Vesiculobullous Lesions of the Oral Cavity

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KEYWORDS

• Cicatricial pemphigoid • Pemphigus vulgaris • Epidermolysis bullosa acquisita
• Bullous pemphigoid • Desquamative gingivitis

KEY POINTS

- Recognize and distinguish the subtle clinical features of the vesiculobullous diseases.
- Develop a clear perception of the susceptible patient group or population.
- Understand the direct immunofluorescence diagnostic features attributed to each important vesiculobullous diseases.
- Become alert in recognizing the possibility of vesiculobullous diseases.
- Develop a global understanding of the etiologies and sharpen skills to manage vesiculobullous diseases.

INTRODUCTION

Vesiculobullous lesions involving the oral cavity may represent the oral manifestations of dermatologic diseases, particularly those that are immune-mediated. Several vesiculobullous conditions may affect the oral cavity, and they must be distinguished from other types of oral ulcerations as they may reflect systemic diseases and require special treatment. Desquamative gingivitis is a hallmark of the majority of vesiculobullous conditions especially benign mucous membrane pemphigoid (BMMP).[1–6] Histopathologic examination with direct immunofluorescence (DIF) studies is the gold standard for diagnosing autoimmune vesiculobullous conditions.[1–7] This article discusses the clinical features, pathogenesis, differential diagnosis, diagnostic features, histology, and immunofluorescence findings as well as management of vesiculobullous diseases. These diseases include pemphigus vulgaris (PV), BMMP, bullous pemphigoid (BP), and epidermolysis bullosa acquisita. They all have a significant impact on the quality of life and can lead to serious complications, depending on the extent of the disease. Therefore, early recognition is crucial to reduce disease-related morbidity and mortality and prevent life-threatening complications.

PEMPHIGUS VULGARIS

PV is an uncommon debilitating vesiculobullous disease characterized by flaccid bullae and erosions affecting the skin and/or mucous membrane. PV is one of the four-pemphigus variants, along with pemphigus vegetans, pemphigus erythematosus, and pemphigus foliaceus, with PV being the most common.[8,9] PV and pemphigus vegetans are the two variants that can affect oral mucosa, however, pemphigus vegetans is considered an extremely rare condition.[5,10] Patients of Mediterranean, South Asian, and Ashkenazi Jews heritages have higher rates of this condition. PV has an estimated prevalence of 30,000 cases in the United States and an incidence of 1 to 10 new cases per 1 million population.[8–11] The pathogenesis of PV is mediated by immunoglobulin G (IgG) autoantibodies directed against structural proteins of the desmosomes at cell–cell junctions. Patients who have developed autoantibodies targeting desmoglein 3 with or without desmoglein 1 will have cutaneous and mucosal disease, whereas patients

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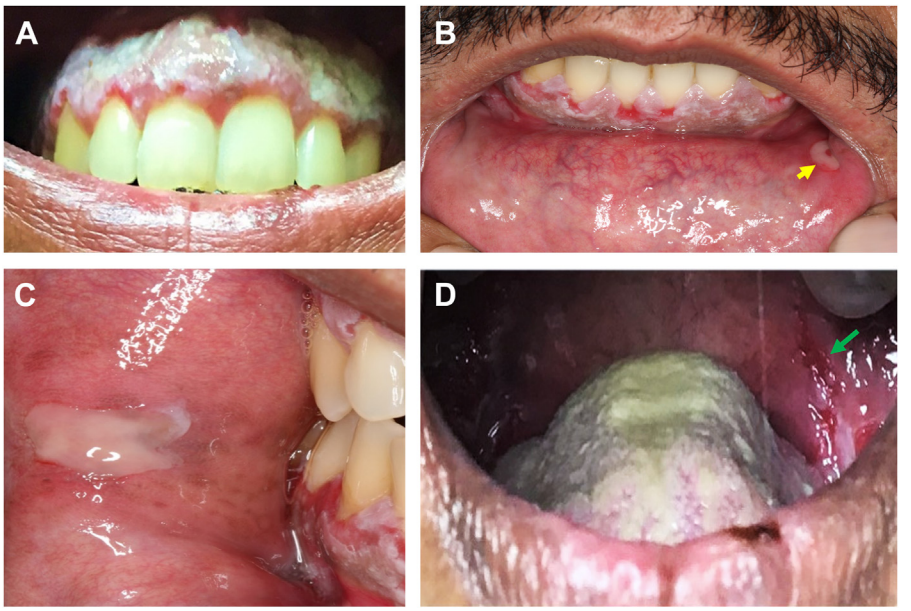

Fig. 1. Diffuse ulceration and mucosal sloughing are prominent on; (*A*) Facial maxillary gingiva and (*B*) facial mandibular gingiva with ulceration are noted on the left labial mucosa (*yellow arrow*). (*C*) Large ulceration of the right buccal mucosa. (*D*) Coated tongue and posterior palatal extension of ulcerations (*green arrow*).

