin and type 4 collagen interrupted by autoantibodies may cause loss of the adherence of basement membrane and epidermis onto the papillary dermis [38]. Another potential mechanism behind mechanobullous disease is that AEB autoantibodies may interfere directly with the antiparallel dimer formation of C7 and anchoring fibril assembly [51].

1.5. Clinical manifestations

Two major clinical types of AEB are recognized: mechanobullous and inflammatory [35]. However, AEB classically presents as a mechanobullous disease, if the disease is defined as autoimmunity to C7 AEB can have clinical presentations that are reminiscent of inflammatory BP, CP and Brunsting-Perry pemphigoid [63]. A rare presentation of AEB is characterized by IgA autoantibodies to C7 [64].

There are five clinical presentations of AEB generally accepted: (1) classical presentation that is first reported and resembles the features seen in patients with inherited forms of DEB, (2) BP-like presentation, (3) CP-like presentation, (4) Brunsting-Perry pemphigoid-like presentation and (5) LABD-like disease [7, 63].

About two thirds of AEB patients present with one of the inflammatory variants. Some patients present with mixed phenotypes or in some, the clinical presentation may change during the course of the disease [65]. Kim et al. found no significant difference between mechanobullous and BP-like AEB with regard to sex, age of onset, oral involvement, treatment intensity or time to remission [22].

1.5.1. Classical AEB

This form is characterized by a mechanobullous disease with acral distribution [13]. Together with the BP-like AEB, classical AEB constitutes the majority of cases [22]. Milder forms of the disease are reminiscent of porphyria cutanea tarda, whereas its more severe forms are reminiscent of hereditary recessive dystrophic EB [14]. Patients present with skin fragility, trauma-induced blisters and erosions. Tense vesicles and bullae, which can be hemorrhagic, appear on non-inflamed or scarred skin [7]. Classical AEB is known to represent over trauma prone extensor surfaces such as back of the hands, knuckles, elbows, knees, sacral area and feet. Scarring reminiscent of hereditary dystrophic EB or porphyria cutanea tarda and pearl-like milia cysts frequently occur by healing of blisters [66]. Crusts, scales, scarring alopecia, nail dystrophy and postinflammatory pigment changes are other secondary lesions which result from healing of blisters and erosions. Involvement of the oral mucosa is prominent with erosions and superficial blisters [12, 62].

1.5.2. BP-like presentation

Although AEB classically presents as a non-inflammatory mechanobullous disease, it may manifests as widespread vesiculobullous lesions on inflamed skin reminiscent of BP [16]. It is the most common type of inflammatory AEB [22]. BP-like AEB manifests as widespread pruritic erythematous vesicobullous eruptions that can occur in any mucocutaneous localization [67]. The bullae are tense and localized on inflamed and/or urticarial skin of the trunk, extremities and skin folds [7]. In contrast to classical AEB, the distribution of the lesions is not confined to trauma-prone sites, skin fragility is not prominent and scarring and milia formation may be minimal or absent. Pruritus is frequent [8].

1.5.3. CP-like presentation

This form is characterized by a predominance of mucosal involvement and closely resemble CP [66]. Patients generally have erosions and scars of the mouth, upper esophagus, conjunctiva, nose, anus and genitals with or without similar lesions on the glabrous skin [68–70]. It can lead to the same complications of CP, including synechia, ankyloblepharon, blindness, nasal synechiae, laryngeal stenosis and dysphagia [71]. Tracheal involvement has also been reported [72]. Patients with the CP-like presentation often do not have trauma-induced lesions or skin fragility [35].

1.5.4. Brunsting-Perry pemphigoid-like presentation

Brunsting-Perry pemphigoid-like AEB presents with clinical features of Brunsting-Perry CP but results from autoimmunity to C7 [73]. Patients have chronic, recurrent subepidermal blisters with atrophic scars confined to the head, neck and upper aspect of the trunk with minimal or no mucosal involvement [74, 75].

1.5.5. LABD-like presentation

LABD-like AEB has common features with LABD, including subepidermal bullous eruption, neutrophilic infiltration and linear IgA deposition on the BMZ [35]. Autoantibodies of these patients are usually identified as IgA, IgG or both [8]. Onset of the disease is usually after third decade but may be in childhood too. Erythematous urticarial plaques, vesicles, bullae, erythema multiforme-like lesions and skin erosions may be seen. Pruritus is significant but scars and milium cysts are rare. Mucosal involvement is seen in 30% of the cases [71]. Ig-A mediated AEB can be defined as immunobullous disease with IgA localized at the level of the (sub)lamina densa zone as witnessed by indirect IEM or direct IEM or by a dermal BMZ staining pattern on salt-split skin. So, it is sufficient to separate this disorder from classic LABD using these immunophenotypic criteria [64].

