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Bullous Systemic Lupus Erythematosus and Cicatricial Pemphigoid

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Abstract

Bullous systemic lupus erythematosus is a rare distinctive subepidermal bullous disease seen in patients with systemic lupus erythematosus (SLE). It has characteristical clinic, pathologic, and immunologic findings including antibodies to type VII collagen, laminin 332, laminin 331, and bullous pemphigoid antigen 230. Clinical presentation combined with histopathology, immunological testing, and concomitant diagnosis of SLE according to the criteria of American College of Rheumatology, are required to distinguish bullous SLE from these bullous diseases. In patients with bullous SLE, SLE disease progression and complications may be worse. Cicatricial pemphigoid is a chronic subepidermal blistering disease which is characterized by erosive lesions of mucous membranes and skin. Pathogenesis of cicatricial pemphigoid is characterized by linear deposition of Immunoglobulin G, A, or complement 3 along the epithelial basement membrane zone. The main target antigens are bullous pemphigoid antigens 180–230, laminin 331–332, type VII collagen, and β-4 integrin subunit. Cicatricial pemphigoid may lead to serious complications such as blindness and airway obstruction. Herein, clinical, histological, immunopathological features, the diagnosis and treatment of bullous SLE and cicatricial pemphigoid diseases are mentioned to raise awareness among the dermatologists about this important but rare heterogeneous bullous disease.

Keywords: bullous dermatosis, bullous systemic lupus erythematosus, nephritis, cicatricial pemphigoid, mucous membrane pemphigoid, ocular, oral, subepithelial autoimmune disease

1. Bullous systemic lupus erythematosus

1.1. Introduction

It has been reported that numerous cutaneous lesions might be seen in 59–76% of patients with systemic lupus erythematosus (SLE) [1, 2]. But, blistering lesions are relatively

uncommon, which is approximately less than 1% of all cutaneous lesions seen in SLE [2]. Patients with SLE may have intense inflammation and basal vacuolar degeneration that induce blister formation [3]. However, SLE with concomitant separate bullae is rare. Bullous SLE (BSLE) is a heterogeneous disease that has distinctive clinical and histologic features [1].

BSLE is caused by several defined autoantibodies. Primary autoantibodies are anti-type VII collagen antibody [4] and antibodies against laminin (Lam)-332, Lam-331, and bullous pemphigoid (BP) antigen-230 have been identified later [5, 6].

Rupture of blisters leads to skin loss and erosions that cause significant dehydration, loss of electrolytes, and proteins, particularly if there is extensive body surface involvement. Moreover, if the oral mucosa, and gastrointestinal system are affected, the patient may not be able to take adequate food and medication. Thus, these changes cause immunosuppression, and eventually infections and sepsis as well. So, it is important to diagnose and treat carefully all autoimmune bullous dermatoses, as they have fatal complications and morbidities [7].

BSLE is characterized by subepidermal, transient, tense vesiculobullous eruptions located on any area of the body. Contrast to BSLE, in all types of cutaneous lupus erythematosus (CLE), vesiculobullous lesions are typically polycyclic erosions with an advancing blistering border on sun-exposed areas of the body [8–11]. Beyond the clinical presentations, pathogenesis and histopathological features are quite different among those types of diseases. In CLEs, a genetic base originated from variations in multiple loci leads to susceptibility to LE and disease activity is provoked by exogenous or endogenous triggers. The best known trigger is exposure to ultraviolet radiation [8, 12–15]. BSLE is associated with an increased prevalence of the human leukocyte antigen (HLA) class II DR2 haplotype-like SLE. Furthermore, it has also been found that the DR2-associated DRB1*1501 allele can be seen in patients who develop antibodies to type VII collagen [16]. However, triggering factors have not been exactly defined in BSLE [9].

Histologic findings of CLEs such as epidermal atrophy, hydropic changes, apoptotic keratinocytes, and mucin deposits are not expected in BSLE either. Direct immunofluorescence (DIF) study in CLEs and BSLE may be similar while IIF studies show different findings [3, 14]. Thus, differentiation of BSLE from other types of CLEs can be possible based on clinical features, histopathology, and immunohistochemical examinations.

Dermatitis herpetiformis (DH), BP, epidermolysis bullosa acquisita (EBA), and linear immunoglobulin (Ig) A bullous dermatoses (LABD) are included in the differential diagnosis of BSLE due to the presence of similarities in clinic, histology, and immunopathology [17]. Briefly, DH can be excluded by light microscopy and direct immunofluorescence (DIF) method. BSLE, BP, and EBA have similar DIF patterns. Salt-split skin test demonstrates IgG antibodies on the epidermal side (roof pattern) of the split skin in BP unlike EBA and BSLE in which IgG antibodies bind on the dermal side (floor pattern) of the split skin. Thus, differentiation between BSLE and EBA is not possible by demonstration of dermal binding in salt-split skin test. Presence of ACR criteria for the diagnosis of SLE points the way to BSLE [6, 18].

To diagnose BSLE, fulfillment of the criteria of SLE is required. The Systemic Lupus International Collaborating Clinic (SLICC) group recently validated the 1997 American College of Rheumatology (ACR) revised criteria for SLE [19, 20]. Also, a new classification was defined by SLICC group. Misdiagnosis of SLE is less likely to occur through this new classification system. During the vesiculobullous presentation of BSLE, also systemic symptoms of SLE may get worse. Particularly, nephritis has been found associated to BSLE in many cases [12, 21–23]. However, the exact underlying mechanism has not been found yet.

A thorough history, the clinical presentation, fulfilling the criteria of ACR for SLE and histo-pathological findings along with DIF, IIF, and ELISA can be helpful in diagnosing most cases of BSLE [24].

BSLE lesions are usually recalcitrant to the systemic corticosteroids which are used to treat the other manifestations of SLE [1]. The corner stone treatment of BSLE is dapsone and response is rapid even with small doses [1, 5, 8]. However, sometimes for the patients who fail to respond to dapsone or have intolerance to dapsone or have significant systemic SLE involvement—includes nephritis—other medications such as systemic steroids or other immunomodulatory treatments such as azathioprine, methotrexate, antimalarial agents, mycophenolate mofetil (MMF), rituximab, and intravenous immunoglobulin (IVIG) may be needed [5, 6].

1.2. Epidemiology and history

BSLE is an uncommon, auto-antibody-mediated subepidermal bullous eruption occurring in patients with SLE [4, 5]. BSLE generally affects young females of all races especially in the second to fourth decades of life. There have been some reported cases in older patients or in children as well [10–13, 25]. Female dominance may be related to SLE. Furthermore, there has been no informed race predominance up to now [8].

There have been case reports on SLE presenting with hemorrhagic bullae on sun-exposed areas of the body of patients in the literature as early as in the late nineteenth century. The clinical photographs of a patient were published in 1961 by Tromovitch and Hyman. She was a 26-year-old woman with SLE and had hemorrhagic bullae on the extensor aspects of the arms and legs, which are thought to be bullae of bullous SLE. The histologic examination of the lesion revealed bullae containing polymorphonuclear cells and some lymphocytes. But in that time, DIF method was not available, and so it could not be performed as well [26]. Also, the first well-documented cases of BSLE were published by Hall et al. [27].

1.3. Immunopathogenesis

In BSLE, main autoantibodies are circulating anti-type VII collagen antibodies (noncollag-enous domain (NC) 1 and 2). Type VII collagen is found in the basement membrane zone (BMZ) as an important element of anchoring fibrils, and maintains adhesion at the dermo-epidermal junction (DEJ). Lam-332, and fibronectin, and especially NC1 domain of type VII collagen play important role in adhesion between the lamina densa, lamina lucida, and keratinocytes. Antibodies against type VII collagen are characteristic for both BSLE and EBA [4, 5].