with autoantibodies targeting only desmoglein 1 will only have cutaneous disease.[9]

PV is a potentially life-threatening disease with a mortality rate of 5% to 15%. Mortality is mainly due to treatment complications, skin infections, and pneumonia. Therefore, early diagnosis and treatment before extensive skin involvement is crucial.[8,11,12]

CLINICAL FEATURES

PV typically affects middle-aged patients, with an average age of 50 years, and equal gender distribution.[8,11,12] Rare cases have been reported in childhood.[8] Oral lesions are usually the first sign and precede skin lesions in 50% of cases. Patients usually present with refractory lesions that can affect any mucosal surfaces. Oral mucosa is the most frequently affected mucosal site, especially the buccal mucosa, labial mucosa, palate, ventral tongue, and gingivae (**Fig. 1**). However, other mucosal surfaces such as esophageal, pharyngolaryngeal, genital, anal, and conjunctiva may be involved.[8,10] Desquamative gingivitis is less commonly seen in PV compared with other vesiculobullous conditions.[5,10] Clinically, oral lesions appear as ragged erosions with shallow and deep ulcerations (**Figs. 2–10**). Oral lesions are

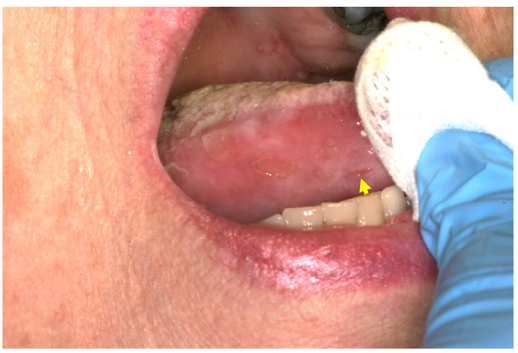

Fig. 2. Multiple shallow and deep (*arrow*) ulcers involving the right lateral border of the tongue and the left palate. The dorsal tongue appears white and thickened.

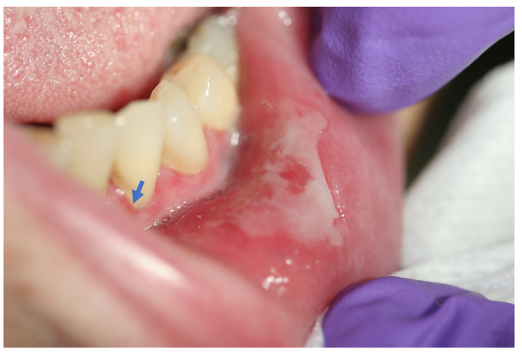

Fig. 3. Large shallow ulcer and erosion involving the lower labial mucosa. Erythematous lesions involving the marginal gingiva (*arrow*).

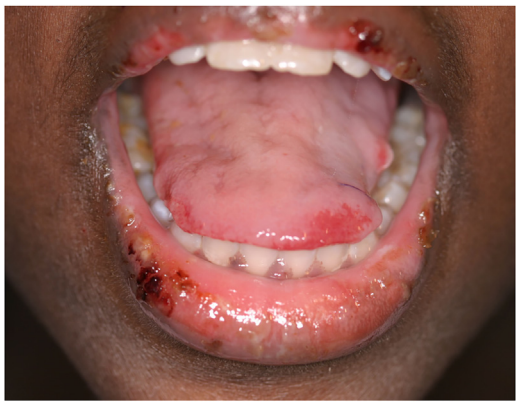

Fig. 4. Hemorrhagic and crusted lip lesions may be mistaken for erythema multiforme.

painful, often occur in posterior locations, and therefore can cause dysphagia and weight loss.[10] A positive Nikolsky's sign is a characteristic feature of PV, in which a new bulla formation can be induced on normal-appearing skin on slight lateral pressure.[3,8] The ocular lesions are uncommon, resemble conjunctivitis and unlike BMMP, and do not usually progress to scarring and symblepharon formation.[7,13]

DIAGNOSIS AND HISTOPATHOLOGIC FEATURES

Diagnosis of PV is based on the clinical scenario, histopathologic examination along with the detection of intercellular autoantibodies within the epithelium by DIF microscopy and/or circulating autoantibodies by indirect immunofluorescence (IIF), enzyme-linked immunosorbent assay (ELISA), or immunoblotting.[8,11,12]

As the lesional tissue is significantly friable and easily detached from the underlying connective tissue, a biopsy must be taken from perilesional mucosa for an accurate diagnosis.[4,6] Ulcerated and eroded mucosa should be avoided as this tissue may not be sufficient for diagnosis due to the lack of intact surface epithelium.