1.5.6. Childhood AEB

Generalized and inflammatory LABD-like skin lesions and mucosal involvement is frequent in this rare form [76]. Callot-Mellot et al. reviewed 14 children with AEB, 5 of the patients presented with a LABD-like disease and 5 patients presented with the BP-like form of AEB. The classical form of AEB was seen in 4 children [77]. Mayuzumi et al. reviewed 33 children with AEB and reported that the inflammatory phenotype, mucosal involvement and favorable prognosis were more common in children than adult AEB patients. Autoantibodies in childhood AEB often target more than one domain of C7 [78].

1.6. Diagnostic methods

Diagnosing AEB based on the clinical picture and skin standard pathology is not possible because of the variety of clinical presentations [71]. Direct immunogold electron microscopy has been considered the gold standard of diagnosis [14]. But at present, diagnosis can be made by serration pattern analysis of direct immunofluorescence (DIF) microscopy and/or detection of serum autoantibodies against type C7 [79]. Linear deposits of IgG, IgA and/or complement 3 (C3) along the DEJ with an u-serrated pattern are diagnostic for AEB. Several test systems for the serological diagnosis of AEB have recently become available. Sophisticated diagnostic approaches only available in specialized centers are required in some patients [63].

1.6.1. Histopathology

Histopathology of a lesional skin biopsy helps to distinguish subepidermal blistering diseases from intraepidermal disorders. Initial histologic changes in the lesional skin are papillary edema

and vacuolar alteration along the DEJ that are followed by subepidermal cleft and blister at a later stage [12]. In the classical mechanobullous form, minimal or no inflammatory infiltrate is detected in dermis. In the inflammatory subtypes of AEB, infiltration of neutrophils with variable numbers of eosinophils, monocytes and lymphocytes are seen in the upper dermis [62, 80]. The infiltrate can be found around vessels, around follicles and in the interstitium. Fibrosis and milia formation are expected to be seen if cicatricial changes are present [12].

1.6.2. Transmission electron microscopy

Paucity of AFs and an amorphous, electron-dense band just beneath the lamina densa were demonstrated in the perilesional skin using electron microscopy [81]. This finding could explain skin fragility by the similarity to that of EB hereditaria [82]. The cleavage plane of the blister does not indicate the diagnosis of AEB certainly. So, AEB cannot be differentiated from inherited epidermolysis bullosa and other pemphigoid disorders by TEM [63]. The cleavage may be seen either in the lamina lucida or the sublamina densa region [83]. Separation of the DEJ through the lamina lucida has been explained by the vulnerability of lamina lucida against proteolytic enzymes released during the inflammatory reaction at the BMZ [84]. The deeper level of separation in the classical form AEB may explain significant scar and milia formation, which is only rarely observed in the inflammatory type [85].

1.6.3. Immunoelectron microscopy

Direct IEM, which is approved as the diagnostic gold standard for AEB, allows to differentiate AEB from other pemphigoid diseases by visualizing the deposits of autoantibodies in the sublamina densa [3, 8]. IEM detects IgG autoantibodies at the lamina densa and sublamina densa of the BMZ, whereas IgG autoantibodies are localized to the upper lamina lucida in BP [7]. Direct IEM is performed to determine the ultrastructural localization of in vivo-bound IgG autoantibodies at the BMZ. Indirect IEM shows the binding site of circulating IgG autoantibodies at the BMZ [85]. Direct IEM is a sensitive diagnostic method, but it is a sophisticated procedure only available in few centers for the diagnosis of AEB [63].

1.6.4. Direct immunofluorescence

Immunofluorescence techniques maintain the pivotal role in the diagnostic algorithm of AEB. DIF on perilesional skin (with a radius of 1 cm) demonstrates linear binding of IgG and/or IgA, and/or C3 deposits along the dermal-epidermal junction [14, 63]. The deposition of multiple conjugates, including IgG, IgA, IgM, C3, complement 4 (C4) and properdin, is more frequently in AEB [85]. In LABD-like presentation, linear Ig A deposition presents without IgG [86].

BP has clinical and histopathological features, which may often be confused with AEB. DIF typically demonstrate linear deposition of IgG and C3 in the BMZ in both conditions [87]. Thus, salt split technique (SST) was introduced in 1984 to differentiate pemphigoid group from other subepidermal bullous diseases [88]. If skin samples are incubated in 1 M NaCl at 4°C for 24–72 hours, the epidermis can be pulled away from dermis with a fine forceps [6, 87–89].

Direct salt-split skin immunofluorescence can be used to distinguish AEB from BP. A routine DIF is performed on perilesional skin from patients who is fractured at the DEJ, through the lamina lucida zone. This cleavage places BP antigen on the epidermal side of the split, and other BMZ components including C7 on the dermal side. Therefore, if fluorescent label is observed along epidermal side of the salt-split skin, AEB is effectively excluded and the diagnosis of BP is suggested [8, 14]. But, this method is not sufficient to confirm AEB because anti-p200, protein-105 pemphigoid (Chan's disease) and anti-laminin-322 CP also show positive staining on the dermal side of the salt-split skin [7, 90–92].

