Autoimmunity Reviews xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Pemphigus and mucous membrane pemphigoid: An update from diagnosis to therapy

Alessio Buonavoglia[a,1], Patrizia Leone[a,1], Rosanna Dammacco[c], Giuseppe Di Lernia[a], Massimo Petruzzi[b], Domenico Bonamonte[d], Angelo Vacca[a], Vito Racanelli[a,*], Franco Dammacco[a,*]

[a] Department of Biomedical Sciences and Human Oncology, Unit of Internal Medicine "Guido Baccelli", University of Bari Medical School, Bari, Italy
[b] Interdisciplinary Department of Medicine, Section of Dentistry, University of Bari Medical School, Bari, Italy
[c] Department of Ophthalmology and Neuroscience, University of Bari Medical School, Bari, Italy
[d] Department of Biomedical Sciences and Human Oncology, Dermatology Unit, University of Bari Medical School, Bari, Italy

ARTICLE INFO

Keywords:
Autoimmune blistering diseases
Cicatricial pemphigoid
Corticosteroids
Desmoglein-1
Desmoglein-3
Immunosuppressive drugs
Pemphigus vulgaris

ABSTRACT

Pemphigus diseases (PDs) and mucous membrane pemphigoid (MMP) are a group of immune-mediated mucocutaneous disorders clinically characterized by the formation of blisters, erosions and ulcers. The skin and mucous membranes are predominantly affected, with the oropharyngeal mucosa as the initially involved site. Ocular involvement is also a frequent feature of these diseases. Because of the considerable overlap in their clinical presentations, the diagnosis of PDs vs. MMP can be challenging. A recognition of their specific immunological and histopathologic features is crucial in the differential diagnosis. Treatment modalities include systemically administered corticosteroids, steroid-sparing immunosuppressive agents, and biologic therapies (rituximab, intravenous immunoglobulins, and anti-tumor necrosis factor agents). Topical, oral, conjunctival, or intralesional corticosteroids as well as anti-inflammatory drugs and antibiotics are prescribed as needed.

1. Introduction

Pemphigus diseases (PDs) and mucous membrane pemphigoid (MMP) are immunologically mediated mucocutaneous disorders characterized by blistering lesions of the mucous membranes, skin, and oral cavity [1]. PDs are a group of rare but serious diseases that encompass three major forms: pemphigus vulgaris (PV), pemphigus foliaceus (PF), and paraneoplastic pemphigus (PP) [2]. Both PDs and MMP are characterized by the presence of autoantibodies that react with antigens found on the cell surface of keratinocytes, causing intraepithelial and subepidermal blister formation, respectively [3]. Although systemic and serious multi-organ involvement may occur, the first manifestations of either disease frequently involve the oral mucosa [4]. Ophthalmic involvement is less frequent but may be sight-threatening and has been inconsistently considered a marker of severity [5]. No ethnic or geographic preferences have been described for either PDs or MMP. Both conditions commonly manifest between the fifth and sixth decades of life, with MMP occurring twice as often in women as in men [6]. Because the oral lesions of PDs and MMP are similar, a correct differential diagnosis rests upon the histological analysis, immunofluorescence microscopy and the use of other immunological techniques. Here we provide an update of the clinical, pathological and therapeutic aspects of these autoimmune, epithelial-blistering diseases.

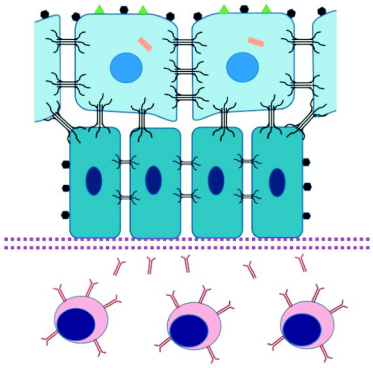
2. Etiology and pathogenesis

2.1. *Pemphigus vulgaris*

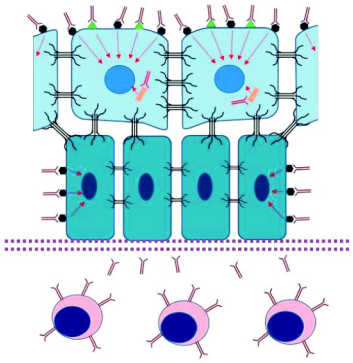
The most common PD in Europe, the United States and Japan is PV, which preferentially affects women and has a peak incidence in those 50–60 years of age [6]. PV is a chronic and severe autoimmune disorder characterized by the formation of blisters on the skin and/or mucosal surfaces. Blister formation is the result of the deleterious action of autoantibodies directed against the surface molecules of keratinocytes, thereby damaging the intercellular substance and resulting in the separation of keratinocytes from one another, a process known as acantholysis [7]. Circulating and skin-fixed autoantibodies are present in about 90% of patients with disease activity. The immune complex

* Corresponding author at: Department of Biomedical Sciences and Human Oncology, University of Bari Medical School, Policlinico - 11, Piazza G. Cesare, 70124 Bari, Italy.
E-mail addresses: vito.racanelli1@uniba.it (V. Racanelli), francesco.dammacco@uniba.it (F. Dammacco).
[1] Alessio Buonavoglia and Patrizia Leone have contributed equally to this work.

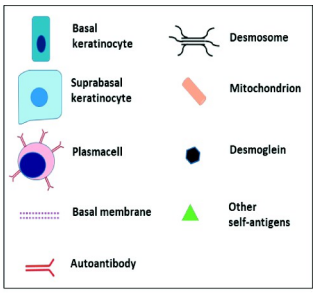
https://doi.org/10.1016/j.autrev.2019.02.005

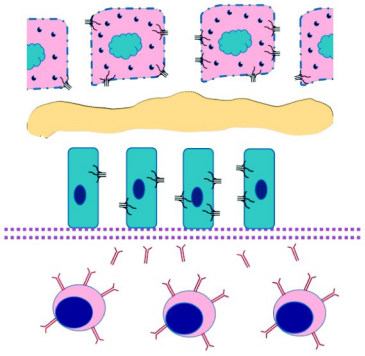


1. Production of autoantibodies targeting desmoglein (Dsg) and other keratinocyte self-antigens

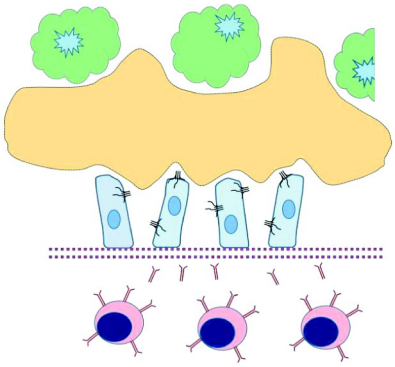


2. Autoantibodies target Dsg, mitochondrial and other keratinocyte self-antigens interfering with structure/function of desmosomes. Dissociation of adhesion complexes (acantholysis) and trigger of downstream signals that launch the cell death cascade (apoptolysis)





3. Dissociation of adhesion complexes with detachment of suprabasal layers and collapse of cytoskeleton, disruption of cell-cell contact (acantholysis); activation of apoptotic enzymes (apoptolysis), basal cell shrinkage, serum accumulation and formation of an intraephitelial blister



4. Suprabasal cellular death; blister enlargement; «tombstoning» of basal cells

Fig. 1. Pathobiology of pemphigus vulgaris. Autoreactive plasma cells produce antibodies directed against keratinocyte self-antigens such as desmoglein, acetylcholine receptors, and mitochondrial proteins. Antibody binding interferes with the structure and function of desmosomes and triggers downstream signals that launch the cell death cascade. Dissociation of the adhesion complexes results in the detachment of suprabasal cell layers (acantholysis) and the activation of apoptotic enzymes, with collapse of the cytoskeleton and disruption of cell-to-cell contacts (apoptolysis). A space forms between the basal and first suprabasal cell layer, allowing serum accumulation and giving rise to a blister. The final evolution of this process is an intra- epithelial blister, suprabasal dead/apoptotic cells, and "tombstoning" of the basal cell layer, with cell shrinkage and a weakening of cell-to-cell contacts.

deposits usually consist of IgG (although IgM, IgA and the complement protein C3 can also be detected) bound to desmosomal transmembrane proteins of keratinocytes, typically desmoglein 1 (Dsg1) and Dsg3. These desmosome-forming proteins belong to the cadherin family and are involved in cell-to-cell adhesion as well as the regulation of cell shape [8].

Investigations of the exact molecular mechanism(s) by which autoantibody binding induces blister formation suggest that acantholysis is a complex process triggered by at least three types of autoantibodies directed against Dsg, other keratinocyte self-antigens, such as acetylcholine receptors [9], and mitochondrial proteins [10] (Fig. 1). These autoantibodies act synergistically, and their binding to self-antigens activates downstream signaling events (activation of Src, epidermal growth factor receptor kinase, p38 MAPK, and mTOR), causing cytoskeleton collapse and the weakening of intercellular junctions, the disruption of cell-to-cell contacts between neighboring keratinocytes (acantholysis), and the activation of apoptotic enzymes, resulting in cell death via a process known as apoptolysis [7,10,11]. The end effect is the formation of an intra- epithelial blister just above the basal-cell layer (Fig. 1).

