Autoimmune Bullous Dermatoses: A Review

Patrícia Patrício,[a] Carlos Ferreira,[a] Manuel Marques Gomes,[b] and Paulo Filipe[b]

[a]Internal Medicine 2 Department, [b]Dermatology Department, Hospital Santa Maria/Faculty of Medicine of Lisbon, Lisbon, Portugal

Bullous dermatoses are a variety of autoimmune skin diseases that are characterized by the presence of bullae or blisters. Most of these diseases are associated with substantial morbidity, and a few may result in death. Although most general approaches to the treatment and diagnosis of these entities are similar, the diagnosis of the specific disease is important, because the most appropriate dosage and timing of some commonly used medications vary considerably. The review covers the management of main autoimmune bullous dermatoses, including bullous pemphigoid and pemphigus vulgaris, linear IgA dermatosis, dermatitis herpetiformis, and bullous systemic lupus erythematosus.

Key words: **autoimmune bullous dermatoses; bullous dermatoses; bullous pemphigoid and pemphigus vulgaris; linear IgA dermatoses; dermatitis herpetiformis and bullous systemic lupus erythematosus**

Bullous Pemphigoid

Bullous pemphigoid (BP) is a chronic, autoimmune, subepidermal, blistering skin disease that rarely involves mucous membranes. It occurs mainly in the elderly and rarely in children. Onset is typically between 60 and 80 years of age. There is equal incidence in men and women, and there are no known racial or ethnic predilections.

The lesions of BP may initially start as an urticarial eruption, which over a course of weeks to months, develops into bullae. The lesions are usually pruritic, and there may be tenderness at the site of eroded lesions. Once formed, blisters are large and tense, with a round or oval shape. Discrete lesions arise on normal or erythematous skin and are scattered throughout the body, including the axillae, medial thighs, groin, abdomen, flexor forearms, and lower legs. The lesions may be localized or generalized. BP involves the mucosa in 10–25% of patients.

Histological examination of a skin biopsy from a bulla reveals a subepidermal blister with superficial dermal inflammation consisting of lymphocytes, histiocytes, and eosinophils. On electron microscopy, blister formation is found to occur within the *lamina lucida* of the basement membrane, causing a loss of anchoring filaments and hemidesmosomes. BP is characterized by the presence of immunoglobulin G (IgG) autoantibodies specific for the hemidesmosomal BP antigens BP230 (BPAg1) and BP180 (BPAg2).[1] The binding of the antibodies at the basement membrane activates complement and inflammatory mediators. Serum levels of autoantibodies against BPAg2 are reportedly correlated with disease activity in some studies. The role of autoantibodies specific for BP antigens in the initiation and the perpetuation of disease is unknown. Although BPAg2 has been identified as the major antigen involved with BP disease development, autoantibodies against alpha 6 integrin

Address for correspondence: Patrícia Patrício, Hospital de Santa Maria, Av. Prof. Egas Moniz, 1894-984 Lisboa, Medicina 2. Voice: +00351919474752. patriciopatricia@gmail.com

Contemporary Challenges in Autoimmunity: Ann. N.Y. Acad. Sci. 1173: 203–210 (2009).
doi: 10.1111/j.1749-6632.2009.04737.x

and laminin-5, two other skin basement membrane components, were identified in human patients affected by BP. Eotaxin, an eosinophil-selective chemokine, is strongly expressed in the basal layer of the epidermis of lesional BP skin and parallels the accumulation of eosinophils in the skin basement membrane zone area. It may play a role in the recruitment of eosinophils to the skin basement membrane area. Moreover, IL-5, an interleukin with eosinophil chemoattractant and activation properties, has been found in the skin of patients with BP.

Interleukin 16, a chemotactic factor responsible for recruiting $CD4^+$ T cells to the skin and for inducing functional interleukin 2 receptors for cellular activation and proliferation, was found to be expressed by epidermal cells and infiltrating $CD4^+$ T cells in lesional skin. In addition, serum levels of different mediators inducting monokine induced by interferon gamma (MIG, a Th1-type chemokine), CCL17, and CCL22 (Th2-type chemokines) were also increased in BP patients compared with healthy subjects.

