Chapter

Skin Blister Formation and Subepidermal Bullous Disorders

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Abstract

Blistering diseases comprise a large group of clinically polymorphic and sometimes devastating diseases. Blistering diseases are evaluated according to the level of the blister, the mechanism of blister formation and the type of inflammation. There are many connections in the normal structure of the skin that hold the cells together. These connections both hold the cells in the epidermis together and ensure that these cells attach to the basement membrane. As a result of damage to these connections by genetic, immune, infectious or physical reasons, intercellular connections are broken and blistering developments due to the accumulation of extracellular fluid in the intercellular spaces. Autoimmune bullous diseases are classified according to the decomposition site of the epidermis. While the pemphigus group is used to classify diseases with intraepidermal separation, the pemphigoid group diseases are used to classify diseases with subepidermal separation. In this section, pemphigoid group diseases, such as bullous pemphigoid, mucous membrane pemphigoid, acquired epidermolysis bullosa, linear IgA bullous dermatosis, and anti-p200 pemphigoid, will be explained with a brief introduction to blistering diseases of the skin.

Keywords: blistering diseases, subepidermal bullous disorders, pemphigoid, linear IgA bullous dermatosis, mucous membrane pemphigoid, anti-p200 pemphigoid

1. Introduction

Skin blistering diseases are clinically polymorphic large-group disorders and they sometimes may be devastating. These disorders may be classified according to [1] the level of the blister: subcorneal, mid epidermis, suprabasal, subepidermal; [2] the mechanism of blister formation (spongiosis, acantholysis, blistering degeneration, or epidermolysis); and [3] the type of inflammation (neutrophilic, lymphocytic, eosinophilic, mixed) [1]. In this section, pemphigoid group diseases such as bullous pemphigoid, mucous membrane pemphigoid, acquired epidermolysis bullosa, linear IgA bullous dermatosis, and anti p-200 pemphigoid will be explained with a brief introduction to blistering diseases of the skin. The features of subepidermal bullous disorders were summarized in **Table 1**.

	Bullous pemphigoid	Mucous membrane pemphigoid	Acquired epidermolysis bullosa	Linear IgA bullous dermatosis	Anti-p200 pemphigoid
Clinical symptoms Pathology Differential diagnosis Treatments	Tight bullae located on erythematous or normal ground in the lower abdomen, flexor surfaces of the limbs, groin, and axilla. It may also present with only pruritus or urticarial plaques. Subepidermal blisters with moderate to dense inflammatory infiltrate, especially eosinophils. DIF: The linear IgG and/ or C3 deposition along the BMZ epidermolysis bullosa acquisita, mucous membrane pemphigoid, anti-p200 pemphigoid, pemphigus vulgaris, Oral/topical corticosteroids Azathioprine Mycophenolate mofetil Oxytetracycline/doxycyclin Methotrexate Dapsone Chlorambucil Cyclophosphamide Omalizumab Intravenous immunoglobulin(IVIG), Plasmaphereses	Mucosal blistering, ulceration, and subsequent scarring in the mucous membranes(oral mucosa, ocular conjunctiva, nasopharynx, larynx, anogenital region, and esophagus) and vesiculobullous lesions, ulceration, erosions, and scars in the head and the upper body. Subepithelial blisters with or without significant mixed inflammatory infiltrates and lamellar fibrosis in the upper dermis. DIF: The linear deposition of IgG, IgA, or C3 along the BMZ Bullous pemphigoid, epidermolysis bullosa acquisita, anti-p200 pemphigoid, pemphigus vulgaris Low-risk patients: Topical or intralesional corticosteroids, topical tacrolimus High-risk patients: Dapsone and/or prednisone, tetracycline, doxycycline pulsed steroid therapy, cyclophosphamide, IVIG, rituximab, azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide	Skin fragility, tense bullae, erosions, milium, and scar formation in trauma areas, especially the extensor surfaces of the acral regions In inflammatory type, the lesions can be seen on all skin and mucous membranes Subepidermal blister with eosinophilic-rich infiltrate, DIF: linear deposition of C3 and IgG along the BMZ Bullous pemphigoid Mucous membrane pemphigoid Linear IgA bullous dermatosis Anti-p200 pemphigoid Protecting from local traumas and infections. topical corticosteroids colchicine dapsone oral prednisone IVIG Pulse steroidsmycophenolate mofetil cyclosporine azathioprine rituximab Methotrexate cyclophosphamide plasma exchange	Vesicles and tense bullae are located on erythematous or normal ground in the trunk, extensor surfaces, buttocks, and face. Annular erythematous lesions with a ring of vesicles skin lesions heal without scarring, mucosal lesions may result in significant scarring. The mucosal involvement is more often in children than in adults Subepidermal blisters are associated with a dermal infiltrate of neutrophils, eosinophils, and mononuclear cells. Neutrophil microabscesses at the tip of the dermal papillae DIF: The linear accumulation of IgA along the BMZ. IgG, IgM, and C3 accumulation may be seen Bullous pemphigoid, Mucous membrane pemphigoid epidermolysis bullosa acquisita, anti-p200 pemphigoid, toxic epidermal necrolysis Dapsone sulfonamides oral corticosteroids, tetracycline and nicotinamide colchicine trimethoprim-sulfamethoxazole	Tense blisters with urticarial papules and plaque Acral and cephalic distribution and mucosal involvement subepidermal separation and a moderate to dense inflammatory infiltrate in the upper dermis, with a predominance of neutrophils DIF: Linear deposits of immunoglobulin IgG and C3 along the BMZ Bullous pemphigoid Mucous membrane pemphigoid Acquired epidermolysis bullosa Linear IgA bullous dermatosis Responds well to bullous pemphigoid treatment