The tissue specificity of the autoantibody-induced loss of cell adhesion and subsequent blister development is determined by the predominant presence of Dsg3 (target of PV autoantibodies) and the absence of Dsg1 in the deeper layer. This arrangement does not allow for the compensation of damaged desmoglein isotypes, as suggested by the desmoglein compensation theory [12–14] which states that the tissue distribution of Dsg3 and Dsg1 regulates the site of blister formation in PV patients. The co-expression of the two isotypes, but also the expression of either Dsg1 or Dsg3 alone, is sufficient to maintain keratinocyte adhesion and prevent the occurrence of intra-epithelial blisters, given that one Dsg isotype compensates for the loss of function of the other, damaged isotype [12–14].

Autoantibody production implies the loss of tolerance of Dsg3 by both T- and B-cells, and thus a strong interaction between these two cell subsets [15,16]. Characterizations of autoreactive B- and T-cell populations have enabled profiling of the immune repertoire of PV patients. Several studies, both in PV patients and in a mouse model of PV, have clearly shown that anti-Dsg3 autoantibodies are generated by somatic mutations through an antigen-driven process [17,18]. These antibodies target Dsg3 amino-terminal extracellular cadherin (EC) domains (usually EC1 and EC2), involved in cis-adhesive interactions. Autoreactive T-cells play an important role in this process, as suggested by

the observation that, while Dsg3-reactive Th1 CD4+ T-cells can be identified in PV patients and in healthy individuals [19], Dsg3-reactive Th2-cells are found only in PV patients [12,19]. Th2-cells recognize Dsg3 peptides based on their conserved anchor motifs, which are required for binding to the P4 pocket of HLA-DR4 molecules, whose class-II-restricted activation drives autoreactive B-cell activity and autoantibody production [20].

The most well-studied DR4 haplotype is HLA-DRB1*0402, which presents the Dsg3-190- 204 self-peptide to T-cells [21] and is associated with the strong susceptibility of Jewish individuals to PV [22]. HLA alleles with a phenylalanine homology at position 26 and a valine homology at position 86 of the DRB1*0402 allele, and thus associated with susceptibility to PV, are the HLA- DQB1*05:03 in non-Jewish individuals of mixed European descent [22,23] and the HLA- DRB1*14 and HLA-DQB1*05:03 alleles that occur in Japanese individuals [24,25]. These HLA genes are probably the most significant genetic PV-predisposition factors, even if alone they are not sufficient to initiate the autoimmune mechanism. Other inducing or triggering external factors may be drugs or physical agents, viruses, allergens, dietary factors and stress [26,27]. However, the etiology of PV remains largely unknown such that in most individuals PV is defined as idiopathic.

2.2. *Pemphigus foliaceus*

The second major form of PD is PF, which is caused by a humoral autoimmune response directed exclusively against Dsg1 [2]. Consistent with the desmoglein compensation theory, anti- Dsg1 IgG antibodies induce superficial blisters in the skin but not in mucosal membranes, given that Dsg1 is largely present in superficial layers of the epidermis and absent in its deeper layers and in mucosal epithelia [13]. In general, the clinical course of PF is benign and faster than that of PV, because of the superficial localization of the lesions.

The epidemiology of PF also differs from that of PV. Endemic forms of PF are common in South America and North Africa, where the disease affects mostly young adults, with a peak incidence in those 20–30 years of age [28,29]. This epidemiological difference suggests a role for environmental agents. It has been postulated that, in some genetically susceptible individuals, a low-level IgG (mainly IgG4) autoantibody response directed against the ectodomain of Dsg1 becomes pathogenic and leads to acantholysis. In Brazil, antibodies against the sand fly salivary antigen LJM11, from *Lutzomyia longipalpis*, may herald the onset of “fogo selvagem” (an endemic form of PF) through a cross-reaction with Dsg1 antibodies [30,31].

Several HLA alleles have been identified as genetic risk factors for PF, including HLA- DRB1*04 and HLA-DRB1*14, which are associated with non-endemic PF, and HLA-DRB1*1402 and HLA-DR*0404 which have been linked to fogo selvagem [20,32].

2.3. *Paraneoplastic pemphigus*

The first reported case of PP was that published by Anhalt, in 1990 [33], and the disease is usually identified with the paraneoplastic autoimmune multiorgan syndrome (PAMS) rather than as a subtype of pemphigus [34,35]. Although PP is by definition associated with an underlying neoplasia (including B-cell non-Hodgkin lymphoma, chronic lymphocytic leukemia, Castleman's disease, or thymoma [36,37]), treatment or surgical removal of the tumor is uncommonly followed by slow-down or arrest in the progression of PP [34]. In addition, PP is a rare disease, with approximately 500 cases reported in the literature [38], and no significant age- or sex-related differences. The HLA-DRB1*03 and HLA-Cw*14 haplotypes may confer a strong susceptibility to PP [39]. Patients with the disease develop IgG autoantibodies directed against a wide array of antigens, including Dsg3, Dsg1 or both, α2-macroglobulin-like protein-1, as well as proteins belonging to the plakin family (envoplakin, periplakin, desmoplakin I/II, plectin, epiplakin) [2]. In addition to a humoral reaction, a cellular autoimmune response to the epidermis occurs that results in T-cell-mediated keratinocyte apoptosis.Mucous membrane pemphigoid and ocular cicatricial pemphigoid

The heterogeneous group of multisystemic, blistering, autoimmune diseases referred to as MMP are characterized by the appearance of blisters on different mucosal surfaces. When the clinical manifestations are restricted to the conjunctiva, MMP is more properly called ocular cicatricial pemphigoid (OCP) [40], although the two terms are often used interchangeably. While clinically similar to PV, the mechanism of blister formation differs in MMP, in which there is also a tendency of the bullae to form scars [4]. Blister development is a consequence of the linear deposition of IgG, IgA, or C3 along the mucosal and epithelial basement membranes [41,42]. The pathogenesis is not well understood, but several studies have demonstrated that subepithelial blister formation reflects the targeting by these autoantibodies of both the hemidesmosomes of basal epidermal keratinocytes and the lamina lucida of the basal membrane [43]. The specific molecular targets of MMP autoantibodies are antigen 2 (type XVII collagen) and type VII collagen [44], laminin 332 (laminin-5) and laminin-6 [45], α-6 and β-4 integrin subunits [46], and a 120-kDa undefined epithelial antigen [47].

The etiology of MMP is unknown, but a genetic association with HLA-DR4 and HLA- DBQ1*0301 haplotypes has been described [41]. Several studies have invoked “epitope spreading” as the mechanism underlying MMP, in which tissue damage from a primary inflammatory process induces the exposure of a previously “hidden” epithelial basement membrane antigen to autoreactive T cells, leading to a secondary autoimmune response against it [48]. Indeed, OCP has been described in patients previously affected by the ocular manifestations of Stevens-Johnson syndrome or Sjögren syndrome [47,49,50].

3. Clinical features

For the sake of clarity, in the following, the ocular manifestations of PD and MMP as well as the clinical and therapeutic periodontal implications of these diseases are treated in separate sections.

With the exception of PF, in which oral lesions are usually absent, the clinical manifestations of PV and MMP are similar and include the formation of blisters of variable size, ranging from minute vesicles resembling red erythematous areas to larger vesicles (blisters < 5 mm in diameter) and bullae (blisters > 5 mm in size) [51]. The lesions affect the mucosal surfaces lined by stratified epithelium (oral, nasal, laryngo-esophageal, genital, anal, and conjunctival mucosa) and/or the skin [3]. In PV, skin involvement manifests as cutaneous blisters or erythematous areas, especially on the scalp, face, axilla, trunk, and groin. In MMP, skin lesions are rare and appear after mucosal manifestations that more frequently include the head, neck, and upper body [4].

The oral cavity, especially the buccal mucosa, soft palate, and lips, is the first site to be involved in 50–80% of PV patients and in 90% of MMP patients [52] (Fig. 2A–C). The oral blisters burst quickly, leaving painful erosions and ulcers that are often the only clinical sign of either disease [53]. Unlike the oral lesions of aphthous stomatitis or viral infections, which heal in a matter of days or weeks, the ulcers of pemphigus are slow-healing.

While the gingiva is rarely involved in PV, it is the most commonly affected oral site in MMP. Gingival involvement is characterized by desquamative gingivitis, which leaves an erythematous band along the teeth, accompanied by dryness, desquamation, and bullae [54] (Fig. 2D). Given its autoimmune etiology, the gingivitis in MMP does not improve with the elimination of plaque and tartar, unlike in common bacterial periodontal diseases associated with the accumulation of a microbial biofilm on tooth surfaces [55].

Compared with PV, involvement of the oral mucosa is more extensive in PP and the involvement of other mucosal sites, such as the conjunctivae, is more frequent. Generalized erosive stomatitis or a painful, persistent, and therapy-refractory hemorrhagic stomatitis that often extends to the vermilion of the lip are common findings.