On the other hand, Chan et al. [6] has described other antigens related to immunopathogenesis of BSLE, which are namely Lam-331, Lam-332, and BP230. Although these molecules have been identified, the exact mechanism of autoimmunity in BSLE has yet to be elucidated, but it is theorized that antibodies to type VII collagen induces epitope spreading which leads to a secondary autoimmune response to the newly exposed targets in BSLE [1, 6, 8].

The NC1 domain of type VII collagen which consists of nine back-to-back homologous fibronectin III-like subdomains and two flanking von Willebrand factor A-like domains, play a role in mediating interactions between type VII collagen and other matrix proteins [28]. The aminoterminal is also termed as cartilage matrix protein and antibodies to this cartilage matrix protein subdomain have been shown to induce dermoepidermal separation *in vivo* [29]. However, the pathogenic relevance of binding of autoantibodies to fibronectin III-like domains which was shown by immunoblotting has not been clarified yet [30]. In both *ex vivo* and *in vivo* studies demonstrated that the Fc portion of the autoantibody, activation of complement and release of elastase and gelatinase B, and reactive oxygen species released from activated neutrophils are important for blister formation in BSLE and EBA [13, 31–33]. As mentioned previously, in addition to complement activation, release of proteases and reactive oxygen species from neutrophils has been shown to be fundamental for dermoepidermal separation induced by autoantibodies to type VII collagen *ex vivo* and *in vivo* in the pathogenesis of BSLE and EBA [11, 12, 20, 31, 32, 34].

An association between susceptibility to LE and autoimmunity to type VII collagen has been suspected for the reason of presence of autoantibodies to type VII collagen are part of the autoantibody repertoire of some patients with LE. Some authors claimed that autoantibodies to type VII collagen are seen in BSLE patients whereas some assumed there is a particular association between EBA and SLE. Also, there have been reported cases with concurrent SLE and EBA, EBA followed by SLE, and SLE followed by EBA [35–39]. Some patients with SLE were reported that had autoantibodies to type VII collagen documented by indirect immunofluorescence (IIF) on split skin, immunoblotting, and immunoelectron microscopy (IEM) methods but no blistering disease [30].

There is a defined genetic base originating from variations in multiple loci in all types of CLEs. While this genetic base leads to susceptibility, exogenous, or endogenous triggers cause the presentation of the disease. The best known trigger is ultraviolet radiation [8, 12–15]. BSLE is associated with an increased prevalence of the HLA class II DR2 haplotype like SLE. This HLA-DR2 haplotype has been found associated with hyperimmunity [40]. Furthermore, antibodies to type VII collagen in BSLE have also been found to be related to the antigen-presenting protein encoded by the DR2-associated DRB1*1501 allele. In other words, this allele was found only in BSLE patients [16]. It is possible that this genetic predisposition is responsible for an increased risk for development of autoimmunity to BMZ antigens. Overproduction of autoantibodies by hyper-reactive B cells as a result of depressed T suppressor activity is an important feature of SLE [8].

In the patients with BSLE, all types of immunoglobulins can be present in the deposits around the DEJ, but the main identified type is IgG, followed by IgA and IgM [22–25]. Ig deposits may be found in biopsies of both lesional and perilesional skin, whereas complement is seen

in particular in perilesional region. Therefore, it is estimated that antibody-mediated activation of complement may lead to blister formation in BSLE patients [31]. Furthermore, *in vitro* studies have revealed that antibodies to type VII collagen lead to the activation of both complement and neutrophils causing the separation within the DEJ [9, 41, 42]. This proteolysis by leukocytes (induced by antibodies) was previously shown to occur in EBA disease, too [42]. Therefore, the immunopathological similarities and clinical presentations may cause diagnostic confusion between BSLE and EBA. Besides that, a distinct immunological divergence could be shown by the determination of IgG subclass concentrations between EBA and BSLE. IgG2 and IgG3 deposits are found more often in BSLE patients, whereas IgG1 and IgG4 deposits are observed in EBA patients. Even if the functional properties of IgG subclasses are well known, the specific contribution of each subclass to the pathogenesis in autoimmunity to type VII collagen is controversial [8, 22, 31, 41]. The determination of quantity and quality of circulating autoantibodies in the serum of patients is important for diagnosis, prognosis and treatment choices in autoimmune blistering dermatoses [31].

Recke et al. reported that recombinant anti-type VII collagen IgG3 antibody and, a lesser extent, IgG1 autoantibodies, were able to activate complement at the DEJ. IgG2 and IgG4 antibodies were found inactive [31].

1.4. Clinical features

Clinically, BSLE is characterized by rapid onset, tense vesicles, and bullae on the erythematous edematous plaques or normal skin and involves both sun-exposed and nonexposed areas in patients who meet the ACR revised criteria for SLE [2, 5, 7]. Bullae are usually multiple and may resemble bullae of BP, or may be small and grouped like DH lesions [1]. The lesions rapidly expand and have a predilection for face, vermillion border, upper trunk, supraclavicular region, and proximal extremities. Previously, it was thought that BSLE is seen only in sun-exposed areas, but now it has been shown that it can also affect any area of the body including the oral, pharyngeal, nasal, and vulvar mucous membranes [1, 2]. In addition, usually herpetiform vesicles are seen if there is facial involvement in BSLE. These lesions can be on malar areas with erythema and/or, perioral region, and vermilion border. Moreover, there have been some BSLE cases reported that present with only facial lesions as well [43, 44].

Other than vesicles or blisters, erythematous plaques with annular configuration, urticarial eruptions, erosions, crusted lesions and targetoid lesions can also be seen [5, 9]. But interestingly, the primary lesions of chronic discoid, subacute, and acute LE are not commonly seen in BSLE [30]. Pruritus or burning sensation may or may not be present [8, 45]. If there is, pruritus is mild. In contrast to DH, lesions are less often seen on extensor surfaces, however some BSLE cases involving extensors such as hands, knees, or feet have been reported [46, 47].

There are many case reports showing that BSLE can be the initial presentation of SLE in both adults and children [11, 12, 21, 48–51]. Moreover, some authors estimated that BSLE may be associated with increased activity of SLE such as renal involvement, serositis such as pericarditis or pleuritis, pulmonary hemorrhage, cutaneous vasculitis, etc. [11, 12, 17, 21, 25, 44]. Nevertheless, the exact underlying mechanism of developing nephritis in BSLE is not clear. It is estimated that glomerular and/or tubular scarring causes injury to renal extracellular

matrix and by this injury, new expression of collagens, which does not locate in normal glomeruli, is oversynthesized and these antigens can trigger autoimmune reactions [2, 44, 52, 53]. Diagnosis of BSLE is important since BSLE may indicate development of lupus nephritis and resistance to treatment [12, 15, 44].

Most of the patients with BSLE have positive ANA tests. Moreover, anti-dsDNA, anti-Sm, anti-La/SS-B, anti-Ro/SS-A, and anticardiolipin antibodies may also be detected as well. Other laboratory findings that are related to SLE such as elevated erythrocyte sedimentation rate, hypocomplementemia, hematologic abnormalities (anemia, thrombocytopenia, leukopenia), and abnormal urinalysis (proteinuria or/and urine casts) can also be observed in BSLE [16].

1.5. Histopathology

Typically, histopathologic examination of early BSLE lesion shows inflammation and dermo-epidermal separation at the BMZ. The epidermis is often intact. In the upper dermis, edema, and dermal papillary, neutrophilic microabscesses are seen similar to histopathological features of DH [1, 8, 25, 30]. In most of the cases, neutrophils are not only seen in the papillae, but also form a continuous linear pattern which is concentrated in the upper dermis, in the blister cavity, and beneath and on the BMZ [30].