DIF: direct immunofluorescence microscopy, Ig: Immunoglobulin, C3: complement 3, BMZ: basement membrane zone.

Table 1.
Features of subepidermal bullous disorders.

2. Blistering formation mechanisms

There are different mechanisms underlying vesicle and bulla formations, these are spongiosis, achantholysis, ballooning degeneration, and cytolysis (epidermolysis) [1, 2].

2.1 Loss of intercellular cohesion

Acantholysis is the loss of intercellular cohesion for various reasons. There may be many causes of primary acantholysis, the most known being pemphigus group diseases caused by autoantibodies against desmosome proteins. This condition can be caused by bacterial toxins, as in staphylococcal scalded skin syndrome, or by a genetic defect in the kertinocyte cell membrane, as in Hailey–Hailey disease [3–5].

Spongiosis, which describes intercellular edema causes secondary loss of intercellular cohesion although the intercellular connections are structurally normal. Loss of cohesion appears as small cavities in the epidermis in histopathology. It is called spongiosis because of its sponge-like appearance. As the severity of inflammation increases, the small spaces formed coalesce to form vesicle-bulla formation. The best example of this situation is allergic contact dermatitis [6].

Ballooning degeneration is the appearance of affected spinous cells with pale cytoplasm swollen due to intracellular edema. Necrosis of these cells and loss of attachment to neighboring cells is the cause of secondary acantholysis. It is characteristically seen in infections caused by some viruses, such as herpes, smallpox, and Coxsakie [7].

Cytolysis of basal layer cells of the epidermis causes loss of epidermal cohesion. In the epidermolytic form epidermolysis bullosa, bullae form due to post-traumatic damage to genetically defective basal layer cells [8].

2.1.1 Desmosomes, hemidesmosomes, and basal membrane

Preservation of the integrity of the epidermis depends on secure adhesion between adjacent keratinocytes, and between basal keratinocytes and the underlying epidermal basement membrane (BM). The major adhesion units are hemidesmosomes and desmosomes. As a result of damage to these connections by genetic, immune, infectious, or physical reasons, intercellular connections are broken and extracellular fluid accumulates in the intercellular spaces. This fluid accumulation appears as vesicles, intact or opened bullae, and erosions [2].

Desmosomes are structures that connect the intracellular skeleton to the cell membrane and other cells. Proteins, such as desmogleins, desmocollins, plakoglobins, plakophilins, and desmoplakins form the structure of the desmosome. The genetic absence of these proteins or the autoantibodies developed against these proteins cause genetic and autoimmune bullous diseases [9–11].

Basal keratinocytes adhere to connective tissue via extracellular matrix proteins that constitute BM [12]. Epidermal BM between the epidermis and dermis contains four principal basement membrane components; laminins, type IV collagens, perlecan, and nidogens [13].

Laminin-332, the most abundant laminin, distribute both throughout the epidermal BM and condenses in hemidesmosomes. Laminin-511 supports keratinocyte adhesion too and both laminins are important in maintaining the structural integrity of the BM and interact with integrin a3b1 and a6b4. In addition to integrin receptors, laminin-332 interacts with multiple proteins such as collagen XVII, syndecan 1 and 4, perlecan, nidogen 1, fibulin 2, and collagen VII [13, 14].