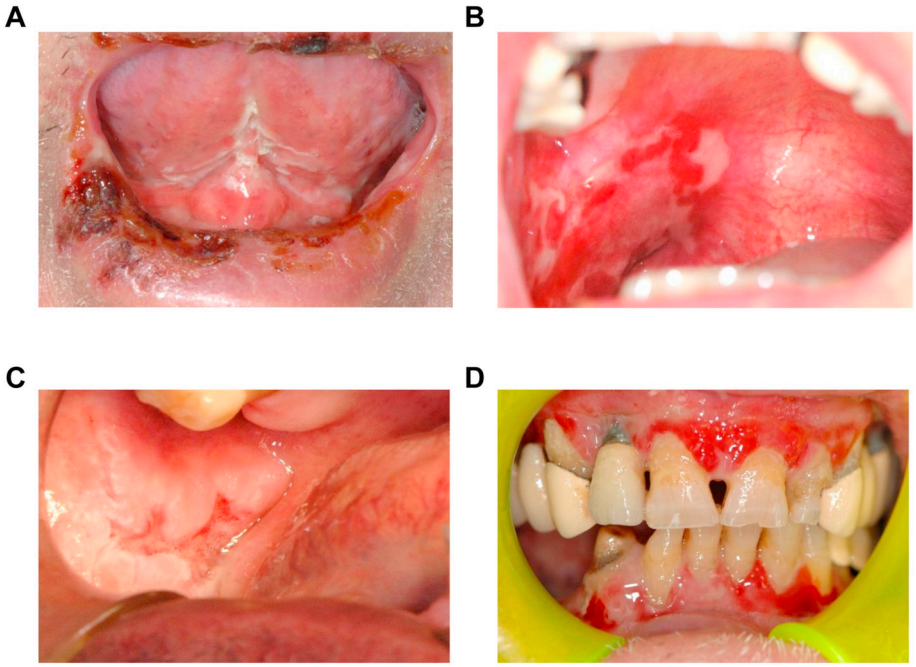


Fig. 2. Mucosal erosions on the lips (A), and cheek mucosa (B−C) in patients with pemphigus vulgaris. (D) Desquamative gingivitis in a patient with mucous membrane pemphigoid.

Cutaneous manifestations are heterogeneous and include polymorphic bullae, erosions, papulae, and lichenoid lesions that predominantly affect the upper body [2]. Extracutaneous manifestations often involve the respiratory system with clinical and pathological features of bronchiolitis obliterans [34].

4. Diagnosis

PD and MMP are potentially life-threatening diseases, with a mortality of up to 90% if left untreated [56], thus emphasizing the importance of an early diagnosis. However, because both diseases are rare, they are not often diagnosed at the first examination, but considered only when the lesions persist for weeks to months and the response to antibiotic, antifungal, or antiviral therapies is negative. A typical diagnostic feature is the Nikolsky sign, in which a firm sliding pressure with a finger on the skin next to a lesion results in the disruption of intercellular adhesion and thereby the formation of a new blister. However, it is neither highly sensitive nor strictly specific, as false-negative results are possible when acantholysis is present but minimal, in which case the damage can only be demonstrated histologically [57].

The clinical manifestations in the oral mucosa are similar to those in other oral diseases, such as aphthae, aphthous stomatitis, bullous and erosive lichen planus, oral candidiasis, and herpetic gingival stomatitis, which initially complicates the differential diagnosis [41]. Thus, important considerations in the differential diagnosis are: (1) aphthous stomatitis affects only non- keratinized mucosae, without blister formation [56]; (2) the Nikolsky sign is generally negative in patients with lichen planus; (3) mucocutaneous reticular lesions are not seen in PV [58]; (4) the ulcers in PD and MMP are multiple, a feature that differentiates these diseases from an ulcerated tumor, which is a single lesion; and (5) classical candidiasis more frequently affects the elderly, infants, or immunocompromised patients and is characterized by white pseudo-membranes (that can be removed with a brush) and angular cheilitis [59].

Nonetheless, the differential diagnosis must be confirmed by a histological analysis of biopsy samples and by immunofluorescence, to show the binding of autoantibodies to the keratinocyte cell surface [2,60,61] (Fig. 3). A biopsy of a PV blister reveals an intra-epithelial vesicle containing inflammatory cells and floating, rounded keratinocytes (Tzanck cells) [62] separated from surrounding cells (acantholysis). The floor of the blister may be lined with intact keratinocytes that are still attached to the basement membrane, leading to a characteristic appearance called “tombstoning.” On direct immunofluorescence, intercellular deposits of IgG and C3 are seen with the typical “fishing net” aspect, whereas there is no staining of the basement membrane (Fig. 4A) [63,64].

At variance from PV and PF, PP is characterized by the occurrence of interface dermatitis, vacuolar changes, dyskeratotic keratinocytes, and less frequently subepidermal splits. Direct immunofluorescence shows, in addition to intercellular IgG as commonly seen in PV, IgG and C3 deposits along the dermal-epidermal junction [34]. Of note, necrotic tissue or dense inflammatory infiltrates may produce false-negative results [2].

The histopathology of MMP is characterized by subepithelial vesicles with an inflammatory infiltrate comprising eosinophils, lymphocytes, and neutrophils, similar to other forms of pemphigoid. There is a complete leakage of epithelium from the basement membrane, and no tombstoning. Direct immunofluorescence reveals the deposition of IgG, C3, and sometimes IgA along the basal membrane (Fig. 4B) [41]. Given that immune deposits precede the appearance of acantholysis in the suprabasal epithelium, direct immunofluorescence is considered more sensitive than conventional histopathology [65]. Indirect immunofluorescence and enzyme-linked immunosorbent assays can be useful to detect circulating autoantibodies against epithelial cell surface antigens and to evaluate the prognosis and response to therapy [66,67].

5. Therapy

First-line treatment consists of topical and systemic corticosteroids [2,68]. Starting doses of prednisone are 0.5–1.5 mg/kg/day. If disease control is not achieved within 1–2 weeks, higher (up to 2 mg/kg) doses of prednisone or equivalent doses of prednisolone can be prescribed. Systemic corticosteroids can be used in combination with immunosuppressive agents, such as azathioprine, mycophenolate mofetil, or/and methotrexate [69,70].

Intravenous immunoglobulin therapy [71,72] or plasmapheresis

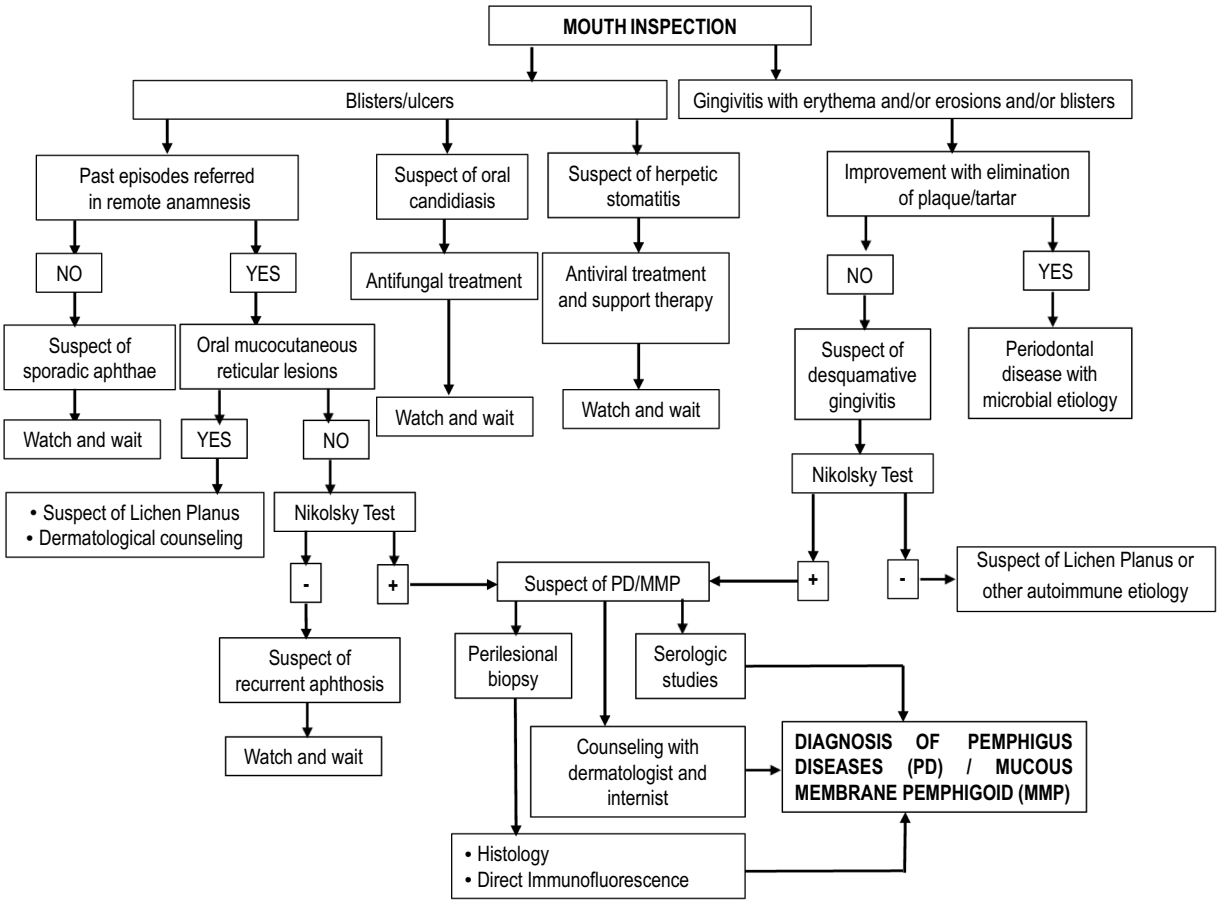


Fig. 3. Flow chart of the differential diagnosis in pemphigus disorders and mucous membrane pemphigoid.

with immuno-adsorption may also be effective in reducing circulating autoantibody levels and in augmenting treatment efficacy [72–76]. However, the failure to achieve long-lasting remission and the occurrence of serious adverse events, such as hypogammaglobulinemia associated with non-specific immunoadsorption, have led to the development of alternative treatments. For example, a novel experimental approach in which antigen-specific immune adsorbents are used to specifically extract disease-causing autoantibodies is an attractive strategy in plasmapheresis therapy [77].