A subepidermal blistering and perivascular (around mid and upper dermal blood vessels) inflammatory infiltrate, including particularly lymphocytes, occasionally eosinophils and monocytes, are other histologic features of BSLE. Moreover, in some cases of leukocytoclasis, erythrocyte extravasation and necrosis of blood vessels, which belong to necrotizing vasculitis, may be seen. But in these cases, which have vasculitis characteristics, clinical features of vasculitis do not exist interestingly. Additionally, dermal vasculitis can be seen more frequently in BSLE than DH [8, 17].

Some characteristic histopathological features of LE such as basal layer vacuolization, epidermal atrophy and thickening of the BMZ, mononuclear cell-predominant inflammation, mucin deposition in the reticular dermis are usually absent or rarely found in BSLE lesions [8, 17, 30].

1.6. Direct and indirect immunofluorescence techniques and immunoelectron microscopy

Classic immunopathologic features of BSLE by DIF examination are immune deposits in the upper dermis and along the BMZ and occasionally in upper dermal venules [8, 15, 30, 50]. These deposits include main Igs (IgG, IgA, and IgM), and complements. Complement proteins are usually present in lesional skin but may be absent in clinically normal skin.

Among the aforementioned Ig types, IgG is most commonly seen, while IgM and IgA are present in approximately 70% of cases. These depositions of Igs have two major patterns: granular in approximately 60% of cases and linear in 40%. In a few cases, fibrillar or thready patterns of depositions have been reported as well [8, 15, 53]. Furthermore, in some cases, a mixed pattern with a linear band of deposits and scattered granular deposits has been shown. In this linear pattern, deposits may be bandlike, thin, or widen. Regardless of the pattern of deposition, clinical and histopathologic features of BSLE does not differ, and they are steady [53].

DIF study of BSLE lesions presents a resemblance of EBA; however, they are different from DH. Granular IgA deposits in DH disease are seen as confined to dermal papillae typically; however, in BSLE, it is not seen. Moreover, IgA deposits appear to be more common in BSLE than in SLE patients without blisters [4, 14, 27, 30, 45]. It should be kept in mind that DIF studies of BSLE can be similar to that of CLEs [17, 35].

The substrate used in IIF studies is normal human skin, and it is processed with patient serum to detect the circulating antibodies. In most cases of BSLE, autoantibodies to type VII collagen is detected by IIF studies; however, in some cases, negative staining may be seen, particularly in the patients with granular Ig deposition pattern by DIF. DIF studies on salt-split skin from patients commonly show deposition along the dermal side, some beneath of the lamina densa, and some shows no deposition [36]. This heterogenicity of BSLE cases does not affect the clinical features in patients [53].

IEM shows deposits of Igs as a linear continuous band along the DEJ of dense granular reaction products in the upper dermis beneath the basal lamina. Depositions may also be seen on the lamina densa and in the perivascular region and occasionally in the deeper dermis as well. The deposits do not localize in the lamina lucida, and thus, the possibility of a primary bullous disease such as BP is excluded; because in BP, antibodies are against hemidesmosomal and/or lamina lucida antigens [1, 8].

1.7. ELISA and immunoblotting

Antibodies against 290- and 145-kDa autoantigens (type VII collagen) [36], can be extracted from the sera of BSLE patients via immunoblotting [28]. As mentioned previously, these autoantigens that are seen in BSLE patients are also target antigens in EBA.

Most recently developed method is ELISA, and the diagnosis of BSLE can be made faster and more accurate via ELISA. In ELISA method, NC1 and NC2 domain epitopes of type VII collagen are used to find the presence of circulating antibodies in sera of patients. By this method, differential diagnosis between BSLE and EBA can be provided easily for the reason of EBA patients to have higher levels of IgG1 and IgG4, while BSLE patients have higher levels of IgG2 and IgG3 in their serum [23, 31, 37].

1.8. Diagnosis

The diagnostic criteria of BSLE was first proposed in 1983 [45] and was revised after the administration of salt split-skin immunofluorescence in 1988 [54]. These criteria include:

1. a diagnosis of SLE based on ACR criteria;

2. a nonscarring vesiculobullous eruption;

3. histopathologic features similar to DH-neutrophil-rich infiltrated subepidermal blisters in papillary dermis;

4. positive DIF of perilesional skin with deposition of IgG and/or IgM and IgA at the BMZ,

5. negative or positive IIF testing for circulating autoantibodies against the BMZ via the salt-split skin technique;

The BSLE patients were divided into three groups (**Table 1**) [15, 30] based on the presence of antibodies to type VII collagen and location of the antibodies against the BMZ [25, 30]. Distinguishing subtypes of BSLE based on clinical features is not possible, but could be performed only through immunohistochemistry. Type I patients have circulating or deposited autoantibodies to type VII collagen, as determined by IIF or IEM and type I patients also have been fulfilling all criteria of ACR. However, type II patients do not demonstrate autoantibodies to type VII collagen; they have autoantibodies against undetermined location of antigen or dermal antigen other than type VII collagen, and furthermore, these type II patients satisfy only one to four criteria of ACR [2, 30]. And, autoantibodies to type VII collagen can be shown bound to either epidermal or both dermal and epidermal in type III patients [30, 49].

Type I	
Clinic	Fulfilling all criteria of SLE of ACR; subepidermal, transient, tense vesiculobullous eruption located on any area of the body
Histopathology	Infiltration of neutrophils in the upper dermis, dermal edema, subepidermal blister
DIF	IgG, IgA, and IgM, complement at the BMZ
IIF	Circulating autoantibodies to type VII collagen (+), positive or negative for dermal staining of salt-split skin
ELISA/immunoblotting	Positive or negative reaction to 290 and 145 kDa proteins from human skin basement membrane extracts
IEM	Ig deposits in upper dermis and beneath and on the lamina densa
Type II	
Clinic	Fulfilling one to four criteria of ACR; same as type I
Histopathology	Same as type I
DIF	Same as type I
IIF	Circulating autoantibodies to type VII collagen (−), negative for staining of split skin
ELISA/immunoblotting	Negative reaction to the 290 and 145 kDa proteins from basement membrane extracts
IEM	Scattered granular deposits in the upper dermis, but none on or beneath the lamina densa
Type III	
Clinic	Same as type I
Histopathology	Same as type I
DIF	Same as type I
IIF	Circulating autoantibodies to type VII collagen (+/−), positive for epidermal staining of salt-split skin
ELISA/immunoblotting	Positive or negative reaction to 290 and 145 kDa proteins from basement membrane extracts
IEM	Ig deposits in the epidermis, sometimes in the upper dermis and lamina densa

Table 1. Subtypes of bullous SLE.

Because of similar features between BSLE and other immunobullous dermatoses, the correct diagnosis of BSLE could be done by sum of the clinical, histological, immunohistological, and IEM features and meeting the ACR criteria for SLE [8]. The criteria proposed by Camisa and Sharma were formed before IEM, ELISA, and immunoblotting techniques [54]. These methods which can detect circulating antibodies in serum provide more accurate diagnosis of BSLE [15, 55].

1.9. Differential diagnosis

As mentioned previously, blisters can be seen in all types of CLE including acute, subacute, and chronic CLE. But, these bullous lesions are different from BSLE in terms of their clinical, histological, and pathogenetical features. In all types of CLEs, a genetic base originated from variations in multiple loci leads to susceptibility to LE and disease activity is provoked by exogenous or endogenous triggers. However, in the pathogenesis of BSLE, these genetic susceptibility or triggering factors have not been mentioned clearly [8, 12, 14]. Blisters in CLEs are polycyclic erosions with an advancing blistering border and always seen over an erythematous base predominantly on sun-exposed parts of body. Subepidermal blister formation in CLEs is caused by extensive interface inflammation and basal layer vacuolization which can be seen in CLE [3]. Histologic findings of CLEs such as epidermal atrophy, hydropic changes, apoptotic keratinocytes, and mucin deposits are not expected in BSLE. DIF study in CLEs and BSLE may be similar, while IIF shows different findings [3, 14]. Thus, differentiation of BSLE from other types of CLEs can be done based on clinical features, histopathology, and immunohistochemical examinations [12, 15].