Collagen IV is the second major component of BM and is vital for maintaining epidermal BM integrity. The laminin and collagen IV networks need to be connected for BM stability. This task in the epidermal BM is performed by nidogens. Perlecan is an additional possible linker. Another BM component, fibrillin 1, interacts with perlecan and forms microfibrils participating in the anchorage of the epidermal BM to the papillary matrix [13, 15].

Collagen VII (anchoring fibrils) expressed by both epidermal keratinocytes and dermal fibroblasts has evolved as a specialized non-redundant component of the DEJ ensuring the firm attachment of the epidermal BM to the papillary matrix [13, 16]. As opposed to anchoring filaments, anchoring fibrils are much larger and have a characteristic structure anti-parallel alignment of type VII collagen molecules [16].

Epidermal BM has evolved to contain additional supportive structures that ensure firm adhesion of the epidermis to the dermis. This zone known as the dermal-epidermal junction (DEJ) is a functional unit composed of the plasma membrane of the basal keratinocyte with its hemidesmosomes, a lamina lucida, lamina densa, and a sublamina densa fibrous zone or reticular layer. DEJ plays a vital role in regulating communication between the epidermis and dermis and tissue reconstruction and repair [13–15].

Hemidesmosomes are cell-matrix junctions that connect epidermal keratinocytes to the BM. The core of each hemidesmosome consists of 180 kDa-bullous pemphigoid antigen (BP180, type XVII collagen, BPAG2), the two subunits of the α6β4 integrin, and a tetraspanin protein termed CD151. In BM, BP180 and α6β4 integrin interact with laminin–332. The cytoplasmic tail of the β4 integrin subunit binds both BP180 and two members of the plakin family, the 230 kDa bullous pemphigoid antigen (BP230 or BPAG1e) and plectin [12].

Subepidermal autoimmune bullous diseases (SABDs) are diseases characterized by subepidermal blisters that develop as a result of antibodies against DEJ components that are important structural proteins for the maintenance of dermo-epidermal integrity [17]. Bullous pemphigoid, mucous membrane pemphigoid, acquired epidermolysis bullosa, and linear IgA bullous dermatosis will be explained in these group disorders in this chapter.

3. Bullous phemphigoid

Bullous phemphigoid is the most common autoimmune blistering disease which affects the elderly, particularly in patients older than 70 years. The median age for bullous pemphigoid is 80 years. The incidence of the disease has increased significantly in last years due to the increased life expectancy of the aging population [18, 19]. BP has a significantly increased fatality, with 1-year mortality rates ranging from 6 to 41% in literature [17]. Infections are most important cause of death. Risk factors for mortality are advanced age, non-white ancestry, low health insurance accessibility, and the presence of neurological comorbidity and functional impairment at presentation [17, 20].

In the previous decades, neurological conditions including Parkinson's disease, dementia, stroke, epilepsy, and multiple sclerosis have been identified to be highly associated with BP patients. This association may be explained by the cross-reactivity between the neuronal (BP230) and epithelial isoforms of BP Ag1 which are both encoded by dystonin gene. Recently, psychiatric comorbidities, such as schizophrenia and bipolar disorder, as well as personality disorders have been reported in BP

patients [17, 21]. A significant association with hematological malignancies between BP was revealed in the pooled analysis of cross-sectional studies while no association between BP and overall cancer was found in any of the study designs in the results of a meta-analysis [17]. Additionally, in BP risk of developing a thromboembolic disease is 15-fold higher [22].

A geographic or ethnic predilection of the disease is defined recently. Certain HLA class II alleles are more prevalent in patients with BP than in the general population. In Caucasians, a significant association with DQB1*0301 and in the Japanese population DRB1*04, DRB1*1101, and DQB1*0302 alleles have been found [17, 23].

It is associated with a humoral and cellular immune response directed against the components of the skin BM zone (BMZ). There are two self-antigens that are components of the hemidesmosomes: BP230 and BP180 [24]. *In vitro* studies have shown that human BP180 antibodies play a key role in the pathogenesis of the disease and are responsible for dermal-epidermal separation and subsequent subepidermal blister formation in patients with BP [18, 25]. In DIF, IgG-type antibodies are observed in 90–95% of cases and C3 accumulation is observed in 100% of cases, and this is a critical test for diagnosis. In a smaller group of patients, accumulation of IgE, IgA, and IgM can also be detected [26]. Those that are associated with pathogenesis are IgG and IgE-type antibodies. In particular, IgG1-type antibodies through complement activation, and IgE-type antibodies through mast cell degradation; cause neutrophil and eosinophil chemotaxis. Proteolytic enzymes released from these cells also cause separation at the dermo-epidermal junction. IgG4-type antibodies can also cause degradation by complement-independent antibody-dependent pathways. IgE-type antibodies are responsible for pruritic urticarial plaques, especially in the prebullous stage [27, 28].