The classic microscopic features seen in PV are acantholysis with suprabasilar separation (**Fig. 11**A). The basal cells remain attached to the basement membrane, forming a row of tombstones appearance. Acantholysis is the result of loss of cell–cell adhesion affecting the spinous cell layer, in which large, free-floating, and rounded acantholytic epithelial cells termed "Tzanck cells" are seen.[8–12] However, the presence of Tzanck cells is not diagnostic for PV, as they can also be seen in other conditions such as herpes simplex virus infection. DIF examination is required for confirmation of the diagnosis which would reveal intercellular deposition of IgG and complement C3 in a "chicken-wire" pattern (**Fig. 11**B).[4,6–8] Circulating autoantibodies in patients' serum are typically detected in 80% to 90% of cases using IIF assay.[7,11,12]

TREATMENT AND PROGNOSIS

The prognosis of PV is highly dependent on the extent of involvement as well as early diagnosis and treatment of oral lesions before the onset of skin disease.[10,14] Oral lesions are the most difficult to resolve with treatment. Hence, the oral lesions are designated as "the first to show and the last to go."[1–5,10]

Systemic corticosteroids in combination with steroid-sparing immunosuppressant agents

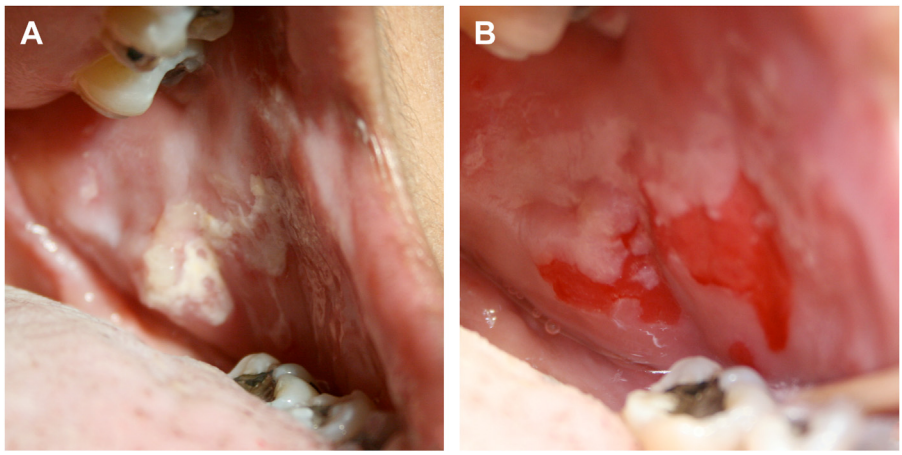

Fig. 5. (*A*) White plaque on the right buccal mucosa. (*B*) Removal of the plaque reveals erosive and erythematous mucosal surface.

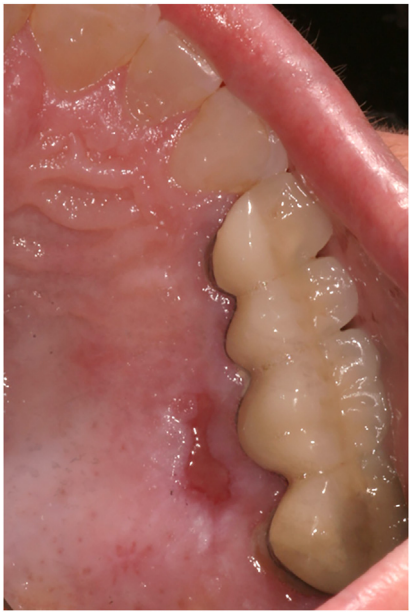

Fig. 6. Deep, well-circumscribed ulceration of the hard palate on the left side.

remain the therapeutic mainstay for pemphigus. The adjuvant immunosuppressant therapies often used are azathioprine, rituximab, methotrexate, or cyclophosphamide.[7,8,10,14]

Dexamethasone pulse therapy (DPT) has been proposed as a treatment modality for pemphigus that has been widely used. The main objective of steroid-pulse therapy is to control the disease and prevent relapses, rather than symptom alleviation.[14] The recommended DPT consists of four phases summarized in **Table 1**.

Oral lesions can benefit from combining topical corticosteroids with the systemic therapy along with maintaining great oral hygiene (**Fig. 12**). Topical corticosteroids may include clobetasol propionate ointment or gel, oral prednisolone (5 mg) dissolved in 10 to 20 mL of water and used as a mouthwash or corticosteroid spray. These might be applied two to three times daily to aid in healing and prevent new blister formation.[8,10] In addition, appropriate antifungal therapy is recommended to prevent fungal superinfection if any.[14]

Although systemic corticosteroids are highly effective in managing the disease, long-term use may be associated with significant adverse effects, including diabetes mellitus, adrenal insufficiency, iatrogenic Cushing's syndrome, osteoporosis, peptic ulcers, and increased risk of opportunistic infections.[8,10]

PV is a chronic disease with periods of exacerbation and remission, even when patients are on treatment. Therefore, circulating autoantibodies serum levels are useful biomarkers for measuring disease activity and clinical follow-up.[8,10–12]