Off-label use of the anti-CD20 antibody rituximab has been effective in inducing complete remission in most patients with refractory disease [78,79]. Rituximab can be used in monotherapy or in combination with immuno-adsorption and/or immunoglobulin infusion and/or conventional immunosuppressive agents [80,81]. The two protocols favored in PV are similar to those used to treat non-Hodgkin lymphoma (four weekly infusions of rituximab at a dose of 375 mg/m2) and rheumatoid arthritis (two intravenous infusions of 1,000 mg every 2 weeks) [82] and they are for the most part equally effective [83,84]. Zakka et al. analyzed 42 studies reporting on a total of 272 patients with pemphigus: 180 were treated with the lymphoma protocol, and 92 with the rheumatoid arthritis protocol. However, the authors concluded that neither protocol produced a sustained clinical remission and both had to be administered as continuous systemic therapy. A major difficulty in the two protocols was the high rate of infections, some of which were fatal [83]. Thus, patients should be carefully monitored during and after rituximab therapy to avoid the development of complications. The clinical response to rituximab is strictly related to the level of anti-Dsg autoantibodies, which decreases in patients who achieve complete remission but remains unchanged or increases in patients with disease relapse [85]. In the majority of pemphigus patients, disease relapse

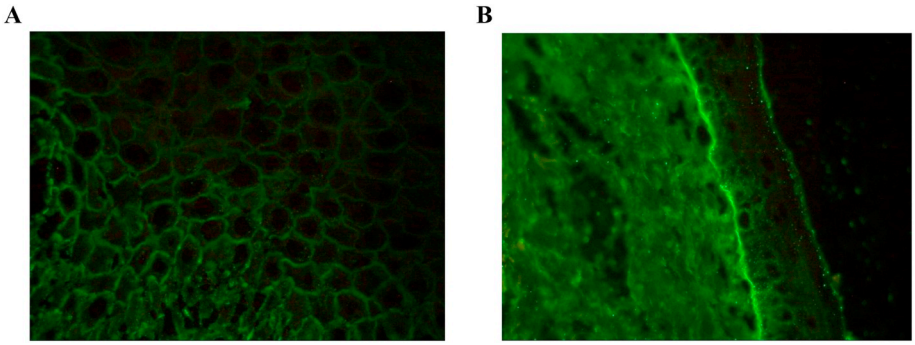


Fig. 4. Direct immunofluorescence analysis of a skin biopsy showing the binding of autoantibodies to the keratinocyte surface, with a typical and suggestive "fishing net" aspect in patients with PV (A) and the binding of autoantibodies along the basal membrane with no involvement of suprabasal keratinocyte in MMP patients (B).

after rituximab treatment can be expected, because of an incomplete B-cell depletion in the bone marrow and secondary lymphoid organs, and the appearance of newly formed Dsg3- autoreactive B cell clones [85]. The inclusion of rituximab in the treatment of PV allows the use of a lower initial dose of oral prednisolone and therefore a reduction in its total cumulative dose [86].

MMP is less responsive than pemphigus to rituximab [87,88]. The poor response of MMP patients with IgA-dominant disease to rituximab is probably due to persistent IgA-secreting plasma cells derived from a memory B-cell population that is resistant to anti-CD20 therapy [89]. Further studies are required to determine the safety and efficacy of rituximab as the first-line agent in PV.

The treatment of PP should target both a T-cell- and a B-cell-mediated attack on epithelial tissues, although combined T-cell and B-cell immunosuppression is related to a high risk of infection [90]. Hwang et al. described the case of a woman with recalcitrant PP associated with follicular dendritic cell sarcoma who responded well to rituximab (375 mg/m2/week) and oral cyclosporin (80 mg twice daily). Unfortunately, because of heavy immunosuppression, the patient developed multilobar pneumonia, which eventually caused her death [91]. Thus, treatment of PP should be considered challenging and often unsuccessful [34].

In addition to rituximab, other anti-CD20 monoclonal antibodies, such as veltuzumab, obinutuzumab, ocaratuzumab, ofatumumab, PRO131921, and anti-B-cell-activating factor (BAFF) have proven to be just as beneficial as rituximab and potentially more cost-effective and safer. These next-generation anti-CD20 monoclonal antibodies have enhanced B-cell-depleting capabilities and higher binding affinities to effector cells than rituximab, resulting in a more specific depletion of autoreactive B-cells. They have shown promise in clinical trials of several autoimmune diseases [86].

Because the target antigens and pathophysiological mechanisms of PV are well characterized, a broad range of innovative approaches aimed at the pathogenic autoantibodies or the immune cells involved in their production are in preclinical and clinical development. A new autoantigen-specific B-cell-depleting therapy was recently proposed in which human T-cells are engineered to express a chimeric receptor specific for Dsg3 autoantigens (CAR T cells) and to specifically kill autoantigen-specific B-cells [92].

In vitro studies and a mouse model of pemphigus have demonstrated that, compared to conventional antibody therapies, the CAR approach is safer, less toxic, and induces and maintains long-lasting disease remission [93]. Based on the lower levels of Dgs3-specific regulatory T-cells (Tregs) in PV patients than in unaffected individuals [94], CAR technology has been exploited in the *in vitro* generation of potent and functional alloantigen-specific human Tregs to maintain and restore natural tolerance against Dsg3 [95]. Thus, the CAR T-cell strategy may be a promising one, although its efficacy and safety in human clinical trials remain to be confirmed.

6. Ocular involvement

Given the relative rarity of autoimmune blistering diseases, there are few published data regarding the epidemiology of their ocular involvement, but it is clear that the actual incidence has been underestimated [96,97] and that the low reported rate reflects an under-diagnosis rather than true eye sparing [98]. Messmer et al. found that, among 28 patients with MMP, 64% had ocular disease determined to be OCP [99]. Ocular involvement was also detected in 16.5% of the 103 Iranian patients with PV [100] and has been estimated to occur in 70% of patients with PP [3]. In the following, we provide a short description of the clinical features of ocular involvement that

characterize PD and OCP. We also discuss the most common therapeutic strategies that, in addition to the above-mentioned, stepwise systemic therapeutic measures, are used to control ocular-specific manifestations.

6.1.1. *Pemphigus vulgaris*

Ocular lesions are rarely observed in PV but, when present, either follow or, less often, occur simultaneously with the appearance of skin and/or mucous membrane lesions. Patients usually complain of conjunctival congestion with eye redness, photophobia, tearing, pain, and a non-purulent discharge [3,100]. Non-cicatrizing bilateral conjunctivitis is diagnosed in the majority of these cases, whereas the iris, lens, cornea, sclera or retina, and hence visual acuity are typically spared [3,100,101], provided that an early diagnosis is made and suitable therapeutic measures are adopted. Giant cobblestone-like conjunctival papillae have been occasionally described [102].

Systemic corticosteroids, frequently administered with immunosuppressive agents, remain the mainstay of treatment when concurrent ocular disease is diagnosed in PV. In addition, lubricating artificial tears and topical ophthalmic corticosteroids are useful in the relief of ocular symptoms, especially when conjunctival ulcerations are detected. Oral mizoribine, an imidazole nucleoside with immunosuppressive activity, was recently shown to induce remarkable improvement in the refractory ocular manifestations of PV in Japanese patients [103].

6.1.2. *Pemphigus foliaceus*

Since the IgG (mainly IgG4) autoantibodies detected in PF are directed against the ectodomain of Dsg1, which is abundantly present in the superficial layers of the epidermis, superficial blisters form in the skin but not in mucous membranes. Consequently, eye involvement is usually absent in PF and in its endemic form, fogo selvagem. However, although the conjunctival mucosa is not affected in PF, erythematous, ulcerous, and crusty plaques disseminated on the skin surface can obviously also occur on one or both eyelids [104]. In such an instance, the above-mentioned systemic treatments are appropriate, rather than ocular-specific therapies.

6.1.3. *Paraneoplastic pemphigus*

Ocular complications, that may occur in up to 41% of patients [105] may include ocular pain and redness, mucus discharge, severe dry eye, epithelial breakdown, and thickening of the eyelid margin. The ophthalmic examination usually reveals an impaired visual acuity, and the slit-lamp examination bilateral pseudomembranous conjunctivitis with early symblepharon formation. Punctate epithelial erosions on one or both corneas may also be detected. These lesions may result in mono- or bilateral cicatrizing conjunctivitis, extensive symblephara formation, and forniceal foreshortening [106,107].

An early and vigorous therapeutic approach is essential to successfully prevent the occurrence of irreversible complications, including blindness. Intensive topical lubrication, topical corticosteroid and/or tacrolimus drops, and sodium hyaluronate have been employed with variable

and often partial results. When extensive conjunctival scarring occurs, the loss or shortening of the fornices usually requires surgical grafting with amniotic membrane [3,96].