Matrix metalloproteinases MMP-2, MMP-9, and MMP-13 were significantly increased in lesional skin, with T cells comprising the majority of MMP cellular sources, suggesting a major role of MMP in the blistering of BP. The BAFF (B cell activating factor belonging to the tumor necrosis factor family) cytokine regulates B cell proliferation and survival and was found to be increased in sera of BP patients. To establish a diagnosis of BP, the following tests should be performed: histopathologic analysis from the edge of a blister and direct immunofluorescence (DIF) studies on normal-appearing perilesional skin. If the DIF result is positive, indirect immunofluorescence (IDIF) is performed using the patient's serum. The preferred substrate for IDIF is salt-split normal human skin substrate. DIF tests usually demonstrate IgG and complement C3 deposition in a linear band at the dermal-epidermal junction.

Rarely, skin biopsy samples placed in transport media (Michel buffer) may yield false-negative results. This observation makes the use of fresh tissue the preferred substrate for DIF studies. IDIF studies document the presence of IgG circulating autoantibodies in the patient's serum that target the skin basement membrane component.

Direct and indirect immuno-electron microscopy (immunoEM) ultrastructurally localize *in vivo*–bound IgG autoantibodies (direct immunoEM) or the binding site of circulating IgG autoantibodies (indirect immunoEM) at the *lamina lucida* of the basement membrane. The sensitivity of immunoblotting varies. In 75% of patients, a reaction occurs with the BP230 antigen, while, in 50% of patients, this is observed with the BP180 antigen. Immunoprecipitation, like immunoblotting, demonstrates reactivity with BP230 and BP180.

In several reports, ELISA has been demonstrated to be highly sensitive and specific.[1] These assays are used only as investigational tools. For the diagnosis of bullous pemphigoid three major criteria must be met or one DIF criterion (major criterion 3) and 1 minor criterion. Major criteria are: (1) (clinical) polymorphic eruption with tense blisters and erosions in skin (rarely mucosa), (2) (histopathological) subepidermal blistering with eosinophils, (3) (DIF) deposition of Ig G and C3 along the basement membrane. Minor criteria are: (1) deposition of Ig G and C3 along the basement membrane (by immunofluorescence), (2) BP antigens 1 or 2 (by ELISA), (3) bands at 180 or 230 kDa (by immuno-blotting).

Treatment consists of systemic prednisone, alone or in combination with a steroid-sparing agent such as azathioprine, mycophenolate mofetil, or a tetracycline. These drugs are usually started simultaneously, followed by a gradual tapering of the prednisone and continuation of the steroid-sparing agent until clinical remission is achieved. Mild cases may require only topical potent corticosteroids. Methotrexate may be used in patients with severe disease who are unable to tolerate prednisone. In most patients who are treated, BP remits within 1.5–5 years.

Pemphigus Vulgaris

Pemphigus vulgaris (PV) is a mucocutaneous autoimmune disease that affects the skin, oral cavity, and other mucosal surfaces. Genetic predisposition is suspected because of the identification of certain major histocompatibility complex (MHC) class II molecules, such as DR4 (DRB1*0402) and DRw6 (DQB1*0503).

Blisters in PV are associated with the binding of IgG autoantibodies to keratinocyte cell-surface molecules. These intercellular or PV antibodies bind to keratinocyte desmosomes and to desmosome-free areas of the keratinocyte cell membrane. PV antibody binds to keratinocyte cell-surface molecules desmoglein 1 and desmoglein 3.[2] Patients with active disease have circulating and tissue-bound autoantibodies of both the immunoglobulin G1 (IgG1) and immunoglobulin G4 (IgG4) subclasses. Disease activity correlates with antibody titer in some patients. Mucous membranes typically are affected in PV. Intact bullae are rare in the mouth, more commonly the lesions are ill-defined, irregular, gingival, oral or palatine erosions. Other areas may be affected, including the conjunctiva, esophagus, labia, vagina, cervix, penis, urethra, and anus. Mucosal lesions may precede cutaneous lesions by months. Lesions in skin folds can form vegetating granulations. The vegetating type of response can be more resistant to therapy and can remain in one place for long periods of time. In patients with active blistering, firm, sliding pressure with a finger separates normal-appearing epidermis, producing an erosion known as Nikolsky sign, which is not specific for PV and is found in other active blistering diseases. The Asboe–Hansen sign occurs when a lateral pressure on the edge of a blister spreads the blister into clinically unaffected skin. PV eventually has classic association with other autoimmune diseases, particularly myasthenia gravis and thymoma. There are some cases associated with drugs and paraneoplastic forms. Diagnosis of the disease is made on the basis of the following data: presence of recurrent blister formation, erosions and crust; presence of Nikolsky sign; histological detection of intra-epidermal blistering; detection of acantholytic keratinocytes by the Tzanck test; detection of pemphigus antibodies; and DIF and/or IDIF positive.