BENIGN MUCOUS MEMBRANE PEMPHIGOID

BMMP is a heterogeneous group of chronic, vesiculobullous autoimmune conditions, mediated essentially by IgG autoantibodies directed against different structural proteins in the basement membrane, including collagen VII, collagen XVII (also called BP180), BP230, integrin α6/β4, and laminin-332.[1–3,15–19] Collagen XVII and laminin-332 are believed to be major target antigens in BMMP. Anti-laminin-332 BMMP has been associated with an increased risk of underlying malignancies in 25% to 30% of patients.[7,20] Autoantibodies against integrin α 6/β4 have been implicated in ocular involvement.[18,20]

BMMP affects predominantly the oral, ocular mucosa and rarely, the skin.[2,15–17,19] BMMP is also called cicatricial pemphigoid derived from the word cicatrix, meaning "scar."[3] However, scarring can affect the conjunctival (ocular) mucosa only and is not seen in the oral mucosa.[3,15–17,19,21] Ocular involvement is the most significant aspect of this condition which occurs in approximately 25% of patients with oral lesions.

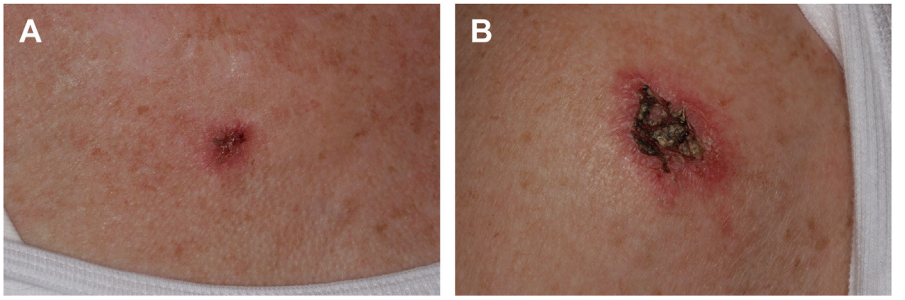

Fig. 7. (*A, B*) Cutaneous pemphigus vulgaris lesions. Hemorrhagic crusted ulcerations developed after bullae ruptured.

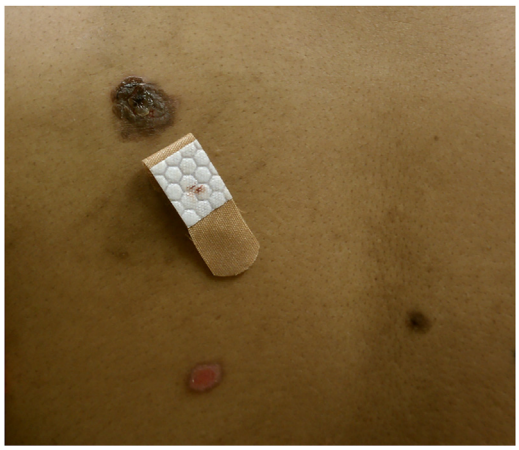

Fig. 8. Elevated, crusted, and pigmented cutaneous lesion.

Blindness may occur if the patient is not treated.[15–17,19,21]

Owing to its clinical resemblance to pemphigus, the disease is called pemphigoid or pemphigus-like. One of the most important differences with pemphigus is the type of vesicles or bullae seen in the two diseases.[7]

As the epithelial separation in pemphigus is intraepithelial compared with stronger subepithelial blisters seen in BMMP, the blisters in pemphigus are more fragile and rarely stay intact for more than a few minutes.[6,7]

CLINICAL FEATURES

BMMP is a disease of the adults and elderly and tends to affect women twice as commonly as men. Rarely, the disease has been reported in children. The average age of onset for BMMP is 60 years (range between 50 and 70 years).[15,16,19,21] Oral lesions are invariably seen (**Figs. 13–15**), but other extraoral sites, such as conjunctival, nasal, esophageal, laryngeal, and genital mucosa as well as the skin may be affected.[5,7,16,21] In two-third of the cases, the lesions are limited to the gingiva but may be seen diffusely throughout the oral mucosa. This gingival pattern of involvement is known as desquamative gingivitis (**Fig. 16**) which may also rarely be seen in other vesiculobullous conditions.[3,4,15]

Oral lesions begin as either vesicles or bullae which are durable and often filled with blood (**Fig. 17**).[3,7,15,16] The clinical finding of blood blisters is highly diagnostic of BMMP. These blisters may last for days to weeks, eventually rupturing, leaving behind superficial, ragged, and denuded areas that are usually painful and persist for weeks to months when untreated (**Fig. 17**C).[5,15,16]

Ocular involvement is the most significant complication of this disease which occurs in one-fourth of the patients with oral lesions. Usually, ocular lesions follow oral involvement.[15,16,21] The conjunctiva may become inflamed and eroded, leading to scarring between the bulbar conjunctiva of the eyeball and palpebral conjunctiva of the eyelid. As a result, adhesions (*symblepharon*) may occur (**Fig. 18**). As a protective mechanism, the cornea may produce keratin resulting in blindness.[16,21]

Laryngeal involvement is uncommon but may be especially significant because of the risk of airway obstruction by the bullae that are formed. Patients who report dysphagia, dysphonia, or dyspnea should undergo examination with laryngoscopy.[16]

DIAGNOSIS AND HISTOPATHOLOGIC FEATURES

Diagnosis of BMMP is based on the clinical findings along with the detection of tissue-bound autoantibodies by DIF microscopy and/or circulating autoantibodies by IIF, ELISA, or immunoblotting.[15,16,22]

A perilesional biopsy is recommended for reasons similar to those mentioned in the previous topic.