Vodegel et al. demonstrated that IgG/IgA deposits at the BMZ can ultrastructurally be seen as upstanding arms between the rootlets of the basal keratinocytes, thus making u shapes [79]. U-serrated immunodeposition pattern in DIF is pathognomonic feature for AEB and bullous systemic lupus erythematosus (SLE), which are characterized with autoantibodies against C7 [65, 93]. Bullous SLE can be ruled out by other serologic and clinical criteria [7]. All other pemphigoid diseases show true linear or n-serrated pattern [93–95]. These patterns can be applied by DIF only. However, serration pattern may not be identified in mucosal biopsies and a number of skin samples [63, 96].

1.6.5. Indirect immunofluorescence (IIF)

IIF microscopy can be applied for detecting circulating antibodies. Standard substrates for this technique are monkey or rabbit esophagus as well as normal human skin. Incubation with 1 M NaCl solution of these substrates leads to cleavage within the lamina lucida [89]. So, IIF can also be done in salt-split skin with increased sensitivity [63]. Salt-split IIF allows to differentiate AEB from BP and LABD. Because AEB sera react on the dermal side (floor of the blister) of the salt-split skin, whereas BP and LABD sera react on the epidermal side (roof of the blister) [96]. A positive IIF result on the dermal side of the cleft does not make the diagnosis of AEB certain because dermal staining is also observed in patients with bullous SLE, anti-p200 pemphigoid, anti-epiligrin (laminin-332) CP and Chan's disease [7, 73, 90, 92, 97].

Another diagnostic method is IIF using substrate deficient in basement membrane molecules. C7-deficient skin from patients with dystrophic EB is required to perform this test. AEB sera does not show any labeling of skin deficient in C7, but linear fluorescence is seen at the BMZ on normal/salt-split human skin as well as on laminin-332-deficient skin [18, 73].

1.6.6. Western immunoblotting

Immunoblotting analyses are effective to confirm the diagnosis of AEB [8]. Dermal extracts from skin, amnion or cell culture are subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and electrophoretically transferred to a nitrocellulose membrane [12]. Recombinant forms of C7 can also be used [8]. When the membranes with immobilized proteins are incubated with AEB and control sera, AEB sera will be visualized by binding to a 290-kDa band, the alpha chain of C7, whereas control sera will not [8]. A second band of 145 kDa, which corresponds to NC1 domain of C7, will also be labeled with AEB antibodies [12]. Anti p-200 pemphigoid and AEB can be differentiated by Western blot. Patients' sera react with 200- and 290-kDa proteins in anti p-200 pemphigoid and AEB, respectively [62].

Although the sensitivity of immunoblotting is approximately 60%, using several recombinant proteins covering four immunodominant epitopes of NC1 domain increases to 80% [42].

1.6.7. Serology

Enzyme-linked immunosorbent assay (ELISA) demonstrates the presence of patient's circulating autoantibodies against specific basement membrane antigens [8]. AEB ELISAs have been developed using recombinant domains of C7, starting from the NC1 domain [35, 98]. The sensitivity and specificity of an ELISA system using NC1 domain were 94.5% and 98.7%, respectively, in the study of Komorowski et al. [99]. Recombinant NC1 and NC2 domains of C7 were also used in an ELISA system for AEB with sensitivity of 93.8% and specificity of 98.1% [100]. Autoantibodies to NC2 domain were detected in 20% of AEB patients by ELISA [71]. A positive correlation between ELISA values and disease severity of AEB patients was found in several studies [22, 101]. Compared to Western blotting and electron microscopy, ELISA is faster and easier to perform. ELISA method is also more sensitive because it detects autoantibodies that recognize the tertiary and quaternary structure of an antigen, whereas Western blotting only detects antibodies binding denatured, reduced proteins [8].

1.6.8. Fluorescence overlay antigen mapping

It is an efficient technique for identifying localization BMZ components and pathogenic antibodies on perilesional skin from patients with autoimmune diseases [8]. The skin samples are subjected to co-incubation with monoclonal antibodies against human IgG and type VII collagen separately and then stained with different fluorescent stains. Computer-aided superposition of the fluorescent-stained images allows to detect IgG deposits, which can be above (BP) or at the same location of C7 (AEB) [102].

1.7. Diagnosis

In a patient with clinical picture compatible with AEB, the initial and the gold standard diagnostic test is DIF microscopy including serration pattern analyses (u-serrated: AEB, n-serrated: other subepidermal diseases). When IgG/IgA/C3 along the DEJ is observed without a serration pattern, IIF microscopy on human salt-split is the next diagnostic procedure. IgA/IgG at the epidermal side refers to the diagnosis of BP, CP or LABD.

If IIF microscopy is negative or IgA/IgG at the dermal side of the split is detected, then C7-specific ELISA or IIF (Euroimmun, MBL) should be performed (even when diagnosis of AEB has been established by pattern analysis of DIF or direct IEM, serum should be analyzed for autoantibodies against C7). Immunoblotting, IIF microscopy on C7 deficient skin, FOAM and direct IEM are the next diagnostic tools (depending on availability), in case of negative ELISA result. Positivity in any of the four assays will allow diagnosis of AEB [63].