Conventional therapy consists of high-dose corticosteroids, immunosuppressive agents, and intravenous immune globulin. In refractory PV, the combination of rituximab[3] and immune globulin is effective.[4,5]

Linear Ig A Dermatosis

Linear IgA dermatosis (LAD) is an autoimmune vesicobullous subepidermal dermatosis. Infections, drugs, or malignant processes may provoke it, but it sometimes has a idiopathic origin. The disease affects people of all ages, but two peaks can be observed: the chronic bullous disease of childhood appearing before the age of five and the adult linear IgA disease appearing after the age of 60 years. The lesions of linear IgA dermatosis consist of pruritic, annular papules, vesicles, and bullae that are found in groups. There is a predilection for the extensor surfaces, with symmetrical distribution. Lesions are seen on the elbows, knees, and buttocks. Because of itching, excoriations will lead to the formation of many crusted papules. Chronic bullous disease of childhood presents with abrupt onset of tense bullae on an inflamed, erythematous base and is accompanied by pruritus and a burning sensation. The lesions are most frequently found on or near the genitalia, but may also be found on other areas, including the face, especially the perioral region. Characteristic "collarettes" of vesicles or blisters often form as new lesions arise in the periphery of old lesions. In both forms of linear IgA dermatosis, mucous membrane involvement may occur and ranges in severity from mild oral ulcers to severe oral or conjunctival disease. On histopathology, in linear IgA dermatosis and chronic bullous disease of childhood, the bullae are subepidermal, with collections of

neutrophils along the basement membrane and occasionally in the dermal papillary tips.

The diagnosis can be confirmed by DIF, displaying linear IgA deposits along the epidermal basement membrane. A complexity and heterogeneity of the target antigens in different patients with LAD have been established. Incriminated antigens are proteins with molecular weight of 285 kDa, as well as 97-kDa and 120-kDa antigens, which appear to be fragments of extracellular domain of bullous pemphigoid antigen BP 180 (type XVII collagen). BP 230 antigen located in the *lamina lucida* of the basal membrane, collagen VII, which is a component of anchoring fibrils as well as some still unidentified antigens, may also be involved. A strong association between the disease and autoimmune haplotypes HLA-B8, CW7, and DR3 has been reported.

The disease is characterized by circulating and tissue-bound IgA antibodies against heterogeneous antigens located in the cutaneous basement membrane zone. Application of split skin technique has demonstrated that the majority of antibodies bind to the epidermal side of the *lamina lucida*, whereas the rest adheres to the dermal side of the artificial blister, and a few are of a combined pattern. In cases triggered by drugs, such as vancomycin, phenitoin, somatostatin, amiodarone, lithium, and captopril, remission may follow the withdrawal of the incriminated drug.

In idiopathic cases, the treatment should be started with a dose of 25–50 mg dapsone daily, which has to be increased stepwise to 100–150 mg daily. As dapsone may cause a hemolytic anemia, decreased hemoglobin values, or even methemoglobinemia, the enzyme glucose-6-phosphate dehydrogenase has to be assayed before beginning the treatment. As an alternative drug, sulphapyridine 250 mg to 3 g daily can be administered. Skin lesions in linear IgA dermatosis and chronic bullous disease of childhood respond rapidly when treated with dapsone or sulfapyridine. Some patients may require low-dose prednisone initially to suppress blister formation.

Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is an autoimmune blistering disorder associated in most patients to a gluten-sensitive enteropathy (GSE). It is characterized by grouped excoriations; erythematous, urticarial plaques; and papules with vesicles. It is exquisitely pruritic, and the vesicles are often excoriated to erosions by the time of physical examination. Onset tends to be between 20 and 40 years of age but may occur at any age, including childhood, and there is a 2:1 preponderance for men. The lesions of dermatitis herpetiformis usually begin as a vesicle, but may also be erythematous papules, urticaria-like wheals, excoriations, crusts, or rarely, large bullae. The lesions may be grouped, giving a "herpetiform" appearance. Once the lesions have resolved, there may be transient hyper- or hypopigmentation. The lesions are usually intensely pruritic, accompanied by burning and stinging. Many patients experience localized burning, stinging, and pruritus approximately 8 to 12 h before the onset of lesions, and many are able to predict an eruption. There is symmetric distribution along the extensor surfaces, including the elbows, knees, buttocks, shoulders, and sacral areas. Less frequently, the lesions are found on the scalp, face, hairline, and the posterior neck. Involvement of the palms and soles is rare, and mucous membrane lesions are uncommon. More than 90% of patients have an associated GSE upon endoscopic examination even if asymptomatic.