Lesions can mimic other vesiculobullous disease such as EBA, BP, DH and LABD [15]. There are two main clinical presentations of EBA: the classical (mechanobullous, non-inflammatory) and the inflammatory subtypes. In classic type of EBA, skin lesions appear over non-inflamed skin. It also has chronic course with skin fragility, usually resistant to therapy, and often causes to debilitating sequelae. The lesions heal with scarring and milia limited to the trauma-prone skin surfaces [15, 56, 57]. However, lesions of inflammatory type of EBA present with transient tense bullae over inflamed skin like BSLE lesions. The similarity of clinical features between inflammatory type and BSLE can cause confusion in diagnosis, especially in patients with no known prior history of SLE. But there are some clues to differentiate; for instance, EBA is more common in the fourth and fifth decades of life and has usually older patients than patients with BSLE [31]. Clinically, in contrary to lesions of EBA which sometimes presents with fragile blisters appearing over hands, knuckles, elbows, knees, and sacrum like dystrophic type, lesions of BSLE are nonscarring, and milia or fragility of the skin on trauma-exposed areas are not expected characteristics [10, 57]. Furthermore, hypo- or hyperpigmentation may remain after healing as well [8]. Also, there is another subset of patients with predominant mucous membrane involvement, and indistinguishable from cicatricial pemphigoid (CP) clinically, presenting with blisters and scarring in the oral, ocular, vaginal, and other mucous membranes, leading to significant dysfunction of organs, and even death [7]. The histopathology of EBA is quite heterogeneous but has much less dermal inflammatory infiltrate in classic type of EBA in comparison to BSLE [8]. Immunopathological similarities and diagnostic challenge that exists between BSLE and EBA can be also surmountable by

IgG subclass concentration analysis. As mentioned previously, IgG2 and IgG3 deposits are more in BSLE patients, while IgG1 and IgG4 deposits are more often in EBA patients [8, 22, 31, 41]. In addition, EBA has been related to many systemic diseases including hematologic, infectious, and endocrine conditions, autoimmune disorders, malignancies, and particularly inflammatory bowel diseases (IBD) [58]. EBA is a chronic autoimmune disease, oral mucosal involvement may be extensive, and more resistant to treatment with steroids, dapsone, and other immunomodulatory agents, whereas lesions of BSLE can recover completely with treatment [56]. Also, occasionally some BSLE cases were reported with features of EBA [39, 59].

BP is one of the main diseases in the differential diagnosis of BSLE. BP is characterized by tense bullae, erosions, and crusts that arise on normal or erythematous skin on the entire body but mostly trunk, extremities. Bullae usually heal without scarring or milia formation and patients mostly have pruritus that may precede blistering by months [60]. BP is more common in elderly patients, especially over 65 years old [10]. Histopathological findings are subepidermal blisters with inflammatory cell infiltrate in the superficial dermis containing predominantly eosinophils. Neutrophilic microabscess does not exist contrast to BSLE [10]. It is thought that eosinophils have an important role in blister formation via degranulation at the BMZ. Early prebullous, urticarial-type lesions may show eosinophilic spongiosis as well. About 70% of BP patients have elevated serum IgE and about 50% have blood eosinophilia. DIF study of perilesional skin shows linear deposits of complement C3 (90–100% of patients) and IgG (70–90% of patients) at the BMZ. It is important to know that if DIF is negative for C3, the diagnosis of BP is suspicious [61]. IIF study shows circulating IgG that binds the epidermal basement membrane in most cases. ELISA test for BP180 and BP230 antibodies is positive. The negative pemphigoid serologies by ELISA tests, incompatible histologic and IF findings help to differentiate BSLE from BP [8].

In patients with LE, all blistering eruptions may not be BSLE all the time. Additionally, these patients tend to have co-morbidities which need many medications that can lead to bullous drug reactions. Also, sometimes patients with a severe acute or subacute CLE may resemble the symptoms of erythema multiforme (Rowell syndrome) or toxic epidermal necrolysis (TEN). In these type of patients, the eruptions are expected to develop rapidly or evolve over several weeks. And also in TEN-like acute CLE, lesions start as diffuse or patchy erythema, more often on sun-exposed part of body and later, and evolve into flaccid annular bullae rapidly. They also show positive Nikolsky sign, whereas in BSLE nikolsky sign is generally negative. Histopathology of these lesions show solitary necrotic keratinocytes at lower epidermis, junctional vacuolar degeneration, intensive periadnexal and perivascular lymphocytic infiltrates, thickened BMZ, the presence of plasma cells or mucin unlike TEN and BSLE [62, 63]. Furthermore, DIF examination of this LE lesions sometimes shows granular deposits of IgG and/or IgM, and less commonly IgA, at DEJ; but this could not be seen all the time, meanly a negative DIF does not rule the LE out [64].

In these patients with TEN-like CLE, often severe systemic disease involvements are seen such as lupus nephritis, or cerebritis, etc. The underlying mechanism of TEN-like CLE may be related to Fas-Fas ligand interactions, which have resulted in the massive keratinocyte apoptosis. This severe condition of CLE, mostly have to be treated with IVIG and/or systemic corticosteroids [16].

Moreover, there have been other primary blistering disorders reported in association with LE, including pemphigus vulgaris, LABD, porphyria cutanea tarda, fixed drug eruption (FDE),

Stevens-Johnson syndrome (SJS), TEN as well. FDE lesions are characterized by sharply marginated, round- or oval-shaped lesions that can have central bullae [8]. These bullae may be seen widespread like TEN. To differentiate FDE from other bullous presentations, some clues are important to know. In FDE, a drug history must be exist like SJS/TEN but, in FDE patients recurrent episodes are typically seen in minutes to hours after re-exposure to a particular medication, whereas in SJS/TEN, recurrent episodes due to the medication can occur in as early as 2 days. FDE lesions occur in the same location as previous episode. Histopathological findings of FDE lesions show superficial and deep perivascular mixed infiltrate with lymphocytes, neutrophils, eosinophils, and histiocytes. However, in TEN, typically there is usually only a superficial perivascular infiltrate with lymphocytes and histiocytes. DIF of FDE lesions is not well described; linear IgG and C3 deposition along the BMZ, perivascular, and intercellular IgG and C3 were reported. Thus, in addition to history, clinical feature, and histopathology, DIF method helps to rule out FDE from BSLE [64].

In SJS/TEN, which have a significant mortality risk, there can be extensive skin involvement with especially annular lesions and moderate-severe mucosal involvement with a clear drug association. However, in BSLE generalized skin involvement is rarely seen and mucosal involvement is uncommon. Also, in BSLE there has been no known drug association either. Prognosis is poor in SJS/TEN; in BSLE prognosis depends on the systemic components of SLE [24, 25, 65]. But differentiation from these diseases depends primarily on history, clinical features, histologic findings, and DIF tests [66–68].