6.1.4. *Ocular cicatricial pemphigoid*

Recurrent conjunctival inflammation develops in 60–80% of OCP patients and may result in subepithelial fibrosis, leading to fornix shortening, symblepharon, cicatricial entropion, and trichiasis. Severe dry eye disease, often leading to corneal ulceration, scarring, and neovascularization, may reflect Meibomian gland impairment and lacrimal duct obstruction [3,108]. Four disease stages have been described: subepithelial fibrosis (stage I), shortened fornices (stage II),

symblepharon formation (stage III), and keratinization with or without globe immobility (stage IV) [109].

Preservative-free lubricants should be applied several times a day to replace tear deficiency, but in many OCP patients the disease nonetheless tends to follow a progressive course, resulting in scarring and blindness. Etanercept, an anti-TNF-α agent, has been used with encouraging results in patients refractory to cyclophosphamide or intravenous immunoglobulins [40,110]. In more advanced disease stages, surgical procedures, such as eye lash ablation, tarsorrhaphy, transplantation of amniotic membrane and, in case of corneal melting, tectonic epikeratoplasty, will become necessary [40,49,97]. To avoid cicatricial shrinkage of the conjunctival fornices, intraoperative topical and subconjunctival applications of mitomycin C has been shown to improve the postoperative outcome [111].

7. Periodontal implications and treatment

Patients with PV and MMP are more susceptible to periodontitis [54], a chronic inflammatory disease of microbial etiology that affects the tooth-supporting structures. Progressive injury of the soft tissues, ligaments, and alveolar bone may result in the loss of the affected teeth [112]. Dental evaluation should include anamnesis as well as clinical and radiographic examinations to identify infectious foci, such as caries as well as periodontal and endodontic diseases, in the oral mucosa, teeth, gums, and alveolar bone. Carious/non-carious lesions with sharp margins can traumatize the oral mucosa, triggering or perpetuating blister formation. For the same reason, it is important to replace an incongruent prosthesis that traumatizes the oral mucosa and/or promotes the accumulation of bacterial plaque [54].

Erosive gingival lesions can also serve as a reservoir of microbial plaque that generates an inflammatory response similar to that seen in desquamative gingivitis, including leukocyte infiltration as well as the release of proinflammatory cytokines and matrix metalloproteinases [112]. Moreover, in patients with PV and MMP, the inflammatory process associated with periodontal disease can trigger and/or perpetuate an autoimmune response [54]. However, gingival lesions respond poorly to systemic immunosuppressive drugs [113]. Professional oral hygiene procedures improve gingival status and decrease gingival-related pain, thus lowering the risk of periodontal diseases [65,114,115]. Nonetheless, oral hygiene measures performed on an inflamed oral mucosa can induce a bacteremia which, associated with an autoimmune disease and immunosuppressive therapy, may increase the risk of developing a focal infection elsewhere in the body, such as infective endocarditis [116].

Topical treatment, such as corticosteroid therapy, e.g., fluocinonide 0.05%, is recommended for mild cases of PV and MMP limited to oral manifestations., whereas severe cases can be treated with clobetasol. Both drugs are applied directly to the lesion, 4–6 times/day, followed by their gradual suspension [117]. The suitably adjusted administration of these drugs and, potentially, their prompt, tapered discontinuation are indicated in patients with background cardiovascular and metabolic diseases [55]. Adjuvant analgesic, anti-inflammatory and anti-infectious therapy can be additionally used. A sodium bicarbonate mouth rinse is useful to control infections, especially those of fungal origin [117]. Benzydamine hydrochloride and antihistamine solution are sometimes employed. A mouth rinse containing chlorhexidine 0.12–0.20%, without a potentially irritating alcohol-based vehicle, or oxytetracycline may also contribute to preventing infections [117].

8. Conclusions

Early diagnosis and suitable treatment are essential to prevent the severe consequences of PD and MMP in their full-blown forms. The cooperation of a multidisciplinary medical team that includes an internist, to determine a tailored systemic therapy; a dermatologist, for the diagnosis and management of cutaneous manifestations; an ophthalmologist, to properly treat potentially sight- threatening complications; and a dentist, for the early diagnosis and management of oral manifestations, is therefore essential.

Take-home messages

- PD and MMP are a group of rare but serious autoimmune mucocutaneous blistering diseases.
- An early diagnosis is not common given the initial occurrence of non-specific symptoms and signs, but it should be achieved as soon as possible to prevent severe consequences.
- The most commonly involved sites are the oral cavity with painful erosions that heal slowly for PD, and recurrent conjunctival inflammation resulting in consequences of increasing severity from subepithelial fibrosis to cicatricial entropion and trichiasis for OCP.
- Available therapies can be topical to treat localized manifestations and systemic to control autoimmune disorder. Systemic corticosteroids, frequently administered in combination with immunosuppressive agents such as azathioprine, mycophenolate mofetil, and methotrexate, remain the mainstay of treatment. Intravenous immunoglobulins, plasmapheresis, rituximab or other anti-CD20 monoclonal antibodies may be considered in patients with resistant or recurrent manifestations.
- It is suggested that PD and MMP should be managed by a multidisciplinary team: the various clinical manifestations (cutaneous, ocular and oral) can be better interpreted through a cooperation among specialists to reach an early diagnosis and to establish a suitable and personalized therapy.

Author contributions

AB, PL and VR conceived and designed the study. AB, GDL, DB and MP collected the data and contributed to their interpretation. AB, PL and VR wrote a large part of the manuscript. RD managed many of the patients with ocular involvement and wrote the section of the manuscript dealing with ocular-specific manifestations of PD and OCP. FD and AV revised the manuscript for important intellectual content. All authors reviewed the manuscript, approved the draft submission, and accept responsibility for all aspects of this study.

Disclosures

The authors have no financial conflicts of interest.

Financial support

This work was supported by the Italian Association for Cancer Research (AIRC) through an Investigator Grant (no. 20441 to VR) and by Fondo di Sviluppo e Coesione 2007-2013 – APQ Ricerca Regione Puglia “Programma regionale a sostegno della specializzazione intelligente e della sostenibilità sociale ed ambientale - FutureInResearch”. The sponsors of this study are public or nonprofit organizations that support science in general; they had no role in gathering, analyzing, or interpreting the data.

Conflict of interests

The authors have no financial conflict of interest.

References

[1] Bystryn JC, Rudolph JL. Pemphigus. Lancet 2005;366(9479):61–73. https://doi.org/10.1016/S0140-6736(05)66829-8.
[2] Kasperkiewicz M, Ellebrecht CT, Takahashi H, Yamagami J, Zillikens D, Payne AS, et al. Pemphigus. Nat Rev Dis Primers 2017;3:17026. https://doi.org/10.1038/nrdp.2017.26.
[3] Broussard KC, Leung TG, Moradi A, Thorne JE, Fine JD. Autoimmune bullous