The disease usually first presents with pruritus accompanied by localized or generalized excoriated lesions, eczematous, papular, and or urticarial lesions [29]. Blisters may accompany the first lesions or occur a few weeks up to months after the development of the first cutaneous signs [22]. Tense bullae can arise on an erythematous base or normal skin [29]. Blisters most commonly disperse symmetrically and predilection sites are the lower abdomen, flexor surfaces of the limbs, groin, and axilla [30]. The disease heals without scarring, but postinflammatory hypo-hyperpigmentation and milia can be seen [18]. Oral mucosal involvement is seen in 10–20% of affected patients [31–33].

The disease has a non-bullous phase in which typical clinical signs have not yet appeared. Classical bullous lesions are not seen in 20% of patients diagnosed with BP at the time of diagnosis [22, 30]. In this prodromal phase, patients may have only mild to severe pruritus. In an elderly patient who had especially neurological disorders, excoriations accompanied by severe pruritus should cause BP suspect. While eczematous patches can persist for months to years before the development of bullae progression from urticarial pemphigoid to bullous form is seen more quickly in approximately 6 weeks [22]. Another presentation form of BP are Prurigo nodularis-like lesions. Most Pemphigoid nodularis patients develop bullae within years but it is not necessary [22].

There is currently no standardized classification of BP. However, it is possible to recognize distinct variants of the disease according to the age of onset, clinical presentation, location of the lesions, and triggering factors [34]. The presence of concomitant lichen planus with BP is defined as lichen planus pemphigoid. Bullae that demonstrate classic immunopathologic findings of BP develop both on lichen planus lesions and on normal skin [22]. Pemphigoid vegetans is a form of BP in which clinical findings are similar to pemphigus vegetans but histopathology and immunofluorescence findings are identic with BP. BP rarely may manifest as exfoliative erythroderma

characterized by generalized erythema and desquamation [34]. Another type is seborrheic pemphigoid involved seborrheic area and resembles pemphigus erythematosus. Also, BP may show ecthyma gangrenosum-like, erosive, toxic epidermal necrolysis-like presentations, and several localized forms. These localized forms that have better prognosis are dyshidrosiform pemphigoid characterized by pompholyx-like palmoplantar lesions, stomal pemphigoid sited stomal region, radiation aggravated pemphigoid limited to the site of radiation therapy, hemiplegic pemphigoid limited to the area of neurologic deficit, stump pemphigoid arised in a stump, pretibial umbilical and vulvar pemphigoid [22].

Pediatric BP is rare and has a more favorable prognosis than adults. Two peaks of incidence, one with an average age of 4 months in infantile BP and another with an age of 8 years in childhood BP were characterized [34]. Infantile BP significantly presents with face and acral involvement [22, 34]. Childhood BP may present localized lesions with genital involvement. Pediatric BP may be related to vaccination [34].

Drug-induced BP has been defined in the literature and several drugs, such as inhibitors of dipeptidyl peptidase-IV (especially vildagliptin and linagliptin, sitagliptin, anagliptin, alogliptin, teneligliptin, and saxagliptin) diuretics (furosemide and spironolactone), ACE inhibitors (captopril, enalopril, and lisinopril), β-blockers, NSAID's, TNF-a inhibitors, antipsychotics, calcium channel blockers and checkpoint inhibitors (Pembrolizumab, Nivolumab, and Durvalumab) are blamed for BP [21, 29, 34, 35].

Histopathology demonstrates subepidermal blister with a moderate to dense inflammatory infiltrate. Inflammatory cell infiltrates usually contain eosinophils and which are often seen in the blister cavity and basement membrane [18, 30]. These infiltrates may also contain neutrophils and lymphocytes [26, 36]. Direct immunofluorescence (DIF) examination shows linear immunoglobulin G (IgG) and/or C3 deposition along the basement membrane [25, 30]. The diagnosis is based on the combination of clinical features, histopathological and immunofluorescence findings.

Salt split DIF is useful in differentiating BP from other pemphigoid group diseases, such as epidermolysis bullosa acquisita, mucous membrane pemphigoid, and anti-p200 pemphigoid. The immune deposits are detected with salt-split DIF on the epidermal side of the skin in BP [18, 29].