1.8. Differential diagnosis

BP is characterized by predominant IgG reactivity by DIF and/or IIF microscopy, no floor binding by IIF microscopy and no predominant mucosal involvement. CP presents with

predominant mucosal involvement. When floor binding is detected by IIF microscopy, laminin-332 reactivity needs to be analyzed. LABD shows predominant IgA reactivity by DIF and/or IIF microscopy. Anti-p200 pemphigoid is characterized by reactivity with the p-200 protein and/or laminin $\gamma 1$ [63].

1.9. The relationship between AEB and other systemic diseases

A variety of other diseases were reported to be coexisting with AEB [12]. Inflammatory bowel diseases, especially Crohn's disease, is the most common disorder associated with AEB [103]. While in the United States, 25% of AEB patients also have inflammatory bowel disease; this association is not found in Korean patients [22, 104]. Rheumatoid arthritis, diabetes, cryoglobulinemia, psoriasis and hematological malignancies were also reported to be associated with AEB in anecdotal reports [105–107].

1.10. Treatment

Management of AEB is challenging, because noninflammatory mechanobullous form is often refractory to treatment, and the inflammatory forms may require the use of high-dose corticosteroids combined with other immunosuppressants resulting in increased morbidity [62]. All patients need supportive therapy to help reduce risk of complications of AEB. Education for avoiding trauma and wound management improve their quality of life [12]. The most widely used medication for treatment of AEB is systemic corticosteroids but the outcome is usually poor. Mild clinical features respond well to low-dose (0.5–1 mg/kg/day) corticosteroid therapy, whereas high-dose (1–1.5 mg/kg/day) corticosteroid therapy is mandatory in some patients [62].

Colchicine (2 mg/day) has been reported to be effective in patients with both classical and inflammatory presentations probably by the mechanism of inhibiting antigen presentation to T cells [108]. The side effect profile of colchicine is relatively benign so it is often used as a first-line drug alone or combined with corticosteroids [62]. Dapsone (25–100 mg/day) is also effective in some patients, especially when neutrophils are present in their dermal infiltration [109].

Because of the unsatisfactory outcome and extensive side effects of systemic corticosteroids, immunosuppressive agents are required as adjuvant regimens [62]. Although a number of patients have been reported to respond to cyclosporine therapy (>6 mg/kg/day), the use of cyclosporine is limited due to the long-term toxicity of the drug [110]. In intractable cases, it is recommended to use cyclosporine (3–60 mg/kg/day) in addition to corticosteroids [62].

Mycophenolate mofetil (1–2 g/day), methotrexate (7.5 mg/week), and pulse cyclophosphamide (500 mg for 1 day) can be used for their steroid-sparing effects in patients with inflammatory forms. The effectiveness of these agents is varied among patients [62].

Intravenous immunoglobulin G (IVIG) has been used successfully in some severe refractory AEB patients. IVIG has the advantage of lacking immunosuppression [111]. It is recommended for patients not responding to conventional therapy [62]. Rituximab decreases the number of circulating B cells, plasma cells and amount of antibody production. It was used successfully in a small number of severe and refractory patients [35, 112]. Plasmapheresis, immunoadsorption and photopheresis are other therapeutic modalities; however, the experience of using

them in AEB is fairly limited [8, 35]. Infliximab is considered to be an alternative treatment of patients with AEB in future [35]. In a study conducted by Le Roux-Villet et al., 206 articles were analyzed; it was emphasized that only two were of an adequate level of proof, with four of intermediate level and all the others of only low level. Therefore, it is difficult to suggest optimal treatment. Further data are needed to establish the optimal treatment approach [113].

2. Linear immunoglobulin A bullous dermatosis

2.1. Introduction

LABD, also known as Linear IgA disease, is a rare autoimmune subepidermal bullous disease affecting adults and children, which is characterized by the linear deposits of IgA antibodies in BMZ [114, 115]. LABD is usually idiopathic, but medications, malignancies and infections may play a role in the etiology of LABD. The primary implicated agent is vancomycin [116]. In the adult-onset form, arcuate or linear tense vesicles and bullae arising on urticarial looking plaques or normal skin localize on the extensor surfaces [115]. Childhood-onset LABD, which is historically known as chronic bullous dermatosis of childhood (CBDC), represents the most common autoimmune bullous disease among children [117]. The childhood-onset form of LABD has a slightly different presentation with perioral, periorbital, genital and lower limb localization. Annular polycyclic “string-of-pearls” sign is more common in the childhood form [115]. Target antigens of circulating antibodies exhibit heterogeneous features as well as the clinical presentations. LABD is immune serologically divided into two subgroups according to the reaction with the epidermal/dermal sides of 1 mol L NaCl-split normal human skin in IIF [118]. In the lamina lucida-type LABD, the major target antigens are the 120-kDa LAD-1 antigen and its carboxyterminal proteolysed form 97-kDa LABD97 antigen. In the sublamina densa-type LABD, the splitting level is deeper and the target antigen is C7 [117, 119]. Other certain incriminated antigens are BP230, BP180 NC16a domain, 285-kDa antigen, laminin-332 and 200-kDa laminin γ 1 [120]. Autoimmune diseases (post-streptococcal glomerulonephritis), inflammatory bowel disease (ulcerative colitis) and lymphoproliferative disorders were reported to trigger LABD with an unknown mechanism [121]. Skin lesions respond rapidly to dapsone or sulfapyridine treatment [122].