diseases with skin and eye involvement: Cicatricial pemphigoid, pemphigus vulgaris, and pemphigus paraneoplastica. Clin Dermatol 2016;34(2):205–13. https://doi.org/10.1016/j.clindermatol.2015.11.006.
[4] Ramos-e-Silva M, Ferreira A, Jacques C. Oral involvement in autoimmune bullous diseases. Clin Dermatol 2011;29(4):443–54. https://doi.org/10.1016/j.clindermatol.2011.01.015.
[5] Balica S, Bulai Livideanu C, Fournie P, Fortenfant F, Soler V, Barbarot S, et al. Is conjunctival mucous involvement a marker of severity in pemphigus vulgaris? J Eur Acad Dermatol Venereol 2013;27(4):520–1. https://doi.org/10.1111/j.1468-3083.2012.04509.x.
[6] Alpsoy E, Akman-Karakas A, Uzun S. Geographic variations in epidemiology of two autoimmune bullous diseases: pemphigus and bullous pemphigoid. Arch Dermatol Res 2015;307(4):291–8. https://doi.org/10.1007/s00403-014-1531-1.
[7] Grando SA, Bystryn JC, Chernyavsky AI, Frusic-Zlotkin M, Gniadecki R, Lotti R, et al. Apoptolysis: a novel mechanism of skin blistering in pemphigus vulgaris linking the apoptotic pathways to basal cell shrinkage and suprabasal acantholysis. Exp Dermatol 2009;18(9):764–70. https://doi.org/10.1111/j.1600-0625.2009.00934.x.
[8] Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. N Engl J Med 2006;355(17):1800–10. https://doi.org/10.1056/NEJMra061111.
[9] Vu TN, Lee TX, Ndoye A, Shultz LD, Pittelkow MR, Dahl MV, et al. The pathophysiological significance of nondesmoglein targets of pemphigus autoimmunity. Development of antibodies against keratinocyte cholinergic receptors in patients with pemphigus vulgaris and pemphigus foliaceus. Arch Dermatol 1998;134(8):971–80.
[10] Marchenko S, Chernyavsky AI, Arredondo J, Gindi V, Grando SA. Antimitochondrial autoantibodies in pemphigus vulgaris: a missing link in disease pathophysiology. J Biol Chem 2010;285(6):3695–704. https://doi.org/10.1074/jbc.M109.081570.
[11] Schmidt E, Waschke J. Apoptosis in pemphigus. Autoimmun Rev 2009;8(7):533–7. https://doi.org/10.1016/j.autrev.2009.01.011.
[12] Amagai M, Koch PJ, Nishikawa T, Stanley JR. Pemphigus vulgaris antigen (desmoglein 3) is localized in the lower epidermis, the site of blister formation in patients. J Invest Dermatol 1996;106(2):351–5.
[13] Amagai M, Tsunoda K, Zillikens D, Nagai T, Nishikawa T. The clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile. J Am Acad Dermatol 1999;40(2 Pt 1):167–70.
[14] Hanakawa Y, Matsuyoshi N, Stanley JR. Expression of desmoglein 1 compensates for genetic loss of desmoglein 3 in keratinocyte adhesion. J Invest Dermatol 2002;119(1):27–31. https://doi.org/10.1046/j.1523-1747.2002.01780.x.
[15] Nishifuji K, Amagai M, Kuwana M, Iwasaki T, Nishikawa T. Detection of antigen-specific B cells in patients with pemphigus vulgaris by enzyme-linked immunospot assay: requirement of T cell collaboration for autoantibody production. J Invest Dermatol 2000;114(1):88–94. https://doi.org/10.1046/j.1523-1747.2000.00840.x.
[16] Tsunoda K, Ota T, Suzuki H, Ohyama M, Nagai T, Nishikawa T, et al. Pathogenic autoantibody production requires loss of tolerance against desmoglein 3 in both T and B cells in experimental pemphigus vulgaris. Eur J Immunol 2002;32(3):627–33. https://doi.org/10.1002/1yo521-4141(200203)32:3<627::AID-IMMU627>3.0.CO;2-1.
[17] Di Zenzo G, Di Lullo G, Corti D, Calabresi V, Sinistro A, Vanzetta F, et al. Pemphigus autoantibodies generated through somatic mutations target the desmoglein-3 cis-interface. J Clin Invest 2012;122(10):3781–90. https://doi.org/10.1172/JCI64413.
[18] Qian Y, Diaz LA, Ye J, Clarke SH. Dissecting the anti-desmoglein autoreactive B cell repertoire in pemphigus vulgaris patients. J Immunol 2007;178(9):5982–90.
[19] Veldman CM, Gebhard KL, Uter W, Wassmuth R, Grotzinger J, Schultz E, et al. T cell recognition of desmoglein 3 peptides in patients with pemphigus vulgaris and healthy individuals. J Immunol 2004;172(6):3883–92.
[20] Sinha AA. The genetics of pemphigus. Dermatol Clin 2011;29(3):381–91. vii https://doi.org/10.1016/j.det.2011.03.020.
[21] Wucherpfennig KW, Yu B, Bhol K, Monos DS, Argyris E, Karr RW, et al. Structural basis for major histocompatibility complex (MHC)-linked susceptibility to autoimmunity: charged residues of a single MHC binding pocket confer selective presentation of self-peptides in pemphigus vulgaris. Proc Natl Acad Sci U S A 1995;92(25):11935–9.
[22] Ahmed AR, Yunis EJ, Khatri K, Wagner R, Notani G, Awdeh Z, et al. Major histocompatibility complex haplotype studies in Ashkenazi Jewish patients with pemphigus vulgaris. Proc Natl Acad Sci U S A 1990;87(19):7658–62.
[23] Sinha AA, Brautbar C, Szafer F, Friedmann A, Tzfoni E, Todd JA, et al. A newly characterized HLA DQ beta allele associated with pemphigus vulgaris. Science 1988;239(4843):1026–9.
[24] Miyagawa S, Higashimine I, Iida T, Yamashina Y, Fukumoto T, Shirai T. HLA-DRB1*04 and DRB1*14 alleles are associated with susceptibility to pemphigus among Japanese. J Invest Dermatol 1997;109(5):615–8. https://doi.org/10.1111/1523-1747.ep12337585.
[25] Niizeki H, Inoko H, Mizuki N, Inamoto N, Watababe K, Hashimoto T, et al. HLA-DQA1, - DQB1 and -DRB1 genotyping in Japanese pemphigus vulgaris patients by the PCR-RFLP method. Tissue Antigens 1994;44(4):248–51.
[26] Ruocco V, Ruocco E, Lo Schiavo A, Brunetti G, Guerrera LP, Wolf R. Pemphigus: etiology, pathogenesis, and inducing or triggering factors: facts and controversies. Clin Dermatol 2013;31(4):374–81. https://doi.org/10.1016/j.clindermatol.2013.01.004.
[27] Sagi L, Sherer Y, Trau H, Shoenfeld Y. Pemphigus and infectious agents. Autoimmun Rev 2008;8(1):33–5. https://doi.org/10.1016/j.autrev.2008.07.021.
[28] Culton DA, Qian Y, Li N, Rubenstein D, Aoki V, Filhio GH, et al. Advances in pemphigus and its endemic pemphigus foliaceus (Fogo Selvagem) phenotype: a paradigm of human autoimmunity. J Autoimmun 2008;31(4):311–24. https://doi.org/10.1016/j.jaut.2008.08.003.
[29] Meyer N, Misery L. Geoepidemiologic considerations of auto-immune pemphigus. Autoimmun Rev 2010;9(5):A379–82. https://doi.org/10.1016/j.autrev.2009.10.009.
[30] Qian Y, Culton DA, Jeong JS, Trupiano N, Valenzuela JG, Diaz LA. Non-infectious environmental antigens as a trigger for the initiation of an autoimmune skin disease. Autoimmun Rev 2016;15(9):923–30. https://doi.org/10.1016/j.autrev.2016.07.005.
[31] Qian Y, Jeong JS, Maldonado M, Valenzuela JG, Gomes R, Teixeira C, et al. Cutting Edge: Brazilian pemphigus foliaceus anti-desmoglein 1 autoantibodies cross-react with sand fly salivary LJM11 antigen. J Immunol 2012;189(4):1535–9. https://doi.org/10.4049/jimmunol.1200842.
[32] Moraes ME, Fernandez-Vina M, Lazaro A, Diaz LA, Filho GH, Friedman H, et al. An epitope in the third hypervariable region of the DRB1 gene is involved in the susceptibility to endemic pemphigus foliaceus (fogo selvagem) in three different Brazilian populations. Tissue Antigens 1997;49(1):35–40.
[33] Anhalt GJ, Kim SC, Stanley JR, Korman NJ, Jabs DA, Kory M, et al. Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med 1990;323(25):1729–35. https://doi.org/10.1056/NEJM199012203232503.
[34] Amber KT, Valdebran M, Grando SA. Paraneoplastic autoimmune multiorgan syndrome (PAMS): beyond the single phenotype of paraneoplastic pemphigus. Autoimmun Rev 2018;17(10):1002–10. https://doi.org/10.1016/j.autrev.2018.04.008.
[35] Nguyen VT, Ndoye A, Bassler KD, Shultz LD, Shields MC, Ruben BS, et al. Classification, clinical manifestations, and immunopathological mechanisms of the epithelial variant of paraneoplastic autoimmune multiorgan syndrome: a reappraisal of paraneoplastic pemphigus. Arch Dermatol 2001;137(2):193–206.
[36] Baum S, Sakka N, Artsi O, Trau H, Barzilai A. Diagnosis and classification of autoimmune blistering diseases. Autoimmun Rev 2014;13(4–5):482–9. https://doi.org/10.1016/j.autrev.2014.01.047.
[37] Kershenovich R, Hodak E, Mimouni D. Diagnosis and classification of pemphigus and bullous pemphigoid. Autoimmun Rev 2014;13(4–5):477–81. https://doi.org/10.1016/j.autrev.2014.01.011.
[38] Czernik A, Camilleri M, Pittelkow MR, Grando SA. Paraneoplastic autoimmune multiorgan syndrome: 20 years after. Int J Dermatol 2011;50(8):905–14. https://doi.org/10.1111/j.1365- 4632.2011.04868.x.
[39] Martel P, Loiseau P, Joly P, Busson M, Lepage V, Mouquet H, et al. Paraneoplastic pemphigus is associated with the DRB1*03 allele. J Autoimmun 2003;20(1):91–5.
[40] Queisi MM, Zein M, Lamba N, Meese H, Foster CS. Update on ocular cicatricial pemphigoid and emerging treatments. Surv Ophthalmol 2016;61(3):314–7. https://doi.org/10.1016/j.survophthal.2015.12.007.
[41] Cizenski JD, Michel P, Watson IT, Frieder J, Wilder EG, Wright JM, et al. Spectrum of orocutaneous disease associations: Immune-mediated conditions. J Am Acad Dermatol 2017;77(5):795–806. https://doi.org/10.1016/j.jaad.2017.02.019.
[42] Sticherling M, Erfurt-Berge C. Autoimmune blistering diseases of the skin. Autoimmun Rev 2012;11(3):226–30. https://doi.org/10.1016/j.autrev.2011.05.017.
[43] Bruch-Gerharz D, Hertl M, Ruzicka T. Mucous membrane pemphigoid: clinical aspects, immunopathological features and therapy. Eur J Dermatol 2007;17(3):191–200. https://doi.org/10.1684/ejd.2007.0148.
[44] Chan LS, Ahmed AR, Anhalt GJ, Bernauer W, Cooper KD, Elder MJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. Arch Dermatol 2002;138(3):370–9.
[45] Chan LS, Majmudar AA, Tran HH, Meier F, Schaumburg-Lever G, Chen M, et al. Laminin-6 and laminin-5 are recognized by autoantibodies in a subset of cicatricial pemphigoid. J Invest Dermatol 1997;108(6):848–53.
[46] Rashid KA, Gurcan HM, Ahmed AR. Antigen specificity in subsets of mucous membrane pemphigoid. J Invest Dermatol 2006;126(12):2631–6. https://doi.org/10.1038/sj.jid.5700465.
[47] Chan LS, Soong HK, Foster CS, Hammerberg C, Cooper KD. Ocular cicatricial pemphigoid occurring as a sequela of Stevens-Johnson syndrome. JAMA 1991;266(11):1543–6.
[48] Chan LS, Vanderlugt CJ, Hashimoto T, Nishikawa T, Zone JJ, Black MM, et al. Epitope spreading: lessons from autoimmune skin diseases. J Invest Dermatol 1998;110(2):103–9. https://doi.org/10.1046/j.1523-1747.1998.00107.x.
[49] Chan LS. Ocular and oral mucous membrane pemphigoid (cicatricial pemphigoid). Clin Dermatol 2012;30(1):34–7. https://doi.org/10.1016/j.clindermatol.2011.03.007.
[50] Olsen KE, Holland EJ. The association between ocular cicatricial pemphigoid and rheumatoid arthritis. Cornea 1998;17(5):504–7.
[51] Parker SR, MacKelfresh J. Autoimmune blistering diseases in the elderly. Clin Dermatol 2011;29(1):69–79. https://doi.org/10.1016/j.clindermatol.2010.07.010.
[52] Sapp JP, Eversole LR, Wysoky GP. Patologia oral y maxilofacial contemporanea. Madrid: Harcourt Editores 1998:244–76.
[53] Gagari E, Damoulis PD. Desquamative gingivitis as a manifestation of chronic mucocutaneous disease. J Dtsch Dermatol Ges 2011;9(3):184–8. https://doi.org/10.1111/j.1610-0387.2010.07543.x.
[54] Jascholt I, Lai O, Zillikens D, Kasperkiewicz M. Periodontitis in oral pemphigus and pemphigoid: a systematic review of published studies. J Am Acad Dermatol 2017;76(5):975–8. e3 https://doi.org/10.1016/j.jaad.2016.10.028.