Topical and systemic treatments can be used in the treatment of BP, depending on the severity of the disease, age, general health, medical history, and any contra-indications of the use of systemic medications for each patient. Topical clobetasol propionate should be the first choice in patients with < 5–10 new blisters per day. Clobetasol propionate cream can be applied only to the affected areas or to the whole body, sparing the face. If > 10 new blisters are present, systemic treatments can be used together with topical treatments. Oral corticosteroids are preferred first in systemic treatment to get the disease under control quickly. Azathioprine 1–3 mg/day, mycophenolate mofetil 2 g/day, oxytetracycline 2 g/day or doxycycline 200 mg/day with or without nicotinamide 2 g/day, methotrexate 15 mg/week, dapsone 1–5 mg/kg/day, chlorambucil 2–4 mg/day, cyclophosphamide 50 mg/day, anti-CD20 and anti-IgE monoclonal antibodies, intravenous immunoglobulin (IVIG), plasmaphereses and can be used to keep the disease under control and avoid steroid side effects in long-term treatment [37–39].

4. Mucous membrane pemphigoid

Mucous membrane pemphigoid (MMP) also known as cicatricial pemphigoid, is a rare subepidermal blistering disease with highly variable clinical heterogeneity and

potential diagnostic delays. It predominantly affects the mucous membranes and, up to 30% of patients may also have skin involvement [37, 40, 41]. The disease most frequently involves the oral mucosa (85% of patients), followed by ocular conjunctiva (65%), nasopharynx, larynx, anogenital region, and esophagus involvement can be seen and results in mucosal blistering, ulceration, and subsequent scarring [41, 42]. The disorder if not recognized and treated early and aggressively in some cases, often may cause blindness, esophageal strictures, and even difficulty speaking and breathing [17, 22]. MMP mainly occurs in the elderly population, commonly observed between 60 and 80 years of age and seen in women more often than men [37, 42].

Certain HLA types like HLA DRB1*1503 have been associated with an increased risk of developing MMP [17, 22]. Autoantibodies against different antigens of the basement membrane zone, such as BP180, BP230, integrin subunits α6/β4, laminin-332 (also called epiligrin and laminin-5), laminin-6, and type VII collagen has been blamed for dermo-epidermal separation and blister formation in MMP [40, 42]. Generally, MMP has been classified into three types based on the antigenic target classic MMP (BP180); ocular MMP (α6β4 integrin); and anti-laminin 332 MMP (laminin 332) [18].

In the clinic, there are vesiculobullous lesions in all cases, but in contrast to BP oral involvement is in up to 85% of cases. The most commonly involved sites are the head and upper body and clinical evidence of scarring can clue in the diagnosis of MMP [18]. Healing of the lesions of the disease with scarring is an important cause of morbidity. Clinically, irreversible damage specific to the location of the lesions can be seen. Therefore, early diagnosis and effective treatment of the disease are important. Complications related to the eyes are very important as the eyes are the most frequently involved area. There may be non-specific conjunctivitis, as well as complications such as lagophthalmos, entropion, trichiasis, keratitis, glaucoma, and even blindness [43]. The most common finding of oral mucosal MMP is desquamative gingivitis. Ulcers and erosions due to the opening of bullae may also be seen. Patients complain of bleeding, pain, and dysphagia. As a result of oral mucosal involvement, speech and feeding difficulties may occur. Organ-specific complications can also be seen due to the involvement of other mucosal tissues [40, 44].

Diagnosis is made by clinical correlation with histopathologic, immunopathologic, and serologic findings [18]. Histology typically demonstrates the subepithelial split with or without significant mixed inflammatory infiltrates (predominantly neutrophilic and lymphocytic and variable eosinophilic) and lamellar fibrosis in the upper dermis [18, 45]. Lamellar fibrosis that can be seen underneath the subepidermal bullae is characteristic but is not always present. If it is, it can help distinguish MMP from other subepidermal blistering dermatoses [18]. In DIF examination, the linear deposition of IgG, IgA, or C3 along the BMZ is seen [45, 46]. As in BP, salt-split skin DIF shows epidermal staining in MMP except in anti-laminin 332 type [18, 41]. ELISA for the C-terminal domain of BP180, and laminin 332 MMP is not widely available so the benefit of serologic testing is limited for MMP diagnosis [18].