2.2. Historical aspect

LABD was firstly described in children with nonpruritic mucocutaneous blisters misdiagnosed as dermatitis herpetiformis (DH) [123]. Subsequent patients were called “bullous pemphigoid of childhood,” “childhood DH” and finally “chronic bullous dermatosis of childhood” by other clinicians [124]. After that, continuous linear deposits of IgA along the BMZ were showed [125]. Currently, it is known as the childhood counterpart of LABD [114].

2.3. Epidemiology

Reported incidence rates were 0.23/million/year in Germany [126], 0.49/million/year in France [19] and 2.3/million/year in Kuwait [127]. Interestingly, LABD was reported to be more frequent

in Uganda [128], South Africa [129], Mali [130] and Tunus [131]. This may be explained with the variation of age distribution in these countries compared to others. No racial or gender predilection has been reported [132]. LABD can affect all ages, but two peaks have been frequently observed: childhood onset and adult onset [133]. The childhood-onset form usually appears between 6 months and 5–6 years of age. Spontaneous remission may occur within 5 years or it may persist until puberty. On the other hand, the adult-onset form generally appears after the sixth decade and tends to be more chronic [114, 117]. Neonatal cases are extremely rare [134].

2.4. Etiology

Several studies were carried out to assess the possible effect of genetic predisposition for LABD. Collier et al. showed an increased frequency of HLA Cw7, B8, DR3, DQ2 and tumor necrosis factor (TNF2) alleles. Genetic association of HLA-Cw7, HLA-B8 and HLA-DR3 with LABD was reported especially in childhood form rather than the adult form. TNF2 allele was associated with worse prognosis in both children and adult groups [135]. HLA-B8 haplotype was found to be related with favorable prognosis [136].

Although LABD is mostly idiopathic, there are several precipitating factors, such as drugs, infections and malignancies, and traumatic events, such as burns and ultraviolet light exposure [114, 117]. Intake of certain drugs, most commonly vancomycin [137], has been implicated as the causal agent. In addition to this, over 20 other medications have been suspected as potential triggers in case reports [138–142]. (Table 1) Drug-related cases are responsible from 37.5% of adult patients [115]. It is possible that these drugs cross-react with autoantigens of the BMZ by changing their conformational structure or unmasking previously hidden antigens to the immune system [143].

Antimicrobials	Ace inhibitors/angiotensin receptor blockers	Antiepileptics
Vancomycin	Captopril	Phenytoin
Penicillin	Eprosartan	Carbamazepine
Cephalosporins	Candesartan	Vigabatrin
Sulfonamide	Antiarrhythmics	Antidiabetics
Piperacillin-tazobactam	Amiodarone	Glibenclamide
Rifampin	Verapamil	Glyburide
Imipenem	Immunomodulating agents	Miscellaneous drugs
Nonsteroidal anti-inflammatory drugs	Cyclosporine	Atorvastatin
Diclofenac	Ustekinumab	Furosemide
Naproxen	Infliximab	Lithium carbonate
Piroxicam	Granulocyte colony-stimulating factor	Somatostatin
Ketoprofen	Interferon- α,γ	Gemcitabine
Oxaprozin	Interleukin-2	

Table 1. Medications associated with drug-induced LABD.

LABD has been associated with lymphoproliferative malignancies, especially non-Hodgkin lymphoma and Hodgkin lymphoma [144]. Besides, association with solid organ malignancies has also been reported, including bladder, esophagus, breast, uterus, colon and thyroid carcinoma [145–147]. There are documented two LABD cases, which occur after influenza and human papillomavirus vaccination [148]. Additionally, LABD is triggered by upper respiratory infections, varicella zoster virus and antibiotic-treated tetanus infections. Perhaps infectious agents may play a role in the development of autoimmune response [149, 150].

Inflammatory bowel diseases, mainly ulcerative colitis, are the most common diseases associated with LABD. The chronic inflammation in the gastrointestinal tract is thought to be responsible in abnormal IgA production. The cross-reaction of colonic epithelial cells and cutaneous BMZ antigens may be related to this coexistence [151]. Although a definite association is yet to be established, LABD has also been reported with primary amyloidosis [152], interstitial pneumonia [153], rheumatoid arthritis [154], SLE [155] and glomerulonephritis (Table 2) [156].

Lymphoproliferative malignancies
Non-Hodgkin lymphoma
Hodgkin lymphoma
Solid organ malignancies
Bladder, esophagus, breast, uterus, colon and thyroid carcinoma
Inflammatory bowel diseases
Ulcerative colitis
Crohn’s disease
Primary amyloidosis
Interstitial pneumonia
Rheumatoid arthritis
SLE
Glomerulonephritis

Table 2. Disorders associated with LABD.