As mentioned previously, DH is also involved in the differential diagnosis of BSLE. DH, also known as Duhring's disease, is a chronic autoimmune bullous disease, associated with celiac disease and gluten sensitivity. It is claimed that DH can be regarded as a skin manifestation of gluten sensitivity, a systemic disorder capable of affecting multiple organs. [69]. DH is characterized by grouped erythematous excoriated papules or plaques with small, clustered herpetiform vesicles, and tense blisters distributed symmetrically over extensor surfaces—particularly elbows, knees, buttocks, and shoulders, rarely on the oral mucosa. The eruption of DH most often begins between the ages of 15 and 50 years and persists indefinitely. Patients have generally intense itching and burning sensation [70]. There is an association with the genotypes HLA DR3, HLA DQw2, found in 80–90% of cases. HLA-Al, -B8 are also found to be as related genotypes. Celiac disease has association with HLA-B8, HLA-DR3, and HLA-DQw2 histocompatibility complex antigens as well. This means DH and celiac disease have a common immunogenetic background [71]. Morbidity is mainly related to the intense pruritus, scratching, discomfort, commonly seen superimposed infections. Also, systemic complications are related to the associated gluten-sensitive enteropathy. Celiac disease is accepted to be present in all patients with DH, but some of these patients have subclinical gastrointestinal disease with no symptoms, only histological findings as well. Gastrointestinal symptoms of patients with DH are milder than those seen in patients with celiac disease without skin lesions [72]. Histopathologic examination of the lesion shows subepithelial bulla with neutrophils in the dermal papillae, fibrin deposition, and edema. Usually, papillary neutrophilic microabscesses progress to subepidermal vacuolization and vesicle formation. In DIF microscopy granular IgA deposits in dermal papillae of perilesional skin is found [48]. The clinical and histopathological features of DH can be the same as those of BSLE. Extensor surface involvement is less common in BSLE and pruritus is usually absent or mild [8]. Contrary to

BSLE, in DH the markers of gluten sensitivity: anti-gliadin, anti-endomysium, and anti-tissue transglutaminase antibodies are important characteristics, and gluten-free diet, dapsone, and sulfone therapy are the main choices of treatment. In BSLE, IgG and IgM can be found in addition to IgA in the BMZ. Thus, this finding helps to differentiate BSLE from DH, in which only IgA deposits are observed [48].

LABD is an autoimmune mucocutaneous disorder that characterized by subepithelial bullae caused by IgA autoantibodies. These autoantibodies are directed against BMZ and the genetic basis of the disease is found related to HLA Cw7. Although it was previously confused with DH; now they are well-recognized distinct entities. Furthermore, in contrast to DH, there is no association with gluten-sensitive enteropathy, and the gluten-free diet is ineffective in LABD disease as well [73]. Bullae may be clear or hemorrhagic, tense like BP bullae, vary in size, and frequently tend to form annular or polycyclic plaques and they have risen out of normal skin, or on an erythematous or urticarial base. LABD can be seen at any age, but there are two peaks of onset: at 40–60 years of age and in children of preschool age. It has a heterogeneous clinic based on age of onset, clinical features, and distribution. In children, vesiculobullous lesions are mainly seen on the lower abdomen and the perineal area, whereas face, hands, and feet are rarely involved. Blisters commonly occur in a "cluster of jewels" pattern [74]. However, in adults, LABD lesions mainly involve extensor surfaces, buttocks, trunk, and the perioral area. These lesions are usually highly itchy. All mucous membranes may be involved; particularly, the oral cavity and eyes are the most common affected mucosal area. Lesions of the oral cavity cause generally severe pain. LABD may be idiopathic or associated with SLE [75], inflammatory bowel disease (IBD), Crohn's disease, and ulcerative colitis [76], infections [77], malignancies-particularly hematologic cancers [78], and drugs such as vancomycin, captopril, acetaminophen, and phenytoin [79]. Physical trauma and ultraviolet exposure have been also reported as triggering factors in the pathogenesis of LABD [80]; however, in the literature, most cases of LABD are idiopathic [7].

The histopathologic examinations of LABD lesions show a subepithelial blister with a predominant neutrophilic infiltrate—occasionally eosinophils and mononuclear cells—in the upper epidermis that forms papillary microabscesses. The DIF examination of LABD shows the presence of IgA deposits along the BMZ in a linear pattern. IIF generally shows a variable positivity of 30–50% of circulating IgA autoantibodies in LABD patients [81]. Usually, dramatic response to sulfones or sulfonamide is seen in LABD patients. In idiopathic cases of LABD, dapsone treatment is the best choice [82]. Based on clinical and histologic features alone, it may be hard to distinguish LABD from BSLE. Therefore, one or more advanced methods such as DIF, IIF, salt-split skin, Western immunoblotting, and IEM should be used to differentiate these diseases [83].

1.10. Treatment

For other cutaneous manifestations of SLE disease, the main treatments are topical and systemic steroids and antimalarials [5]. Differently from these cutaneous lesions, BSLE lesions are often recalcitrant to the high dose systemic corticosteroids which are used to treat the other systemic manifestations of SLE [1]. The primary treatment choice in BSLE is dapsone and this is one of distinguishing features of BSLE from most of other autoimmune bullous dermatoses. Even with low doses (25–50 mg/day) of dapsone, improvement of skin lesions is expected to be observed within the first 24–48 h of the therapy. However, during dapsone

therapy, improvement in the systemic involvement often does not parallel the cutaneous response. For example, Kettler et al. [84] reported a child case of BSLE whose cutaneous eruptions responded rapidly to the treatment of dapsone, whereas the oral ulcers did not improve without prednisone therapy. Beside this, they used prednisone treatment alone, but cutaneous eruption of the patient did not improve either. Oral ulcers healed after starting the combination therapy of dapsone, prednisone, and sulfapyridine. As distinct from most of BSLE cases, Alarcón et al. reported a case of BSLE whose rashes worsened by dapsone treatment. The patient was recovered by systemic steroid therapy [85].

Total regression of cutaneous lesions is generally seen within weeks [1, 8, 27, 37, 86]. Dapsone has several mechanisms that mainly act via interference with the chemotaxis-adherence-cytotoxic enzymes of neutrophils [87].

The main adverse effects of dapsone treatment are methemoglobinemia, hepatitis, headache, motor neuropathy, exfoliative dermatitis, and fatal agranulocytosis. Especially patients with glucose-6-phosphate dehydrogenase deficiency may present with severe hemolysis after dapsone treatment. Therefore, patients should be tested for this enzyme deficiency before being treated with dapsone. Furthermore, in BSLE patients, the risk of hemolysis is higher than DH patients. So, it is recommended that the dapsone dosage per day should not exceed 1.5 mg/kg to minimize this side effect [21, 87]. Interestingly, it has been reported that in some cases with BSLE, dapsone treatment lead to exacerbation of lesions [5, 85].

Dapsone can be stopped by tapering, but there is no exact time to stop the treatment and usually there has been no relapse reported in BSLE patients [8, 88]. Recurrences are often seen rapid after the withdrawal of dapsone. However, restarting the treatment can provide prompt remission [88]. In general, discontinuance of dapsone therapy is usually recommended after 1 year.

Furthermore, sometimes—especially if systemic involvement is significant such as nephritis—dapsone is not sufficient. Steroid treatments or other immunomodulatory treatments such as azathioprine, methotrexate, cyclophosphamide, antimalarial agents, and MMF can be used for these patients or for the patients who fail to respond to dapsone or have intolerance to dapsone [4, 5]. In addition, rituximab was recently reported to be effective in cases of BSLE with no response to dapsone and other immunomodulatory treatments [15, 18, 89]. Anyanwu et al. reported an oral BSLE case treated successfully with rituximab [90].

Moreover, Pehr [91] reported that in the youngest case of BSLE, the combination of MMF and erythromycin was found to be effective. Interestingly, in that case, neither dapsone nor medium- to high-dose systemic steroid treatments provided benefit. Near-perfect control of BSLE was provided in some cases after combination therapy of erythromycin and MMF was administered. MMF had been used in other bullous diseases of children with good results and for systemic manifestations of childhood LE [92–94]. MMF acts via blocking de novo purine synthesis, thereby interfering with lymphocyte proliferation. Although erythromycin is an antibiotic, it also probably acts as an anti-inflammatory agent via interference with matrix metalloproteinase 9. Thus, MMF used in combination with erythromycin is thought to have synergistic effect. Furthermore, in the previous cases of bullous LE in childhood, following treatments were used: systemic steroids, dapsone, azathioprine, cyclophosphamide, sulfapyridine, and hydroxychloroquine [91, 95, 96].