Histopathologically there are neutrophilic micro-abscesses in dermal papillae, dermal infiltration of neutrophils and eosinophils, and the formation of subepidermal vesicles. Blisters form within the *lamina lucida*, the weakest portion of the dermo-epidermal junction, due to neutrophil lysosomal enzymes. Dermal blood vessels may be surrounded by a lymphohistiocytic infiltrate, as well. Granular IgA deposits alone or in association with C3 in dermal papillae of perilesional skin observed by DIF is the standard criterion of diagnosis. Because

deposits are found throughout normal-appearing skin, the standard practice is to obtain biopsy specimens from normal-appearing perilesional skin for DIF staining. In areas corresponding to IgA deposits, there may also be complement deposition. IgA and IgG antireticulin and anti-endomysial antibodies have been detected in DH patients' sera. An increased incidence of antinuclear and antithyroid microsomal antibodies is also found in these patients.[6] An underlying genetic predisposition to DH has been demonstrated. Both DH and celiac disease (CD) show an increased expression of HLA-A1, HLA-B8, HLA-DR3, and HLA-DQ2 haplotypes. Evidence is mounting that epidermal transglutaminase 3 (TGase3), a cytosolic enzyme involved in cell envelope formation during keratinocyte differentiation, is the autoantigen of DH. Theoretically, DH is caused by dermal deposition of circulating immune complexes containing both IgA and TGase3. This is supported by the finding that precipitates of skin-bound IgA from DH lesions contain TGase3. In addition, it has been demonstrated that serum from DH patients contains high-affinity anti-TGase IgA autoantibodies.

The leading theory for DH is that a genetic predisposition for gluten sensitivity, coupled with a diet high in gluten, leads to the formation of IgA antibodies to gluten-TGase complexes. These antibodies cross-react with TGase3, and IgA/TGase3 complexes deposit within the papillary dermis to cause the lesions of DH. These IgA deposits can disappear after long-term avoidance of dietary gluten. Cutaneous IgA deposits in DH have been shown to function *in vitro* as a ligand for neutrophil migration and attachment. Although IgA deposition is pivotal for disease, an increased serum IgA is not necessary for pathogenesis. When the disease is active, circulating neutrophils have a higher level of CD11b and an increased ability to bind IgA. Collagenase and stromelysin 1 may be induced in basal keratinocytes either by cytokines released from neutrophils or by contact with keratin from damaged basement membrane matrix. Stromelysin 1 may contribute to blister formation. Mild local trauma may also induce the release of cytokines and attract the partially primed or activated neutrophils, which is consistent with the typical location of DH lesions on frequently traumatized areas, such as the knees and elbows. Hormonal factors may also play a role in DH; recent reports describe DH induced by treatment with leuprolide acetate, a gonadotropin-releasing hormone analog. Androgens have a suppressive effect on immune activity, including decreased autoimmunity, and androgen-deficient states may be a potential trigger for DH exacerbation. Apoptosis may contribute to the pathogenesis of epidermal changes in DH, and recent research demonstrates a markedly increased apoptotic rate within the epidermal compartment in DH.

Most patients with DH have histologic evidence of enteropathy, even in the absence of symptoms of malabsorption. IgA circulating immune complexes are present in 25–35% of patients with DH, although no association with disease severity has been noted. IgA antibodies to gliadin (a portion of wheat protein), reticulum, and smooth muscle endomysium have also been noted in patients with DH and in those with isolated GSE. The presence of IgA anti-endomysial antibodies correlates with the extent of the gut disease.