2.5. Pathogenesis

Linear IgA disease is a subepidermal immunobullous disease characterized by IgA auto-antibodies directed against several antigens located in the BMZ of the skin and mucosal tissues lined with stratified squamous epithelia. Despite many studies over several decades, the pathophysiologic mechanism that triggers the autoimmune response in LABD still

needs to be better clarified [114]. Target antigens of circulating autoantibodies are classified into two groups, those residing in lamina lucida and those in sublamina densa. From this point of view, LABD is divided into two subgroups, lamina lucida-type and sublamina densa-type [157, 158].

Using 1 mol/L NaCl-split normal human skin as a substrate for IIF, the majority of the patients' sera shows epidermal binding, which implies an antigen associated with hemidesmosomes or the upper lamina lucida, and a minority of those bind to the dermal aspect of the artificial blister suggests a lower lamina lucida or dermal antigen. However, some patients' sera show reactivity to both epidermal and dermal sides (mixed type) [159]. In patients with lamina lucida-type LABD, IgA autoantibodies react most frequently with the 97-kDa protein (LABD-97) and 120-kDa protein (LAD-1) [160, 161]. These two most common LABD antigens are fragments of BP180 ectodomain [162, 163].

BP180, or collagen XVII, is a transmembrane hemidesmosome-associated protein with an extracellular collagenous domain spanning the lamina lucida [164]. The extracellular domain of BP180/collagen XVII molecule is partly shed and is further fragmented by proteolytic action into neoepitopes [162]. The LAD-1 is generated when collagen XVII is cleaved by keratinocyte metalloproteinases, ADAM-9 and 10 [165]. This cleavage is just in the noncollagenous (NC)16A domain of the BP180, and this explains that 20% of the sera of LABD patients react with the NC16A domain [117, 166]. NC16A domain, which is the major pathogenic epitope in the extracellular domain of BP180 in BP, is also a target for IgA antibodies in LABD, frequently in conjunction with other antigenic targets [167]. LABD97 is cleaved from NC16 domain of collagen XVII as well as LAD1, and further C-terminal processing of LAD1 induces LABD-97 [168, 169]. IgA antibodies to 290-kDa antigen (C7) and 255-kDa dermal antigen are most frequently detected in patients with sublamina densa-type LABD [170, 171]. Tsuchisaka et al. demonstrated that C7 is the major autoantigen for sublamina densa-type LABD [119]. A 285-kDa antigen (LAD285) has been found in patients whose sera have both dermal and epidermal binding on immunofluorescence testing using split skin [172, 173]. LAD285 is thought to be the immunodominant dermal-associated antigen, which represents the site of the original antibody attack in patients with a response to dermal and epidermal antigens [173]. The full-length BP180, BP230, laminin-332, laminin γ 1 and α 6 β 4 integrin are less common antigenic targets of IgA [174–176].

Most of the patients' sera have more than 1 target antigen suggesting that there is a primary disease-provoking epitope with spread of the immune response to other epitopes on the same or adjacent molecules. It is also demonstrated that the phenomenon of intermolecular epitope spreading is common, age dependent in LABD and is associated with IgA antibodies rather than IgG antibodies [173].

The pathogenesis involves IgA and less frequently IgG autoantibodies directed against BMZ antigens [172]. Previous investigations have demonstrated that A1 subclass is responsible for development of the disease [177]. IgA is a chemoattractant of neutrophilic granulocytes. Antigen-antibody binding leads to complement activation, predominantly neutrophilic inflammatory infiltration and proteolysis mainly occurs through the cooperation of

neutrophil elastase and MMP-9/gelatinase B that result in tissue injury and blister formation [114, 142, 178, 179]. There is indirect evidence for the pathogenicity of the IgA antibodies. A recent research has demonstrated that transfer of monoclonal IgA antibodies against the 97-kDa LAD antigen into severe combined immunodeficient mice with human skin grafts resulted in IgA deposits along the BMZ, recruitment of neutrophils, and subepidermal vesicle formation [180].

2.6. Clinical features

Clinical manifestations of LABD are heterogenous and often resemble those of BP and DH. Characteristic clinical features are tense vesicles and/or bullae on the normal/erythematous/urticarial base [181].

These lesions may occur in various size and form as annular or polycystic plaques. As referred before, there are two forms of LABD: adult onset and childhood onset (CBDC). The distribution of the lesions differs in these two forms.

Lesions in CBDC mostly occur in the lower abdomen and anogenital areas, with a frequent involvement of the perineum and less often perioral area. New lesions appear in the periphery of older ones, named as “cluster of jewels.” The localization in the lower abdomen and the anogenital region is typical for childhood form. Patients complain of severe itching and burning and rupture of blisters may develop secondary infections [114, 182].