The choice of treatment depends on the severity of the disease and the patient's response to previous treatments. As in other chronic diseases, the patient's age, comorbid conditions, drug use, and severity of the disease are effective in the choice of treatment. In addition, a multidisciplinary approach and careful clinical examination are important in treatment because of irreversible tissue damage due to the disease [42].

In the choice of treatment, patients are evaluated as low and high risk. The "low-risk" patients are those with involvement of oral mucosa and/or skin. Patients with involvement of the ocular, nasopharyngeal, esophageal, laryngeal, and genital mucosa are considered "high-risk" patients [37].

Topical agents are the first line of treatment in low-risk patients. Topical or intralesional corticosteroids can be used. Topical tacrolimus can also be used for treatment, but topical steroids are more effective. When patients do not respond to topical treatments or in case of partial response to these treatments, systemic treatments should be started. Dapsone 50–200 mg/day and/or prednisone 0.5–1.0 mg/kg/day, tetracycline 1–2 g/day, and doxycycline 100 mg/day are the preferred agents in systemic therapy. In high-risk patients and low-risk patients who have a partial response to treatment, treatment should be more aggressive, and systemic therapy should be preferred primarily. Prednisone 1–2 mg/kg/day treatment can be used as the first choice for these patients. With or without prednisone treatment, depending on the patient's response to treatment; methylprednisolone 500 mg–1 g/day - 3 days (pulsed steroid therapy) or cyclophosphamide 1 g + dexamethasone 100 mg/day every 28/28 days or IV Immunoglobulin 2 g/kg/cycle and/or rituximab 375 mg/m2/week can be preferred. Also, azathioprine 1–3 mg/kg/day, mycophenolate mofetil 2–3 g/day, methotrexate 10–17.5 mg/week, and cyclophosphamide 1–2 mg/kg/day are also agents that can be used in the treatment [18, 37, 38, 42].

5. Epidermolysis bullosa acquisita (EBA)

Epidermolysis bullosa acquisita (EBA) is a rare, acquired subepidermal blistering disease of skin and mucous membranes, which is characterized by autoantibodies to collagen VII [47]. The disease occurs at similar rates in males and females and is common in the fourth and fifth decades, but 4.6% of patients are younger than 17 years of age [48].

The disease is divided into two types mechanobullous (non-inflammatory) and inflammatory type. Mechanobullous EBA is the most common type of EBA [49]. Skin fragility, tense bullae, erosions, milium, and scar formation can be observed in areas exposed to trauma, especially the extensor surfaces of the acral regions, in the mechanobullous type [50, 51]. Although mucosal involvement is less common than the inflammatory type, esophageal stenosis may develop. Milia, atrophic scars, hyper and hypopigmentation, nail dystrophy and loss, cicatricial alopecia, and digital contractures can be seen due to scar formation during healing [47]. This type should be distinguished from porphyria cutanea tarda in particular. While bullous lesions and erosions in acral areas seen in both are similar; In porphyria, hirsutism, photosensitivity, scleroderma-like skin changes, and high porphyrin in the urine are expected [52].

In the inflammatory type, the lesions can be seen in not only trauma-prone areas but also all skin, involving the trunk, central body, extremities and skin folds, and mucous membranes, so it is different from the mechanobullous type. It shows clinical findings similar to other subepidermal bullous diseases and is divided into subtypes named according to the diseases they resemble; BP-like EBA, cicatricial pemphigoid-like EBA, linear IgA bullous dermatosis (LABD)-like EBA and Brunsting-Perry pemphigoid-like EBA [47, 48].

Among inflammatory subtypes, BP-like EBA is the most common [47, 49]. Significant itching is observed in patients with BP-like EBA. It is usually present with tense bullae and erosions on urticarial or erythematous skin, which can occur in any part of the skin, including the face, and may affect the oral mucosa. In addition, lesions surrounded by intact skin can also be seen at trauma sites. Formation of cicatrice or millium is rare during healing [49]. Histopathology reveals a subepidermal blister with eosinophilic-rich infiltrate, and u-serrated pattern linear deposition of C3 and IgG in the basement membrane zone is detected in DIF examination [18, 47].

LABD-like EBA (IgA-EBA) patients present with tense bullae with annular or polycyclic array are seen on urticarial plaques with or without oral mucosal involvement. Milia and scar development are not expected. Subepidermal blisters are characterized by linear IgA deposits in the BMZ on direct immunofluorescence (DIF) [47, 53, 54].

MMP-like EBA mainly affects mucous membranes such as mouth, pharynx, esophagus, conjunctiva, anus, genital area, and respiratory tract and heals with scarring. As in MMP, organ-specific complications may occur due to scar formation in the mucous membranes [54, 55].