In H & E sections, a clear separation between the surface epithelium and the underlying

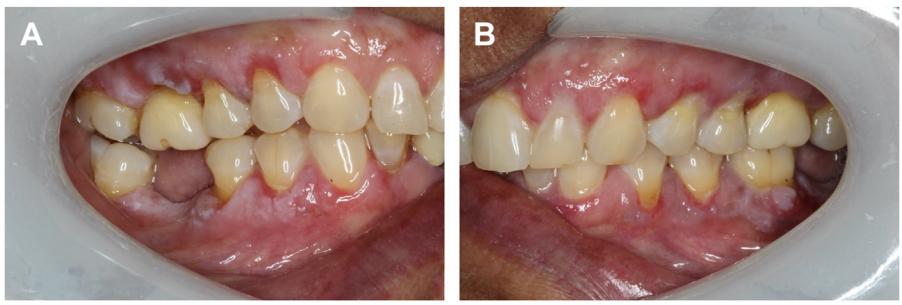

Fig. 9. (*A*, *B*) Multiple erosions with diffuse white, mildly thickened plaque lesions on the gingiva.

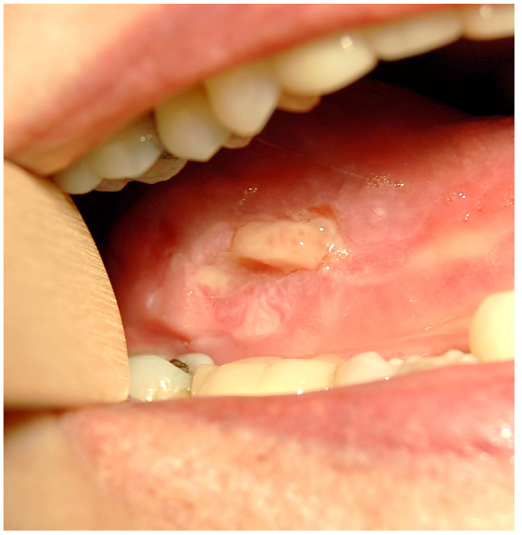

Fig. 10. Pyogenic granuloma in a sitting of pemphigus vulgaris. Hyperkeratotic and ulcerated mass arising on the right lateral border of the tongue. Note the surrounding mucosal erosions, which represent pemphigus vulgaris.

connective tissue is characteristically seen (Fig. 19). DIF examination is required for confirmation of the diagnosis and reveals a linear band of IgG and complement C3 deposited at the basement membrane zone (Fig. 20). Immunoreactivity of IgA and IgM may also be identified. One isolated study has reported that simultaneous IgG and IgA immunoreactivity may be associated with a more aggressive form of the disease.[4,15,16,22]

Unlike pemphigus, circulating autoantibodies in BMMP are usually difficult to detect and are detected in only 17% to 53% of BMMP cases using IIF assay.[16,22]

TREATMENT AND PROGNOSIS

BMMP treatment depends on the extent of involvement and severity of the disease. Mild disease usually limited to the gingiva can be treated with potent topical steroids, but once the lesions progress and especially if they involve other mucous membranes, the eyes, or the skin, then systemic therapy and referral to dermatology and/or ophthalmology are indicated. Current guidelines recommend using dapsone, methotrexate, or tetracyclines, and/or topical corticosteroids as first-line treatment.[3,4,15,16,22] For more severe cases, dapsone with systemic cyclophosphamide and/or oral corticosteroids is recommended.[15,16]

Mild to moderate oral lesions may be treated by topical corticosteroids, particularly the high-potency clobetasol propionate ointment (Figs. 21 and 22). Fluticasone propionate 400 μg (1 mg/mL) may also be used as a mouthwash twice daily. For severe oral lesions, dapsone with oral or topical corticosteroids is usually recommended. Systemic corticosteroids combined with dapsone and immunosuppressive agents, particularly mycophenolate mofetil, are best reserved for more severe and extensive cases.[22]

For gingival lesions, a soft medication delivery tray fabricated in the dental laboratory may be used for better contact with tissues and absorption. The custom tray should be placed in the mouth with the topical steroid in it for 10 to 12 minutes once or twice daily. Adjuvant analgesics and anti-inflammatory therapies such as chlorhexidine (0.12%–0.20%) can be used. In addition, patients