Also, there have been some reported BSLE cases that were successfully treated with IVIG therapy [13, 97, 98].

If the treatment of BSLE is summarized, after diagnosis of BSLE was made based on criteria first of all, it should be asked whether systemic complications of SLE are present or not. If answer is no, then dapsone treatment can be first choice drug with or without immunosuppressants. If answer is yes, a systemic complication is present; then corticosteroids, azathioprine, cyclophosphamide, antimalarials, methotrexate, MMF and rituximab, IVIG may be the drug choices and they could be applied alone or in combination [15].

1.11. Prognosis

Treatment with dapsone is successful in most cases of BSLE [5]. Frequently, lesions resolve spontaneously in less than 1 year and, to prevent recurrences, discontinuance of dapsone therapy is usually recommended after 1 year [88]. In some BSLE cases with severe systemic manifestations of SLE, prognosis is similar to systemic SLE. But, the development of BSLE in patients with SLE does not cause to increased mortality. In these patients, immunosuppressants and immunomodulatory drugs are preferred rather than dapsone [5, 6].

2. Cicatricial pemphigoid

2.1. Introduction

Cicatricial pemphigoid, (synonyms: mucous membrane pemphigoid, oral pemphigoid, desquamative gingivitis, ocular cicatricial pemphigoid) is an inflammatory disorder characterized by subepidermal blisters. CP affects particularly mucous membranes but cutaneous involvement can also be seen in some cases [99, 100]. The lesions usually heal with scarring, and CP may cause fatal outcomes such as airway obstruction. So, clinicians should recognize this rare entity as immediate as possible to prevent its complications [99]. CP patients must be evaluated by multidisciplinary team approach which involves primary care physicians, dentists, ophthalmologists, dermatologists, gynecologists, gastroenterologists, and otolaryngologists [100].

2.2. Epidemiology

CP is the second most frequent subepidermal blistering disease. It usually affects the older population (60–80 years of age), and children are rarely encountered as well. CP is seen approximately 1.5–2 times more in women than men [101]. There are about 20 cases of childhood onset CP reported, of which the youngest is 10 months old [102–104]. There is no known racial or geographic predilection [105].

The actual incidence of CP is unknown, however it was found as about 1.3–2.0/million/year in France and also a prevalence of 24.6/million in 2014 was reported in Germany [106, 107]. For ocular pemphigoid—a CP type with conjunctival involvement exclusively—an incidence of one new case/million/year was reported in England as well [108, 109].

2.3. Etiopathogenesis

The etiopathogenesis is still unknown; however, it is thought that environmental factors combined with genetic susceptibility lead to CP. There have been some reported cases of CP triggered by human immunodeficiency virus, diphtheria vaccination, and some medications such as methyldopa, clonidine, and D-penicillamine [110, 111]. In addition, other autoimmune diseases may occur more frequently in patients with CP [112]. Moreover, some bullous diseases may indicate the presence of an underlying malignancy. Especially, lymphomas and epithelial malignancies should be ruled out in autoimmune bullous diseases as well as MMP [113]. A possible association with HLA haplotypes (HLADQB1* 0301) and HLA-4 have been described in CP patients [105, 114]. It is suggested that a genotype of the interleukin (IL) 4 receptor A-1902 A/A, which is found in 90% of patients with oral pemphigoid, reduces the response to IL-4 and this may be connected with low risk of scarring in oral involvement [115].

Production of autoantibodies responsible for the disease is initiated by the loss of immunologic tolerance against the components of the basal membrane. A variety of different autoantigens including BP antigen (Ag) 230 (BPAg1, a 230-kDa protein, BP1), the BPAg180 (a 180-kDa protein, BP2), Lam-332 (also called epiligrin), integrin α6, integrin β4, the 97/120-kDa LABD antigen, type VII collagen, and some antigens such as a 45-kDa protein, uncein, a 168-kDa epithelial protein, and a 120-kDa epithelial protein have been described in patients with CP. The two major autoantigens of CP are BPAg2 and Lam-332. BPAg1 and BPAg2 are components of hemidesmosome structure. BPAg1 is an intracellular protein implicated in the organization of the keratin filament network; whereas, BPAg2 and integrin α6-β4 are transmembrane proteins that contribute to the assembly and stabilization of hemidesmosomes. Autoantibodies predominantly identify the C-terminal epitopes of BP180, but, NC16A is the second immunodominant domain. Lam-332 establishes connection between anchoring ligaments and transmembrane proteins. It is a heterotrimeric glycoprotein situated on the BMZ, including α3, β3, and γ2 subunits. Most of CP patients with anti-Lam-332 antibodies were reported to have autoantibodies to the α3 and γ2 subunits, and less frequently to the β3 subunit of the Lam-332 [99, 116–118].

Complement is activated by antigen antibody ligation and the cytokine/chemokine release leads lysis of cell membrane, infiltration, and degranulation of effector cells that cause clinical inflammation and tissue destruction. Thereafter, aggregation of inflammatory cells induces subsequent activation of fibroblasts. Fibroblasts multiply and secrete collagen, and by this action, subepithelial fibrosis has been started. Cytokines, particularly transforming growth factor beta (TGF-β), IL-13, tumor necrosis factor (TNF-α) may play a significant role in the pathogenesis of conjunctival scar tissue formation in CP patients [119, 120].

2.4. Clinical features

The oral mucosa is the most affected part of the body, ocular, nasal, nasopharyngeal, anogenital, laryngeal, esophageal mucosa, and skin can be involved. If there is cutaneous involvement, mostly skin of head and upper body are affected. More than one mucosal region may be simultaneously affected. In CP cases with predominantly mucosal involvement, scarring is more often. CP lesions are recalcitrant to treatment and this is a distinctive feature of CP from

other bullous diseases. Although scarring is an important clinical feature of CP, it may not be present in areas such as the oral mucosa. Complications such as blindness, airway obstruction are observed on the areas where the disease leads to scar formation [99, 121].

The distribution of disease may be local or widespread. The severity of the disease is associated with the magnitude of effected area. Localized lesions may progress to the extensive disease. The patients with only oral mucosa and/or skin involvement have less risk for scarring and this group is defined as "low-risk" CP patients. On the contrary, "high-risk" patients have lesions in any of the following sites: ocular, nasopharyngeal, esophageal, laryngeal, and genital mucosa [99, 122, 123].

Murrell and colleagues have established the Mucous Membrane Pemphigoid Disease Area Index for use in clinical studies for intervention and evaluation of CP patients (**Table 2**) [124].

Oral mucosa is the most frequently involved and is often the first (or sometimes solely) affected region in patients with CP. Desquamative gingivitis is generally the first finding of oral CP. Painful, erosive/blistering lesions occur often in the gingival, buccal mucosa, and palatal region. Tongue, lips, and alveolar ridge are rarely affected. The lesions can frequently recur at the same region. Erosions, desquamative gingivitis are observed in the acute period of the oral disease, whereas complications such as delicate pattern of reticulate scarring, periodontal ligament damage, loss of bone mass, teeth loss, or adhesions are noted during the chronic period [121].

Ocular involvement is also seen commonly in patients with CP. Isolated ocular involvement is present in some patients. Generally, the mean age of onset is 65 in this clinical subtype, but it is more aggressive in younger patients. Ocular findings may be nonspecific in the early stages of the disease (such as burning, dryness, photophobia, or foreign body sensation). Blisters are rarely observed. The ocular involvement is usually unilateral at the beginning, but the opposite eye is also involved in following years. Ocular CP may result in development of symblepharon, ankyloblepharon, entropion, trichiasis, corneal ulceration, neovascularization, and blindness. Ocular CP should be evaluated by an experienced ophthalmologist and distinguished from other ophthalmologic diseases. Slit-lamp examx may be useful for early diagnosis of ocular CP [99, 125].