In adults, there may be several clinical manifestations such as papular, vesicular, bullous, erythematous and edematous lesions that localized on extensor surfaces, including trunk and buttocks. Erythema multiforme-like, prurigo nodularis-like [183] and contact dermatitis-like lesions [184] may occur. These lesions may distribute symmetrically or asymmetrically in both child and adult forms. It is difficult to distinguish disease from DH especially in the presence of symmetrical excoriated pruritic papules. LABD should be considered when the annular lesions are present. Larger bullae can be seen in some patients with BP or AEB. Histopathological and serological examinations should be performed to differentiate LABD from all these diseases [181, 185].

Oral mucosa and ocular surface are the most common locations in LABD [186]. Larynx, pharynx, trachea, esophagus and vaginal mucosa may be affected. The involvement of oral mucosa occurs in 60–70% of LABD patients. It is more common in adults. These mucosal lesions may be the only clinical manifestation in truly minority of patients. Painful erosions or ulcers or desquamative gingivitis may occur in oral mucosa [187, 188]. Ocular lesions heal with scar just like CP. Ocular findings include dry eye, foreign body sensation, entropion, conjunctival scarring with trichiasis, corneal opacification, neovascularization and potential blindness [189].

Recent case series demonstrated that the course of drug-induced LABD is atypical and more severe compared to the idiopathic form. Lesions usually occur within 5 to 26 days

(median 10 days) after drug intake and usually resolve within 4 weeks after drug withdrawal. But exceptional cases may persist for months. Vancomycin is the most commonly prescribed drug. Drug-induced LABD may clinically resemble toxic epidermal necrolysis with large erosions and positive Nikolsky sign [190, 191]. Morbilliform and localized palmar variants have been defined and the responsible drug in these variants is usually vancomycin [192, 193].

2.7. Diagnosis

The diagnosis of LABD is based on clinical, histopathologic and immunologic parameters [114]. Routine histopathology of the lesional skin classically shows subepithelial blister formation with a diffuse underlying neutrophilic infiltrate in the dermis accompanying mononuclear cells and eosinophils. These findings are identical to those of DH [194]. But neutrophils are usually much less diffuse and are more common in papillary tips in DH [116]. These findings can be observed in other subepidermal blistering diseases such as BP and AEB [195].

Owing to the fact that clinical and histologic features of LABD are frequently overlap with those of other subepidermal bullous diseases, it is essential to verify the presence of IgA autoantibodies using at least one of the immunopathologic examinations, including DIF, IIF, Western immunoblotting or IEM [114]. The gold standard test for diagnosis of LABD is DIF microscopy of perilesional, clinically normal-appearing skin or mucous membrane that reveals linear IgA deposits along the BMZ [196]. The forearm is not a suitable biopsy site, as antigen expression is detected to be insufficient [197]. In cases of lamina lucida-type of LAD, immunofluorescence analysis of perilesional skin biopsies show linear Ig A deposits that have n-serrated pattern in contrast to sublamina densa-type LAD where the deposits have an u-serrated pattern [117]. Deposition of IgG, IgM, or C3 in conjunction with IgA may be seen in some cases [114]. The presence of linear IgG deposition in addition to IgA along the BMZ has provoked some controversy [116]. In some cases of DH, the pattern of the IgA deposition may be linear. So, it might be necessary to use another confirmatory immunologic test for distinguishing DH from LABD [198].

Serum and, rarely, blister fluid are used for IIF to detect circulating IgA antibodies [199]. IIF shows a variable positivity of 30–50% of LABD patients and tends to be more positive in children ($\geq 75\%$) than in adults (30%) [133, 182, 200]. As the low circulating autoantibody titers make difficult to detect positivity, it should be done on salt-split human skin for increased sensitivity [201]. IgA deposits can be detected on epidermal, dermal or both sides of the salt-split skin by IIF. In most cases, sera of the patients show epidermal bindings (lamina lucida-type LABD) [159]. Sublamina densa-type LAD accounts for the minority of the patients and shows dermal binding [202]. Some cases show a mixed pattern [203]. IIF on salt-split skin is usually negative in drug-induced LABD [191].

IEM is a specific diagnostic tool, which detects the exact location of immune deposits but it is expensive and only used by small numbers of centers [114]. By direct IEM, the IgA deposits

were found in lamina lucida, basal surface of hemidesmosomes, lamina densa and sublamina densa region [204]. “Mirror image” is defined as the IEM finding of several cases in which the immune deposits are located at the both sides of lamina densa [205].

Western blot is not commonly used because it is time-consuming, expensive and not feasible in most centers [116]. But multiple target antigens have been identified by the Western blot analysis within last 20 years [114]. It is a sensitive method for detecting IgA antibodies against LABD97 and LAD-1 [117, 172]. Remaining recognized antigens, including BP180, BP230 and C7 that are shared by other subepidermal bullous diseases, make the diagnosis more challenging [114]. When the mentioned methods do not provide information, Western blot analysis can enable to reach an accurate diagnosis [206].