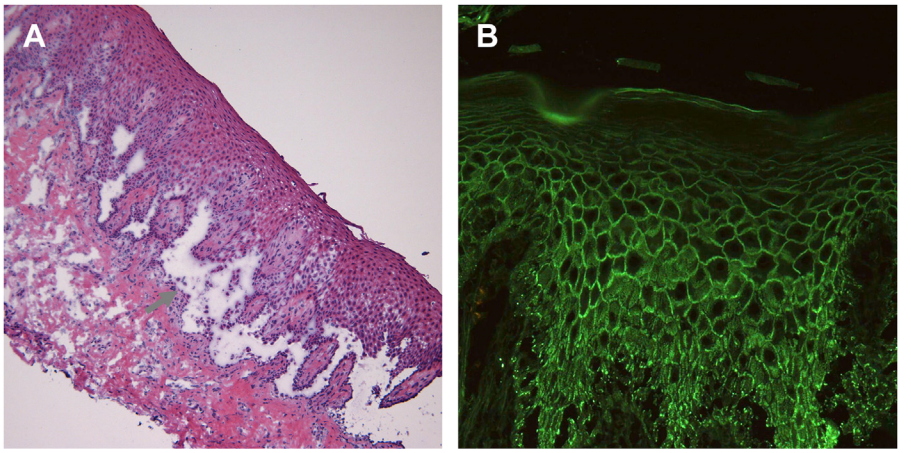

Fig. 11. (*A*) Light microscopic examination of a perilesional mucosa reveals intraepithelial separation, located just above the basal cell layer (*arrow*). (*B*) Direct immunofluorescence microscopy shows IgG deposition in intercellular spaces of the epithelial cells resulting in a network or chicken wire pattern.

Table 1
The recommended dexamethasone pulse therapy

	The Standard Dexamethasone Cyclophosphamide Pulse (DCP) Regimen	Dexamethasone Azathioprine Pulse (DAP)	Dexamethasone Methotrexate Pulse (DMP)
Phase I	Monthly doses of dexamethasone (100 mg dissolved in 500 mL of 5% dextrose) by slow intravenous infusion over 2 h on 3 consecutive days. Cyclophosphamide (500 mg) is added to the infusion on day 2. In between, low-dose oral cyclophosphamide (50 mg) and oral calcium (500 mg) daily. Vitamin D $\geq$300,000 IU once a month	Monthly doses of dexamethasone No bolus dose of azathioprine is given during the pulse. Cyclophosphamide is replaced with oral azathioprine (50 mg) daily	Monthly doses of dexamethasone No bolus dose of methotrexate is given during the pulse. Cyclophosphamide is replaced with oral methotrexate (7.5 mg, "3 doses of 2.5 mg each at 12 hourly intervals") weekly.
Phase II	Monthly dosage of DCP therapy. Low-dose oral cyclophosphamide (50 mg) and oral calcium (500 mg) daily. Continued for 9 mo, even if patients achieved complete remission. Vitamin D $\geq$ 300,000 IU once a month	Monthly dosage of DAP therapy. Oral azathioprine (50 mg) daily. Continued for 9 mo, even if patients achieved complete remission.	Monthly dosage of DMP therapy. Oral methotrexate (7.5 mg, "3 doses of 2.5 mg each at 12 hourly intervals") weekly. Continued for 9 mo, even if patients achieved complete remission.
Phase III	Continue low-dose oral Cyclophosphamide (50 mg) and oral calcium (500 mg) daily for an additional 9 mo.	Oral azathioprine (50 mg) daily for an additional 9 mo	Oral methotrexate (7.5 mg, "3 doses of 2.5 mg each at 12 hourly intervals") weekly, for an additional 9 mo.
Phase IV	Withdrawal of all treatments, and long-term follow-up for relapse if any.	Withdrawal of all treatments, and long-term follow-up for relapse if any.	Withdrawal of all treatments, and long-term follow-up for relapse if any.

with gingival involvement benefit and respond better to treatment when oral hygiene is good.[22]

Early recognition is crucial, helping to reduce disease-related morbidity and mortality and prevent life-threatening complications.

BULLOUS PEMPHIGOID

BP is the most common form of autoimmune skin blistering disease, constituting about 80% of skin autoimmune blistering cases. The estimated incidence in the United States is 6 to 13 per 1 million population diagnosed each year.[23–25]

BP is characterized by subepidermal blisters with intense generalized pruritus as well as alternating periods of remission and relapse. Most of the BP cases are mediated by autoantibodies directed against hemidesmosomes, the multiprotein structures that attach the basal epithelial cells to the basement membrane and underlying connective tissue. The target proteins (antigens) are BP antigen 1 (BPAG1, also known as Dystonin or BP230) and BP antigen 2 (BPAG2, also known as BP180 or type XVII collagen).[23–25]

A clear association of BP with certain major histocompatibility complex class II alleles, specifically