Brunsting-Perry pemphigoid-like EBA; subepidermal blisters located on the head and neck with atrophic scars with minimal or no mucosal involvement [56].

It is not clinically and histopathologically possible to distinguish all these inflammatory and non-inflammatory EBA forms from other subepidermal bullous diseases. As with most other subepidermal bullous dermatoses; linear deposits of IgG and C3 in BMZ can be demonstrated in perilesional skin. Diagnosis requires a demonstration of the presence of in situ and/or circulating IgG autoantibodies against collagen VII. At this point, the salt-split skin immunofluorescence test is can be used. EBA sera react on the dermal side of the salt-split skin, while BP sera react on the epidermal side [47, 55].

EBA may be associated with cancer as well as infectious, cardiovascular, metabolic, neurological, and chronic inflammatory diseases, such as inflammatory bowel disease, thyroiditis, rheumatoid arthritis, and psoriasis [48].

The choice of treatment for EBA depends on the severity of the disease. Although there are various methods to determine the severity of the disease, in recent research, patients with body surface area < 10%, without functional loss and severe mucosal involvement, are classified as non-severe. Patients with body surface area involvement > 10%, functional loss, and severe mucosal involvement are classified as severe [37, 47].

First of all, it is important to be protected from local traumas and infections. Topical corticosteroids are the first choice in mild and localized diseases. Depending on the condition of the disease, firstly colchicine(0.5–2 mg/day) or dapsone(50–100 mg/day) should be added to the treatment as an adjuvant in non-severe disease. If there is a partial response, oral prednisone (0.5–1 mg/kg/day) can be added to the treatment. In severe disease or resistance to other treatments, first-line treatment is intravenous immunoglobulin(IVIG) (2 g/kg over 5 days) and oral prednisone (1–1.5 mg/kg/day) or pulse therapy with methylprednisolone (1 g IV for 3 days). In case of partial response or unresponsiveness to previous treatments, mycophenolate mofetil (2–3 g/day) or cyclosporine (5 mg/kg/day), or azathioprine (100–200 mg/day) can be added to the treatment. If there is still no response to treatment, rituximab (1 g IV on D0 and D14 or 375 mg/m2 weekly for 4 weeks) is used every 6 months. Methotrexate, cyclosporine, cyclophosphamide, and plasma exchange are other treatment methods that can be used [37, 38, 47].

6. Linear IgA bullous dermatosis

Linear IgA bullous dermatosis (LABD) is a rare autoimmune subepidermal vesiculobullous disease, characterized by linear deposition of IgA along the basement membrane zone [57]. The disease is caused by IgA autoantibodies directed against different antigens of the basement membrane zone (BMZ) which are extracellular polypeptides of BP180 or collagen VII [58]. LABD may be idiopathic or due to different triggering factors including drugs and systemic autoimmune diseases (rheumatoid

arthritis, psoriasis, systemic lupus erythematosus, Crohn's disease, and ulcerative colitis), infections (upper respiratory tract, gynecological infections, typhoid, brucellosis, varicella zoster, and tetanus), malignancies(bladder cancer) or less frequently, traumatic events such as burns and exposure to ultraviolet light [59–61].

The relationship between disease with drugs is well known. Vancomycin is the drug that most commonly causes LABD, followed by phenytoin and trimethoprim/sulfamethoxazole. The other commonly responsible drugs are antibiotics, non-steroidal anti-inflammatory agents, antiepileptic agents, or antihypertensives [60, 62].

The disease can occur in both adults and children. In children, the disease is known as "chronic bullous disease of childhood", that occurs in prepubertal children and has a self-healing course until adulthood [63].

LABD lesions, as in other subepidermal bullous diseases present as vesicles and tense bullae located on erythematous or normal skin and usually involve the trunk, extensor surfaces, buttocks, and face [61]. The typical clinical manifestation of LABD is an annular erythematous lesion with a ring of vesicles, a so-called "string of pearl, cluster of jewels, or rosette pattern" configuration [63, 64]. This configuration is more common in children and common locations are the trunk, the limbs, the perineum, and the perioral areas [65].

Mucous membrane involvement is common in both adults and children. The mucosa is involved more often in children than in adults [63]. While skin lesions heal without scarring, mucosal lesions may result in significant scarring. The disease is most commonly seen in the oral mucosa and conjunctiva. Mucosal strictures and corneal and conjunctival scars are the most important causes of morbidity [53, 66].