2.8. Differential diagnosis

Clinically, LABD can resemble other blistering disorders such as BP, DH, AEB, CP and bullous SLE [114]. BP is characterized by linear deposition in the BMZ of IgG and C3 while immunofluorescence studies for DH demonstrate granular IgA deposits in the dermal papillae [207]. Cases reported to show IgA autoantibodies to the 290-kDa C7 may be diagnosed as sublamina densa-type LABD or IgA-mediated AEB. However, other clinical characteristics, such as milia and atrophic scarring, can be used to differentiate AEB from LABD [208]. LABD with predominant mucosal involvement can mimic CP clinically, but differentiates by immunofluorescence findings from other bullous diseases.

Salt split-skin immunofluorescence assays demonstrate that both circulating and tissue-fixed IgA autoantibodies mostly deposit on the roof of the split in LABD. In CP, antibodies are seen on the floor or roof of the split [209]. AEB is always recognized by dermal deposits. In LABD patients' sera, autoantibodies are mainly against 97- or 120-kDa antigens, whereas autoantibodies in BP patients target 180 and/or 230 kDa antigens [210]. Circulating and tissue-bound antibodies target 180-kDa or laminin-322 in CP patients [209] and 145- or 290-kDa antigens in AEB patients [64].

Although several authors have suggested their own criteria, there is no diagnostic guideline or consensus about LABD [116]. Some investigators suggest that solely linear IgA deposition with no other immunoglobulins or complement deposition at the BMZ in DIF is essential [202]. However, others proposed that prominent linear IgA deposition at the BMZ, irrespective of concurrent weak IgG deposition, is consistent with a diagnosis of LABD [211, 212]. Moreover, IF staining intensity depends on the experimental conditions, such as dilution and the type of second step antibodies. Thus, it is often difficult to assess predominance [116]. Several cases of subepidermal blistering diseases including BP, CP and AEB with linear IgA deposits reported previously point to the complicated immunopathological features of these disease spectrums [213–215].

In minority of the cases, circulating IgG anti-BMZ antibodies can be detected and deposition of linear IgG may be seen by DIF parallel to IgA although in less intensity [158]. A Japanese review of 213 patients with LABD found both IgA and IgG anti-BMZ antibodies in approximately 20% of the cases [216]. Therefore, several authors consider them to be overlap syndromes and

prefer the designation of linear IgA/IgG bullous dermatosis (LAGBD) [120, 194, 208]. LAGBD comprises a heterogeneous group of diseases, and most cases show pruritic vesiculobullous eruptions similar to those of LABD [212].

2.9. Treatment

The involvement site and the severity of the disease should be considered for treatment choice. Potent topical corticosteroids (clobetasol propionate) may be effective in mild disease [217]. The possibility of a drug effect or an association with underlying malignancy or bowel disease should be evaluated because discontinuation of the offending drug or treating the underlying disease may produce a remission. If there is no evidence of an associated medication or disease, dapson is the drug of choice for the initial treatment of patients with LABD [194]. Many cases often respond dramatically within 24–48 hours to dapsone. It is used in doses of 50–200 mg/day. Prednisolone (0.5–2 mg/kg/d) treatment may be added in cases with dapson resistance [114]. When there is intolerance to dapson or inadequate response, alternative treatments with sulfapyridine, colchicine, tetracycline and niacinamide, mycophenolate, azathioprine or rituximab should be considered [194]. In case of ocular disease, rituximab is indicated in patients with dapson resistance [218]. Cyclophosphamide or other immunosuppressants are the next options [194].

In general, same drug regimens can be used for both children and adults, but dose adjustment is required in children. Legendre et al. have used botulinum toxin A for LABD located in the axillae and observed a decrease in severity of symptoms [219]. Although treatment-discontinuation modalities were not investigated, it is commonly accepted that treatment should not be ended before DIF becomes negative in skin with a previously positive lesion site [174].

2.10. Prognosis

The natural course of the disease cannot be estimated precisely because of the rare occurrence of LABD and the inadequate long-term follow-up of patients. According to Gottlieb study, it is achieved that one-third of patients had complete remission. One-third of the patients had chronic disease and the other one-third had relapses. Major risk factors for chronic disease are mucosal involvement, age over 70 years and pure linear IgA deposits at the BMZ. Mucosal lesions are more resistant to treatment and may lead to stricture formation or conjunctival and corneal scarring [174].

The clinical course of CBDC is mild, and mucosal involvement is less common than adult form [131]. CBDC is self-limited disease. The average duration of the disease is 3–4 years, but it may be longer in some patients.

3. Conclusion

To conclude, AEB and LABD are distinct autoimmune blistering diseases with various subtypes some of which share overlapping clinical and immunohistopathologic features. No

histologic features differentiate LABD from AEB or other subepidermal bullous diseases. Immunofluorescence microscopy is mandatory for diagnosis. However, diagnosis and management of these diseases still remain challenging because of the polymorphous clinical picture, sophisticated diagnostic approach and lack of prospective controlled clinical trials. Future studies are required to clarify the exact role of numerous basal membrane antigens/epitopes, border lines between overlapping autoimmune bullous diseases and new therapeutic options.

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