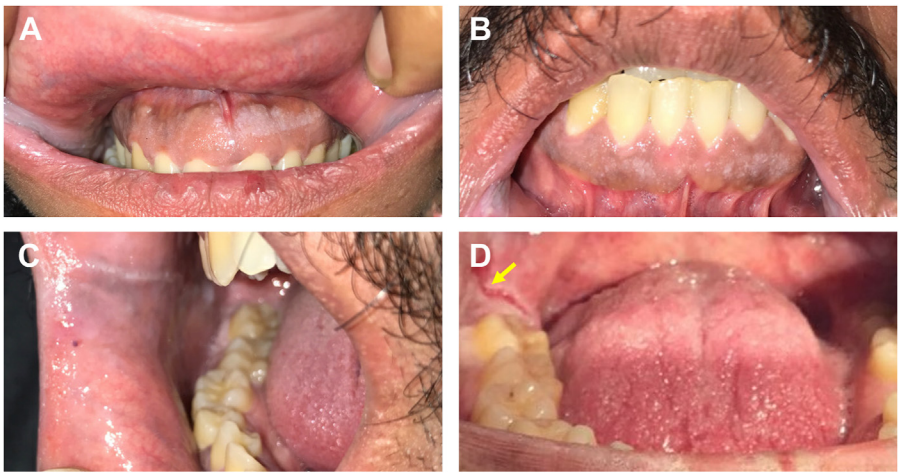

Fig. 12. Same patient as Fig. 1 after treatment with high doses of corticosteroids. (*A*) Facial maxillary gingiva. (*B*) Facial mandibular gingiva. (*C*) Scar tissue in an area of previous large ulceration of the right buccal mucosa. (*D*) Non-coated tongue, and lesion-free palatal mucosa, with only one persistent ulcer, is noted on the right mucosa (*arrow*). At this point, the patient was asymptomatic and reported weight gain.

the human leukocyte antigen class II is found in BP patients.[26]

A few cases have also been associated with certain medications. Drug-induced BP typically affects a younger subset of patients and may arise up to 3 months after initiation of the medication.[27,28] Medications most implicated in drug-induced BP are listed in **Box 1**.

CLINICAL FEATURES

BP predominantly affects elderly patients with the peak incidence in the seventh and eighth decades of life. The disease is rare in the pediatric population. BP has an equal gender distribution with no racial/ethnic predilection.[23,24] However, affected individuals may have a genetic susceptibility to developing BP.[25]

Lesions typically appear on the skin of the trunk and extremities. Usually, patients develop tense, large bullae preceded by or associated with moderate to severe pruritus, and erythematous papular eruption. However, about 20% of patients will present with pruritus without blisters at the onset of the disease. The bullae are tense, large, and range between 1 and 4 cm in diameter. They are typically filled with clear fluid but sometimes can be hemorrhagic. The duration of the bullae varies but they eventually rupture resulting in shallow ulcers, erosions, and crusts that heal without scarring. Approximately one-third of patients will have concurrent mucosal lesions.[7,23,24] Oral lesions of BP (**Fig. 23**) are similar to those of BMMP. The

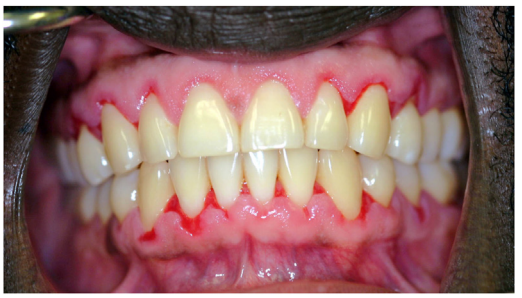

Fig. 13. Multiple erosions affecting the marginal gingiva, producing erythema and tenderness.

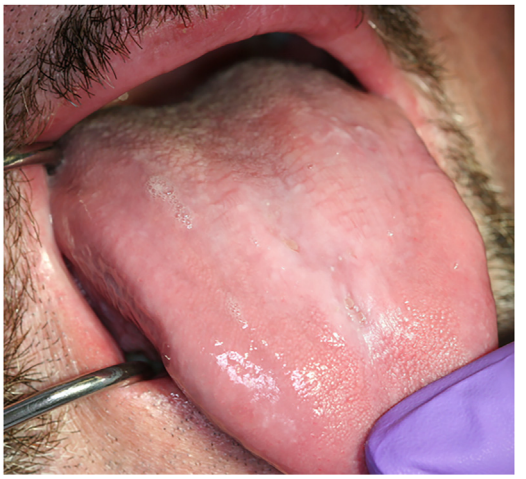

Fig. 14. Ulcerations with white striation involving the dorsal tongue resembling lichen planus.