LABD clinical findings may be similar to toxic epidermal necrolysis (TEN), and even Nikolsky positivity may be seen. This situation should be kept in mind when making a differential diagnosis and a direct immunofluorescence examination should be performed [60].

Histopathological examination reveals the presence of subepidermal blisters associated with a dermal infiltrate of neutrophils and eventually eosinophils and mononuclear cells [64]. Neutrophil microabscesses at the tip of the dermal papillae may be seen [61]. In DIF examination, there is a linear accumulation of IgA along the basement membrane. IgG, IgM, and C3 accumulation may also be observed [67].

When the diagnosis of LABD is made, first of all, the patient's drug history should be well questioned. In drug-related diseases, first of all, the responsible drug should be discontinued [59]. Because drug-induced LABD has a good prognosis and most cases resolve within 2–6 weeks after discontinuation of the causative drug [66].

Topical potent corticosteroids can be used as the first choice in mild and localized diseases. In severe diseases, they are preferred in addition to systemic treatment [61].

Dapsone is considered the first-line therapy for LABD. The disease shows improvement within 2–3 days after dapsone therapy is started [66]. The dosage is 0.5–3 mg/kg/day for children and 25–150 mg/day for adults. The treatment should be started with a low dose, and the dose should be increased at intervals of 1–2 weeks until the disease is under control. Before starting treatment, the patient's glucose 6 phosphate dehydrogenase (G6PD) enzyme levels should be checked. This treatment should not be started for those with low enzyme levels. Due to the side effects of dapsone such as hemolytic anemia, agranulocytosis, dapsone hypersensitivity syndrome, leukopenia, methemoglobinemia, peripheral neuropathy, nephrotic syndrome, and abnormalities of liver function tests, patients should be followed closely during

treatment and laboratory tests should be repeated at regular intervals. Hemogram and liver tests should be checked weekly for the first 1 month, then monthly for 6 months. In long-term treatment, controls can be made every 6 months [61, 66, 67].

Sulfonamides, including sulfapyridine and sulfamethoxy-pyridazine, oral corticosteroids, tetracycline and nicotinamide, colchicine, and trimethoprim-sulfamethoxazole can be used in the treatment of cases that do not response or partial response to dapsone [59, 61, 66].

7. Anti-p200 pemphigoid

Anti-p200 pemphigoid is a rare, recently described subepidermal autoimmune blistering disease characterized by autoantibodies against a 200 kDa glycoprotein localized within the lower lamina lucida in the basement membrane zone [68].

The disease presents as tense blisters with urticarial papules and plaque, as in bullous pemphigoid, and develops in the younger population, along with significant acral and cephalic distribution and mucosal involvement. Cases with similar findings with other subepidermal bullous diseases have also been reported. An association with psoriasis has been reported in 28.3% of patients mostly in Asian patients. In addition to the rarity of the disease, its exact incidence is unknown because it is clinically similar to other bullous diseases and unavailable detective technology in most countries.

Histopathological examination reveals subepidermal separation and a moderate to dense inflammatory infiltrate in the upper dermis, usually with a predominance of neutrophils but sometimes with significant numbers of eosinophils. Linear deposits of immunoglobulin (Ig)G and C3 are detected along the dermal-epidermal junction by direct immunofluorescence microscopy of perilesional skin [68]. In indirect immunofluorescence examination of salt-split skin, the serum sample is bound to the dermal side of the skin. Diagnosis of anti-p200 pemphigoid should be confirmed by the detection of antibodies directed against a 200 kDa dermal protein by enzyme immunoassay(ELISA). In addition, autoantibodies against the 200 kDa protein in the dermal extract can also be demonstrated by immunoblot [68].

Since the disease has been described recently, a standard treatment algorithm has not been defined. The disease usually responds well to bullous pemphigoid treatment [68]. As in other bullous diseases, topical corticosteroids are primarily used in the treatment of localized diseases. A combination of systemic corticosteroids and adjuvant immunomodulatory agents is preferred for systemic treatment. Unlike bullous pemphigoid, dapsone is the most preferred adjuvant agent in this disease [69].

8. Conclusion

Subepidermal bullous diseases are a group of diseases with skin and mucosal findings. To distinguish these diseases, which have many clinical similarities with each other, it is necessary to use tests such as histopathology, immunofluorescence, and ELISA. Complications due to these diseases themselves and the treatments applied are the cause of serious morbidity and mortality. Therefore, close follow-up of these patients and a multidisciplinary approach to treatment management are very important.

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