Genital involvement in males generally results in erosions on the glans, urethral strictures, and phimosis [126]. Interestingly, female patients may be asymptomatic. But erosions on the labia minora/majora, dysuria, vaginal discomfort, dyspareunia may be present and consequently fusion of the labias may be seen [127].

Nasopharyngeal involvement is another clinical output of CP and findings such as epistaxis, dysphagia, dysphonia, nasal obstruction, and nasal crusting can be seen [128]. Laryngeal involvement may cause fatal airway obstruction requiring tracheostomy [125]. There is esophageal involvement in approximately 2–7% of patients that may cause dysphagia, odynophagia, aspiration, strictures, and malnutrition as well [129].

Skin involvement is detected in 25–35% of CP patients. Clinical presentation is frequently small, tense vesicles, or bullae on the scalp, head, neck, and upper trunk. The cutaneous lesions are usually smaller in size and sometimes recur in the same region. Accompanying atrophic scars and milia can be observed in the lesion sites [121].

Disease activity		Damage	
Erosions-blisters and new erythema in ears, forehead, rest of the face, neck, chest, abdomen, shoulders, buttocks, arms and hands, legs and feet, anal, genital sites	0 = absent; 1 = 1–3 lesions; furthest 1 lesion >2 cm in any diametery, none >6 cm; 2 = 2–3 lesions, at least 2 lesions >2 cm diameter, none >6 cm; 3= >3 lesions, none >6 cm diameter; 5= >3 lesions, and/or at least 1 lesions >6 cm, 6= > 3 lesions, and/or at least 1 lesions >16 cm diameter of entire are	Erythema/ postinflammatory hyperpigmentation/ scar	Absent = 0 Present = 1
Erosions-blisters and new erythema in scalp	0 = absent 1 = 1 quadrant 2 = 2 quadrants 3 = 3 quadrants 4 = affects complete scalp 10 = at least 1 lesion >6 cm	Erythema/ postinflammatory hyperpigmentation/ scar	Absent = 0 Present = 1
Erosions/blisters in eyes	0 = No erythema 1 = Light pink 2 = Moderate pink 5 = Dark pink 10 = Bright red	Erythema/ postinflammatory hyperpigmentation/ scar	Absent = 0 Present = 1
Erosions/blisters in other mucosa	0 = absent 1 = 1 lesion 2 = 2–3 lesions 5= > 3 lesions or 2 lesions >2 cm 10 = whole area	Erythema/ postinflammatory hyperpigmentation/ scar	Absent = 0 Present = 1

Table 2. Mucous membrane pemphigoid disease area index [124].

CP is divided into subsets according to antibody profiles and sites of involvement. The disease caused by Lam-332 antibodies is called antiepilegrin CP (AECP). AECP is estimated to comprise of 5–20% patients of CP. The patients in this group are clinically indistinguishable from other forms of cicatricial pemphigoid and some of these patients may occasionally have antibodies directed against Lam-331. Egan et al. demonstrated that 100% of the patients had mucous membrane involvement and 86% had mild to moderate skin involvement in AECP [130, 131].

Some of the patients with CP may have restricted disease with ocular mucosa involvement or may have a clinical course that predominantly not only affects the ocular mucosa, but also involves other mucosal sites. This form of disease is called ocular CP and antibodies to a portion of the intracytoplasmic component of human integrin-β4 and/or BP-180 are detected in

this group of patients [132]. Another variant within the CP phenotype is anti-BP180 MMP, where the patients have circulating IgG antibodies to BP antigens. Both of the skin and mucous membranes are involved in this variant. BP180 C-terminal domain and BP180 NC16a domain are considered to be the major antigenic domains in anti-BP180 MMP [133].

Another subset of CP is called oral pemphigoid, in which the autoantibodies to human alpha-6 integrin subunit are thought to be responsible for the disease. The patients with this type of CP have limited disease to the oral mucosa with no skin or other mucosal involvement [134, 135].

CP is rarely seen in children and it is called childhood CP. Ocular and genital mucosa involvement is common in children. Linear IgA deposits was detected and reported like LABD. In view of the fact that conjunctival scarring can also be seen in patients with LABD, it has been discussed whether CP and LABD should be classified as the same disease or whether they are different entities [136] .

Brunsting-Perry CP is a rare variant of CP characterized by blisters, hemorrhagic crusts, and mainly atrophic scars. The lesions are observed predominantly located on the head, neck, scalp, and upper aspects of the trunk with only mild or no mucosal involvement. There is no specific antigen of Brunsting-Perry CP. This variant is seen in middle-aged or elderly patients, with a male predominance [137, 138]. Some authors have suggested that Brunsting-Perry CP may a clinical variant of EBA [139].

2.5. Diagnosis

Diagnosis of CP is made based on clinical, histological, and immunopathological findings. The diagnosis of CP is often difficult, especially in early stages, because of variations in clinical presentation and on histopathological examination.

Histopathological examination of CP lesions shows subepidermal split (without acantholysis) and dermal leukocytic infiltrations mostly composed of lymphocytes, histiocytes, as well as variable number of neutrophils and eosinophils. The inflammatory infiltrates in mucosal lesions contain plasma cells. Mast cells may be detected in biopsy specimens of the conjunctiva as well. Similar findings can be seen in BP, LABD and EBA. Histopathological examination of older lesions shows fibroblast proliferation and fibrosis [140].

The electron microscopic examination shows epithelian findings including intracellular edema, decreased number of goblet cells, granular materials and fragmentation, duplication, thickening in BMZ. According to Thorne et al., the sensitivity and specificity of electron microscopy in ocular CP were found as 51 and 72%, respectively [141].

IEM studies have shown that the immune deposits are located in lamina lucida, lamina densa, hemidesmosomes, and basal keratinocyte cytoplasm [140].

DIF microscopy characteristically shows a continuous, linear n-serrated pattern of IgG (frequently IgG4), C3, less commonly IgA, IgM, and fibrin or a combination of these along the BMZ. DIF is the gold standard test for diagnosis of CP, but it is also known to have high false negative rates especially in ocular CP. Shimanovich et al. found that DIF staining was positive in 74 of 78 patients (95%); however, multiple and recurrent biopsies were taken from the patients.

The sensitivity of DIF microscopy was increased with multiple and repeated biopsies. [142]. Power et al. claims that using immunohistochemistry which includes immunoperoxidase technique may increase the sensitivity of conjunctival biopsy in the diagnosis of ocular CP [143, 144].

ELISA systems and IIF can be used to determine circulating antibodies. Normal human epithelial substrate (e.g., 1.0 M sodium chloride–split skin) is used in IIF and IIF reveals binding to the roof (epidermal) or floor (dermal) of the blister depending on the antigen targeted. While, patients with integrin and BP180 autoantibodies display circulating IgG autoantibodies that bind to the epidermal side, Lam-332 autoantibodies bind to dermal side of salt-split skin by IIF [99, 140].

According to Amber's study, which included the patients with positive immunoblot or immunoprecipitation to NC16a, ELISA test including both NC16a and C-terminal portion of BP180 demonstrated 73% sensitivity and 93% specificity. But, when they tested IgG reactivity against the C-terminal domain of BP180 in the same patients, both the sensitivity and specificity decreased to 43 and 56%, respectively. The sensitivity of ELISA reached 75% in the patients who have IgG reactivity against the Lam-332-a3 subunit [145]. According to another study, the titer of IgA antibodies to NC16a in saliva was found correlated with sera [144].