Patients will experience prompt relief of lesions within 1 to 2 days of initializing treatment with dapsone or sulfapyridine. It is important to remember to always check G6PD and baseline complete blood count levels before starting dapsone. Other methods of treatment include dietary modification. One form is the gluten-free diet, which has been found to improve both intestinal and skin lesions. The onset is slow, taking from 5 months to 1 year before the effect is noted; however, close adherence to the diet will allow patients to stop or significantly decrease the medications. Alleviation of skin lesions can occur within a few weeks of starting the diet, even if the patient ingests large amounts of gluten, but this diet is difficult to tolerate. Control of the skin disease can be achieved with

medications, dietary avoidance of gluten, or both. Avoidance of dietary gluten for 10 years or more has resulted in loss of cutaneous IgA deposits, which then return upon reinstitution of gluten in the diet. Dapsone does not improve GI mucosal pathology. Other, less effective treatments for DH include colchicine, cyclosporine, azathioprine, and prednisone. UV light may provide some symptomatic relief. Cyclosporine should be used with caution in patients with DH because of a potential increase in the risk of developing intestinal lymphomas. DH responds well to medications and diet, and has a good prognosis. Association of DH with other GI conditions include gastric atrophy, gastric hypochlorhydria, and pernicious anemia. Associated autoimmune diseases include dermatomyositis, type 1 diabetes mellitus, myasthenia gravis, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, and thyroid abnormalities. Thyroid abnormalities include hypothyroidism, hyperthyroidism, thyroid nodules, and thyroid cancer. Neoplastic conditions include GI lymphomas and non-Hodgkin's lymphoma.

Bullous Systemic Lupus Erythematosus

Bullous systemic lupus erythematosus (BSLE) is an autoantibody-mediated subepidermal blistering disease that occurs in patients with systemic lupus erythematosus (SLE). These blisters result from toxic necrolysis of the skin, mediated by deposition of immunoreactants at the basement membrane, and underlying dermal vasculitis. Blisters may arise on erythematous or normal skin and are nonscarring. Lesions occur on sun-exposed or flexural skin. Skin biopsy shows subepidermal vesicles containing neutrophils with micro-abscesses, nuclear dust, and fibrin. Blistering often parallels flares of SLE involving other organ systems, in particular renal disease. Camisa and Sharma proposed criteria for this distinct subset of vesiculobullous skin lesions occurring in patients with SLE: (1) a diagnosis of SLE based on American Rheumatism Association criteria; (2) vesicles and bullae arising upon but not limited to sun-exposed skin; (3) histopathology compatible with DH; (4) negative IDIF for circulating basement membrane zone antibodies; (5) DIF positive for IgG and/or IgM and often IgA at the basement membrane zone. Yell and colleagues suggested this classification be revised because of the heterogeneity of clinical and immunohistological presentation. They defined BSLE as an acquired subepidermal blistering disease in a patient with SLE, in which immune reactants are present at the basement membrane zone on direct or IDIF. DIF microscopy demonstrates immunoglobulin G (with or without immunoglobulin A [IgA] and immunoglobulin M) deposits at the basement membrane zone (BMZ). Evidence of antibodies to type VII collagen via DIF or IDIF on salt-split skin, immunoblotting, immunoprecipitation, ELISA, or immuno-electron microscopy can be demonstrated.[7] All five criteria are needed for a diagnosis of type 1 BSLE, whereas only the first four criteria are needed to diagnose type 2 (undetermined location of antigen or dermal antigen other than type VII collagen) and type 3 (epidermal antigen) BSLE. Type VII collagen, a component of anchoring fibrils, is also targeted in epidermolysis bullosa acquisita (EBA). However, unlike EBA, BSLE tends to respond dramatically to treatment with dapsone, and these disease can usually be differentiated from lupus by characteristic changes (including immune deposits) and serum antibodies (which react with different parts of the dermis). Not all blistering eruptions that occur in patients with lupus erythematosus (LE) represent BSLE as defined above. Such patients may present with a severe form of acute or subacute cutaneous LE (SCLE) that resembles erythema multiforme (Rowell syndrome) or toxic epidermal necrolysis (TEN). Because EBA and BSLE share the same target antigen, distinguishing between the two may be difficult.

In patients with BSLE, antibodies directed at the BMZ likely mediate the blistering phenotype by directly interfering with adhesive connections at the dermo-epidermal junction and

through induction of complement-dependent inflammation that leads to tissue injury and dermo-epidermal separation. Proteolytic damage caused by recruited neutrophils contributes to the latter process.

In type 1 BSLE (which accounts for most cases), antibodies against type VII collagen may weaken or block anchoring fibril-mediated connections between the lamina densa of the basement membrane and the papillary dermis. In both EBA and BSLE, antigenic epitopes reside within the NC1 and NC2 domains of type VII collagen, which are localized to the lamina densa and the underlying dermis, respectively. Antibodies recognizing bullous pemphigoid antigen 1, laminin-5, and laminin-6 have also been described in patients with BSLE.