[55] Herbst A, Bystryn JC. Patterns of remission in pemphigus vulgaris. J Am Acad Dermatol 2000;42(3):422–7.
[56] Edgar NR, Saleh D, Miller RA. Recurrent Aphthous Stomatitis: a Review. J Clin Aesthet Dermatol 2017;10(3):26–36.
[57] Uzun S, Durdu M. The specificity and sensitivity of Nikolskiy sign in the diagnosis of pemphigus. J Am Acad Dermatol 2006;54(3):411–5. https://doi.org/10.1016/j.jaad.2005.10.019.
[58] Ismail SB, Kumar SK, Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. J Oral Sci 2007;49(2):89–106.
[59] Mun M, Yap T, Alnuaimi AD, Adams GG, McCullough MJ. Oral candidal carriage in asymptomatic patients. Aust Dent J 2016;61(2):190–5. https://doi.org/10.1111/adj.12335.
[60] Schmidt E, Zillikens D. Modern diagnosis of autoimmune blistering skin diseases. Autoimmun Rev 2010;10(2):84–9. https://doi.org/10.1016/j.autrev.2010.08.007.
[61] Shamim T, Varghese VI, Shameena PM, Sudha S. Pemphigus vulgaris in oral cavity: clinical analysis of 71 cases. Med Oral Patol Oral Cir Bucal 2008;13(10):E622–6.
[62] Angelini G, Bonamonte D. The Tzanck smear: an auspicable return to the past. J Eur Acad Dermatol Venereol 2011;25(11):1365–6. https://doi.org/10.1111/j.1468-3083.2011.04046.x.
[63] Grando SA. Pemphigus autoimmunity: hypotheses and realities. Autoimmunity 2012;45(1):7–35. https://doi.org/10.3109/08916934.2011.606444.
[64] Nguyen VT, Ndoye A, Shultz LD, Pittelkow MR, Grando SA. Antibodies against keratinocyte antigens other than desmogleins 1 and 3 can induce pemphigus vulgaris-like lesions. J Clin Invest 2000;106(12):1467–79. https://doi.org/10.1172/JCI10305.
[65] Scully C, Paes De Almeida O, Porter SR, Gilkes JJ. Pemphigus vulgaris: the manifestations and long-term management of 55 patients with oral lesions. Br J Dermatol 1999;140(1):84–9.
[66] Ettlin DA. Pemphigus. Dent Clin N Am 2005;49(1):107–25. (viii-ix). https://doi.org/10.1016/j.cden.2004.08.002.
[67] Tampoia M, Giavarina D, Di Giorgio C, Bizzaro N. Diagnostic accuracy of enzyme-linked immunosorbent assays (ELISA) to detect anti-skin autoantibodies in autoimmune blistering skin diseases: a systematic review and meta-analysis. Autoimmun Rev 2012;12(2):121–6. https://doi.org/10.1016/j.autrev.2012.07.006.
[68] Hertl M, Jedlickova H, Karpati S, Marinovic B, Uzun S, Yayli S, et al. Pemphigus. S2 Guideline for diagnosis and treatment–guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol 2015;29(3):405–14. https://doi.org/10.1111/jdv.12772.
[69] Martin LK, Werth VP, Villaneuva EV, Murrell DF. A systematic review of randomized controlled trials for pemphigus vulgaris and pemphigus foliaceus. J Am Acad Dermatol 2011;64(5):903–8. https://doi.org/10.1016/j.jaad.2010.04.039.
[70] Virgolini L, Marzocchi V. Anti-CD20 monoclonal antibody (rituximab) in the treatment of autoimmune diseases. Successful result in refractory Pemphigus vulgaris: report of a case. Haematologica 2003;88(7):ELT24.
[71] Amagai M, Ikeda S, Shimizu H, Iizuka H, Hanada K, Aiba S, et al. A randomized double-blind trial of intravenous immunoglobulin for pemphigus. J Am Acad Dermatol 2009;60(4):595–603. https://doi.org/10.1016/j.jaad.2008.09.052.
[72] Tan-Lim R, Bystryn JC. Effect of plasmapheresis therapy on circulating levels of pemphigus antibodies. J Am Acad Dermatol 1990;22(1):35–40.
[73] Izaki S, Yoshizawa Y, Kitamura K, Kato H, Hashimoto H, Korman NJ, et al. Paraneoplastic pemphigus: potential therapeutic effect of plasmapheresis. Br J Dermatol 1996;134(5):987–9.
[74] Jing L, Shan Z, Yongchu H, Xixue C, Xuejun Z. Successful treatment of a paraneoplastic pemphigus in a teenager using plasmapheresis, corticosteroids and tumour resection. Clin Exp Dermatol 2011;36(7):752–4. https://doi.org/10.1111/j.1365-2230.2011.04081.x.
[75] Sondergaard K, Carstens J, Jorgensen J, Zachariae H. The steroid-sparing effect of long-term plasmapheresis in pemphigus. Acta Derm Venereol 1995;75(2):150–2.
[76] Turner MS, Sutton D, Sauder DN. The use of plasmapheresis and immunosuppression in the treatment of pemphigus vulgaris. J Am Acad Dermatol 2000;43(6):1058–64. https://doi.org/10.1067/mjd.2000.109297.
[77] Langenhan J, Dworschak J, Saschenbrecker S, Komorowski L, Schlumberger W, Stocker W, et al. Specific immunoadsorption of pathogenic autoantibodies in pemphigus requires the entire ectodomains of desmogleins. Exp Dermatol 2014;23(4):253–9. https://doi.org/10.1111/exd.12355.
[78] Ahmed AR, Shetty S. A comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab. Autoimmun Rev 2015;14(4):323–31. https://doi.org/10.1016/j.autrev.2014.12.002.
[79] Mouquet H, Musette P, Gougeon ML, Jacquot S, Lemercier B, Lim A, et al. B-cell depletion immunotherapy in pemphigus: effects on cellular and humoral immune responses. J Invest Dermatol 2008;128(12):2859–69. https://doi.org/10.1038/jid.2008.178.
[80] Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med 2006;355(17):1772–9. https://doi.org/10.1056/NEJMoa062930.
[81] Kasperkiewicz M, Shimanovich I, Meier M, Schumacher N, Westermann L, Kramer J, et al. Treatment of severe pemphigus with a combination of immunoadsorption, rituximab, pulsed dexamethasone and azathioprine/mycophenolate mofetil: a pilot study of 23 patients. Br J Dermatol 2012;166(1):154–60. https://doi.org/10.1111/j.1365-2133.2011.10585.x.
[82] Shimanovich I, Nitschke M, Rose C, Grabbe J, Zillikens D. Treatment of severe pemphigus with protein a immunoadsorption, rituximab and intravenous immunoglobulins. Br J Dermatol 2008;158(2):382–8. https://doi.org/10.1111/j.1365-2133.2007.08358.x.
[83] Zakka LR, Shetty SS, Ahmed AR. Rituximab in the treatment of pemphigus vulgaris. Dermatol Ther (Heidelb) 2012;2(1):17. https://doi.org/10.1007/s13555-012-0017-3.
[84] Sharma VK, Khandpur S. Evaluation of cyclophosphamide pulse therapy as an adjuvant to oral corticosteroid in the management of pemphigus vulgaris. Clin Exp Dermatol 2013;38(6):659–64. https://doi.org/10.1111/ced.12073.
[85] Colliou N, Picard D, Caillot F, Calbo S, Le Corre S, Lim A, et al. Long-term remissions of severe pemphigus after rituximab therapy are associated with prolonged failure of desmoglein B cell response. Sci Transl Med 2013;5(175):175ra30https://doi.org/10.1126/scitranslmed.3005166.
[86] Sharma VK, Bhari N, Gupta S, Sahni K, Khanna N, Ramam M, et al. Clinical efficacy of rituximab in the treatment of pemphigus: a retrospective study. Indian J Dermatol Venereol Leprol 2016;82(4):389–94. https://doi.org/10.4103/0378-6323.174379.
[87] Horvath B, Huizinga J, Pas HH, Mulder AB, Jonkman MF. Low-dose rituximab is effective in pemphigus. Br J Dermatol 2012;166(2):405–12. https://doi.org/10.1111/j.1365-2133.2011.10663.x.
[88] Joly P, Maho-Vaillant M, Prost-Squarcioni C, Hebert V, Houivet E, Calbo S, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. Lancet 2017;389(10083):2031–40. https://doi.org/10.1016/S0140-6736(17)30070-3.
[89] He Y, Shimoda M, Ono Y, Villalobos IB, Mitra A, Konia T, et al. Persistence of autoreactive IgA-secreting B cells despite multiple immunosuppressive medications including rituximab. JAMA Dermatol 2015;151(6):646–50. https://doi.org/10.1001/jamadermatol.2015.59.
[90] Gergely L, Varoczy L, Vadasz G, Remenyik E, Illes A. Successful treatment of B cell chronic lymphocytic leukemia-associated severe paraneoplastic pemphigus with cyclosporin A. Acta Haematol 2003;109(4):202–5. https://doi.org/10.1159/000070972.
[91] Hwang YY, Chan JC, Trendell-Smith NJ, Kwong YL. Recalcitrant paraneoplastic pemphigus associated with follicular dendritic cell sarcoma: response to prolonged rituximab and ciclosporin therapy. Intern Med J 2014;44(11):1145–6. https://doi.org/10.1111/imj.12576.
[92] Savoldo B, Ramos CA, Liu E, Mims MP, Keating MJ, Carrum G, et al. CD28 costimulation improves expansion and persistence of chimeric antigen receptor-modified T cells in lymphoma patients. J Clin Invest 2011;121(5):1822–6. https://doi.org/10.1172/JCI46110.
[93] Ellebrecht CT, Bhoj VG, Nace A, Choi EJ, Mao X, Cho MJ, et al. Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease. Science 2016;353(6295):179–84. https://doi.org/10.1126/science.aaf6756.
[94] Veldman C, Hohne A, Dieckmann D, Schuler G, Hertl M. Type I regulatory T cells specific for desmoglein 3 are more frequently detected in healthy individuals than in patients with pemphigus vulgaris. J Immunol 2004;172(10):6468–75.
[95] MacDonald KG, Hoeppli RE, Huang Q, Gillies J, Luciani DS, Orban PC, et al. Alloantigen- specific regulatory T cells generated with a chimeric antigen receptor. J Clin Invest 2016;126(4):1413–24. https://doi.org/10.1172/JCI82771.
[96] Laforest C, Huilgol SC, Casson R, Selva D, Leibovitch I. Autoimmune bullous diseases: ocular manifestations and management. Drugs 2005;65(13):1767–79.
[97] Lifshitz T, Levy J, Cagnano E, Halevy S. Severe conjunctival and eyelid involvement in pemphigus vulgaris. Int Ophthalmol 2004;25(2):73–4.
[98] Daoud YJ, Cervantes R, Foster CS, Ahmed AR. Ocular pemphigus. J Am Acad Dermatol 2005;53(4):585–90. https://doi.org/10.1016/j.jaad.2005.02.061.
[99] Messmer EM, Hintschich CR, Partscht K, Messer G, Kampik A. Ocular cicatricial pemphigoid. Retrospective analysis of risk factors and complications. Ophthalmologe 2000;97(2):113–20. https://doi.org/10.1007/s003470050021.
[100] Akhyani M, Keshtkar-Jafari A, Chams-Davatchi C, Lajevardi V, Beigi S, Aghazadeh N, et al. Ocular involvement in pemphigus vulgaris. J Dermatol 2014;41(7):618–21. https://doi.org/10.1111/1346-8138.12447.
[101] Chirinos-Saldana P, Navas A, Ramirez-Miranda A, Jimenez-Martinez MC, Graue-Hernandez EO. Pemphigus: an ophthalmological review. Eye Contact Lens 2016;42(2):91–8. https://doi.org/10.1097/ICL.0000000000000155.
[102] Namba H, Narumi M, Sugano A, Murata I, Suzuki T, Yamakawa M, et al. Pathological findings of pemphigus vulgaris showing giant cobblestone-like conjunctival papillae. Case Rep Ophthalmol 2013;4(3):114–21. https://doi.org/10.1159/000355374.
[103] Oyama N, Togashi A, Nomura E, Kaneko F. Successful treatment with oral mizoribine in refractory ocular manifestation of mucosal pemphigus vulgaris: a unique response to different immunosuppressive drugs. Dermatol Ther 2016;29(6):442–5. https://doi.org/10.1111/dth.12386.
[104] Pires CA, Viana VB, Araujo FC, Muller SF, Oliveira MS, Carneiro FR. Evaluation of cases of pemphigus vulgaris and pemphigus foliaceus from a reference service in Para state, Brazil. An Bras Dermatol 2014;89(4):556–61.
[105] Ohzono A, Sogame R, Li X, Teye K, Tsuchisaka A, Numata S, et al. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. Br J Dermatol 2015;173(6):1447–52. https://doi.org/10.1111/bjd.14162.
[106] Ahuero AE, Jakobiec FA, Bhat P, Ciralsky JB, Papaliodis GN. Paraneoplastic conjunctival cicatrization: two different pathogenic types. Ophthalmology 2010;117(4):659–64. https://doi.org/10.1016/j.ophtha.2009.09.006.
[107] Tam PM, Cheng LL, Young AL, Lam PT. Paraneoplastic pemphigus: an uncommon cause of chronic cicatrising conjunctivitis. BMJ Case Rep 2009;2009. https://doi.org/10.1136/bcr.12.2008.1306.
[108] Hong GH, Khan IR, Shifera AS, Okeagu C, Thorne JE. Incidence and clinical characteristics of ocular involvement in mucous membrane pemphigoid. Ocul