Serum autoantibodies against BP230 are more frequently detected when anti-Lam-332 autoantibodies are also present. This association was thought to be possibly related to epitope spreading [107]. Bekou's study showed that 78% of patients with CP had serum anti-Lam-332 autoantibodies. Sensitivity and specificity of the Lam-332 ELISA for CP were 75 and 84.3%, respectively, in the same study [146].

Some authors have also suggested that a dual IgG and IgA serum anti-BMZ antibodies are associated with a more severe disease. Additionally, serum titers of anti-BMZ IgG autoantibody often correlate well with disease severity [147]. LAD-1 is an extracellular C-terminal domain of BP180. Dual IgG and IgA reactivity with BP180 and LAD-1 was found to be associated with severe phenotype [148].

Also, there is another popular technique, BIOCHIP mosaic slides have been found to be useful in screening autoantibodies in autoimmune bullous diseases (AIBD). These consisting of different antigen substrates (monkey esophagus, primate salt-split skin, recombinant BP180 NC16A, membrane-bound Dsg 1 ectodomain, Dsg 3 ectodomain, and the C-terminal globular domain of BP230) allow polyvalent IF tests and provide antibody profiles in a single incubation. Technically, it is a modified-IIF, wherein serum from patients with suspected AIBD is added to these slides and examined under fluorescence microscopy. BIOCHIP technique is a simple, standardized, and readily available technique which is useful to screen autoantibodies in AIBDs as well as to identify the target antigen [149].

2.6. Differential diagnosis

Disorders that should be differentiated from CP include pemphigus, other subepidermal immunobullous disease, erythema multiforme, SJS, lupus erythematosus, lichen planus, lichen sclerosus (especially in the anogenital area), drug-induced hypersensitivity reaction. If there is ocular involvement, other conditions causing fibrosis in the conjunctiva should be considered, such as Sjogren's syndrome, scleroderma, severe chronic infectious conjunctivitis,

burns. Some drugs (e.g., pilocarpine, guanethidine, ephedrine, idoxuridine, epidermal growth-factor receptor tyrosine kinase inhibitors) may cause inflammation and fibrosis in the conjunctiva as well. This is called pseudopemphigoid. These patients are clinically indistinguishable from other autoimmune bullous diseases. Specialized immunopathologic studies and/or IEM may be required for diagnosis [112, 125]. It also has been reported that ocular CP developed after Steven Johnson syndrome and Lyell syndrome in some cases. It is thought that the chronic eye surface damage in these cases may trigger the autoimmune process [150].

2.7. Treatment

The main purpose of CP therapy is to prevent scar development, complications such as blindness and airway obstruction. Treatment should be initiated in the early period to prevent complications. Co-operation of oral medicine experts, dermatologists, ophthalmologists, otolaryngologists, and gastroenterologists is important for treatment. The factors determining the treatment regimen in CP are localization, disease severity, and progression rate. CP patients were divided into two groups according to an international consensus. The first group includes patients with oral mucosa and/or skin involvement (low risk); second group includes ocular, laryngeal, esophageal, or genital involvement (high risk) patients. Topical treatment is an initial choice for low-risk patients. However, a more aggressive treatment plan is proposed for high-risk patients even in early period of disease [99]. For the low-risk patients, an initial treatment of moderate-high potency topical corticosteroid can be tried. Depending on the condition of the patient, dapsone (50–200 mg/day), tetracycline (1–2 g/day)/nicotinamide (2–2.5 g/day), sulphamethoxypyridazine (0.5–1 g/day), sulphapyridine (0.25–1 g/dl) can be administered. In the condition of partial response to treatment or progressive disease, systemic corticosteroids are needed for treatment of the patients with no contraindication. If there is an existing contraindication about systemic corticosteroid, other medications like azathioprine, mycophenolat mofetil, cyclophosphamid can be used. IVIG and/or rituximab are the options if there is no response to other mentioned drugs. The treatment begins with systemic corticosteroid, azathioprine or MMF in patients with severe clinic/high risk. The agents may be changed according to clinical course [151].

High potency topical glucocorticoids (fluocinonide, clobetasol propionate, and betamethasone dipropionate) are the first choice agents. They can be applied as a spray, gel or ointment base. Mouthwash (dexametasone 100 mg/ml, 5 ml per rinse) can be used by shaking and spitting for oral lesions. Oral insertable prosthetic device may facilitate the symptoms for oral mucosa. Intralesional corticosteroid therapy may be used instead of topical corticosteroid. Systemic absorption should be considered during application of topical corticosteroid. Antifungal treatments should be used in cases with secondary candidiasis infection [125, 151]. Patients should be recommended to improve oral hygiene and try to avoid rigid foods. Topical formulations of tacrolimus, cyclosporin, mitomicin C (topical and subconjunctival applications) have been described for advanced treatment of CP [152, 153].

Systemic corticosteroid (prednisolone 0.5–1.5 mg/kg/day) have a rapid onset of action; however, the adverse effects such as hyperglycemia, hypertension, hyperlipidemia, osteoporosis, gastric ulcers, secondary infections, and alterations of mood or even psychosis associated with long-term use limit their value [151, 154].

Dapsone therapy is accepted to be the first line of treatment for mild to moderate ocular CP. Adverse effects include hemolysis, methemoglobinemia, dapsone hypersensitivity syndrome (fever, lymphadenopathy, hepatic damage, and generalized erythematous pustules). Patients should be monitored periodically for these side effects [155].

Biologic agents including etanercept, rituximab, infliximab, and daclizumab can be effective in controlling severe CP cases that are resistant to conventional immunosuppressive agents [156–158]. Lymphoma protocol is used for rituximab therapy, which involves a dose of 375 mg/m² administered weekly for four consecutive weeks. In patients treated with rituximab, the clinical response was usually obtained 3–6 months after the first dose [159, 160].

IVIG therapy (1–3 g/kg/cycle) can be used in treatment of CP patients who do not respond to conventional therapy or are unable to use them because of various side effects. For recalcitrant ocular CP, combination therapy of rituximab and IVIG is a potent treatment regimen. The most common side effect is headache, followed by nausea [161, 162]. Plasmapheresis has found to be effective in some recalcitrant patients, as well [163].

Eyelid abnormalities such as trichiasis, distichiasis, entropion, lagophthalmos, and symblepharon stenosis of the upper airway, esophageal, and anogenital stricture may need to be managed surgically. Surgical management aims to achieve temporary symptomatic relief and is not a curative treatment for CP [132].

2.8. Prognosis

CP is typically a chronic and progressive disease. CP rarely undergoes spontaneous remission and relapses are seen commonly. Ocular, nasopharyngeal, esophageal, and laryngeal involvement are related with high risk. Anti-Lam-332 antibodies are associated with severe disease and internal malignant neoplasms including solid tumors and lymphomas. The risk of cancer is highest during the first year of disease [107]. Egan's study demonstrated that the relative risk for cancer was 15.4 in the first year of disease onset. Adenocarcinoma (lung, colon, stomach, endometrial) was frequently detected in this study [131]. In a study, various internal malignancies were found in BP180-CP, but the relationship between BP180-CP and internal malignancy is still unclear [133].

3. Conclusion

BSLE and CP are rare autoimmune bullous disorders that have their own characteristics. But sometimes, BSLE may resemble other autoimmune bullous disorders and CLE associated bullae. Moreover, BSLE may be related to increased systemic disease activity of SLE, especially nephritis. So, diagnosis of BSLE is very important and accurate diagnosis requires a high index of clinical suspicion. Scarring of the lesions in CP causes significant complications such as blindness. Early diagnosis and early treatment have a critical role for preventing the scar development. Systemic adjuvant immunosuppressive therapy is required for patients with progressive disease.

Acknowledgements

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