The term *acute syndrome of apoptotic panepidermolysis* (ASAP) has been proposed for the TEN-like cutaneous injury pattern that can occur in settings of LE, acute graft-versus-host disease, pseudoporphyria, and the classic drug-hypersensitivity syndrome. Fas–Fas ligand interactions have been implicated in the massive keratinocyte apoptosis that characterizes ASAP. TEN-like cutaneous LE must be differentiated from drug-induced TEN occurring in a patient with LE. Patients with TEN-like acute cutaneous LE often have significant systemic disease activity (such as lupus nephritis or cerebritis).

In LE-specific vesiculobullous skin disease, the lesions are distinct from BSLE, representing severe variants of acute, subacute, or (rarely) discoid cutaneous LE. The eruptions can develop rapidly or evolve over several weeks. In TEN-like acute cutaneous LE, photodistributed diffuse or patchy erythema evolves (usually rapidly) into flaccid bullae (positive Nikolsky sign, unlike BSLE) and widespread sheet-like, full-thickness epidermal detachment. Certain individuals may have a genetic predisposition to develop autoimmunity to BMZ antigens and to SLE. For example, EBA, BSLE, and SLE are all associated with an increased prevalence of the HLA class II DR2 haplotype. The antigen-presenting protein encoded by the DR2-associated DRB1*1501 allele (found in both EBA and BSLE patients) has been postulated to be involved in presenting type VII collagen epitopes to T lymphocytes.

Histopathologically, a BSLE-like picture is seen in DH and DH-like drug eruption. The presence of mucin among the collagen bundles in the dermis, the depth of the infiltrate, and the thickened BMZ in BSLE differentiates it from DH and DH-like drug eruption.

BSLE occurs in the setting of SLE; thus, ANA test results generally are positive. Anti-dsDNA, anti-Sm, anti-Ro/SS-A, anti-La/SS-B, and anticardiolipin antibodies may also be detected. Other laboratory abnormalities related to SLE can include low levels of complement (C3, C4, CH50), anemia, leukopenia, thrombocytopenia, proteinuria or cellular casts upon urinalysis, and an elevated erythrocyte sedimentation rate. Anticardiolipin antibodies and lupus anticoagulant have also been reported in individuals with Rowell syndrome.[8] Leukocytoclastic vasculitis (LCCV) and septic vasculitis have a histopathologic picture similar to BSLE, but in LCCV the infiltrate invades the walls of the blood vessels, while in BSLE it is perivascular. Clinically, generalized vesicles and bullae can occur in LCCV, but they usually become purpuric. In septic vasculitis thrombi are seen inside the blood vessels. BSLE generally responds well to medical therapy, and treatment with dapsone is particularly effective. Although type 1 BSLE and EBA are both characterized by antibodies targeting type VII collagen, EBA differs considerably in its marked resistance to therapy.

Dapsone is the initial treatment of choice for BSLE. The response is usually dramatic, with cessation of new blister formation within 1–2 days and rapid healing of existing lesions. Low doses (25–50 mg/day) are often effective, although a higher dose is sometimes required. Rapid recurrences may occur upon withdrawal of dapsone, with prompt remission after reinstitution of therapy. However, discontinuance of dapsone therapy is usually possible within a year. Prednisone may be effective in patients

who are intolerant of dapsone, have a poor response to dapsone, or require treatment of concurrent systemic manifestations of SLE. Combination therapy with prednisone and dapsone can also be beneficial. Methotrexate (MTX), azathioprine, and mycophenolate mofetil are additional therapeutic options. Extensive eruptions of TEN-like LE require prompt institution of therapy with intravenous immunoglobulin and/or systemic corticosteroids. Less fulminant manifestations of erythema multiforme–like LE can be treated with antimalarials, corticosteroids (topical or systemic), and (in the presence of systemic disease) other agents in the therapeutic armamentarium for LE.[9]

The basic understanding of inflammatory dermatoses and autoimmune-mediated skin disorders has greatly advanced and broadened our understanding of the underlying immune mechanisms that shape the complex network of chronic inflammation and autoimmunity. New treatements, including B-cell-directed therapy, are the new therapeutic frontier for this kind of diseases. With this resume, we summarize the process of establishing and revising the diagnosis criteria and clinical and therapeutic aspects of the main types of autoimmune bullous dermatoses diseases.

Conflicts of Interest

The authors declare no conflicts of interest.

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