Immunol Inflamm 2018:1–5. https://doi.org/10.1080/09273948.2018.1455879.
[109] Goldich Y, Ziai S, Artornsombudh P, Avni-Zauberman N, Elbaz U, Rootman DS, et al. Characteristics of patients with ocular cicatricial pemphigoid referred to major tertiary hospital. Can J Ophthalmol 2015;50(2):137–42. https://doi.org/10.1016/j.jcjo.2014.11.012.
[110] Sobolewska B, Deuter C, Zierhut M. Current medical treatment of ocular mucous membrane pemphigoid. Ocul Surf 2013;11(4):259–66. https://doi.org/10.1016/j.jtos.2013.02.003.
[111] Secchi AG, Tognon MS. Intraoperative mitomycin C in the treatment of cicatricial obliterations of conjunctival fornices. Am J Ophthalmol 1996;122(5):728–30.
[112] Schellinck AE, Rees TD, Plemons JM, Kessler HP, Rivera-Hidalgo F, Solomon ES. A comparison of the periodontal status in patients with mucous membrane pemphigoid: a 5-year follow-up. J Periodontol 2009;80(11):1765–73. https://doi.org/10.1902/jop.2009.090244.
[113] Carbone M, Broccoletti R, Gambino A, Carrozzo M, Tanteri C, Calogiuri PL, et al. Clinical and histological features of gingival lesions: a 17-year retrospective analysis in a northern Italian population. Med Oral Patol Oral Cir Bucal 2012;17(4):e555–61.
[114] Gambino A, Carbone M, Arduino PG, Carcieri P, Carbone L, Broccoletti R. Conservative approach in patients with pemphigus gingival vulgaris: a pilot study of five cases. Int J Dent 2014;2014:747506. https://doi.org/10.1155/2014/747506.
[115] Arduino PG, Lopetuso E, Carcieri P, Giacometti S, Carbone M, Tanteri C, et al. Professional oral hygiene treatment and detailed oral hygiene instructions in patients affected by mucous membrane pemphigoid with specific gingival localization: a pilot study in 12 patients. Int J Dent Hyg 2012;10(2):138–41. https://doi.org/10.1111/j.1601-5037.2011.00527.x.
[116] de Souza AF, Rocha AL, Castro WH, Ferreira FM, Gelape CL, Travassos DV, et al. Dental care before cardiac valve surgery: is it important to prevent infective endocarditis? Int J Cardiol Heart Vasc 2016;12:57–62. https://doi.org/10.1016/j.ijcha.2016.07.001.
[117] Castellano Suarez JL. Gingival disorders of immune origin. Med Oral 2002;7(4):271–83.