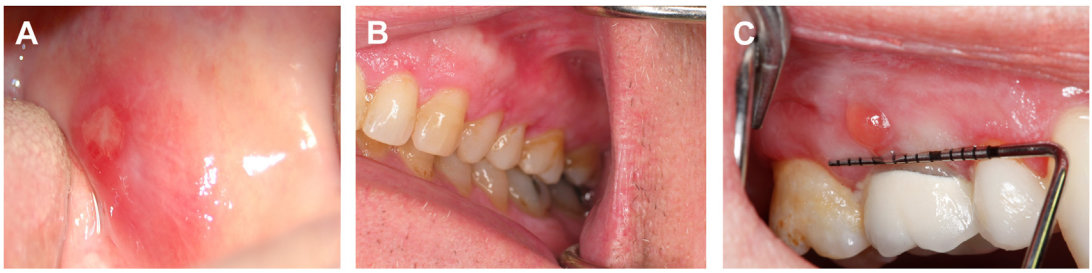

Fig. 15. (*A*) Ill-defined keratotic striae with erythematous zones and ulceration of the left buccal mucosa. (*B*) Erythematous lesion involving the left maxillary buccal vestibule. (*C*) Vesicle on the right attached gingiva that would eventually rupture, leaving raw, and painful ulceration.

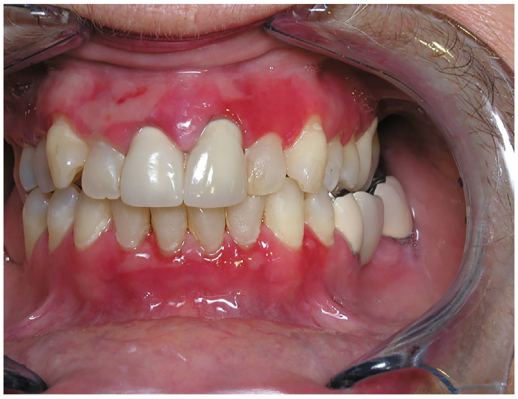

Fig. 16. Desquamative gingivitis presentation. The gingiva appears erythematous, tender, glazed, and friable.

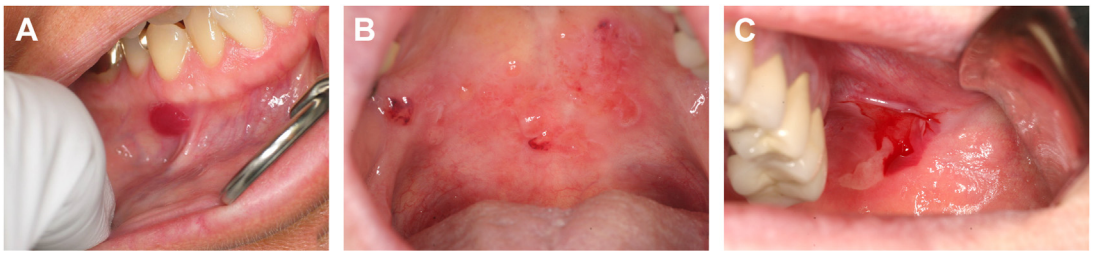

Fig. 17. (*A*) The characteristic blood-filled blister affecting the right mucogingival margin. (*B*) Multiple vesicles, and erosions on the hard and soft palate. (*C*) Raptured bulla resultant in a shallow and hemorrhagic ulcer.

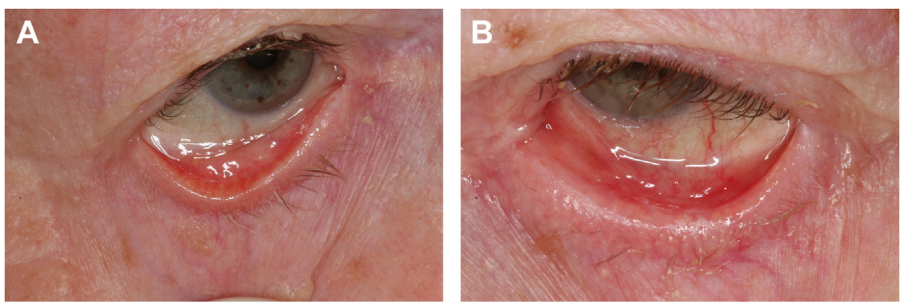

Fig. 18. (*A*) Inflamed and eroded conjunctiva. (*B*) Example of symblepharon; adhesion between the bulbar and palpebral conjunctivae.

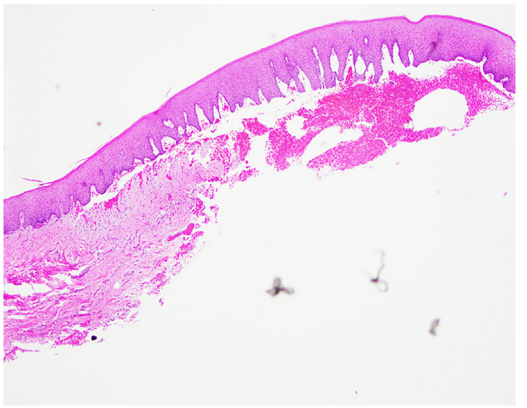

Fig. 19. Light microscopic examination of a perilesional mucosa shows a clear separation between the surface epithelium and the underlying connective tissue.

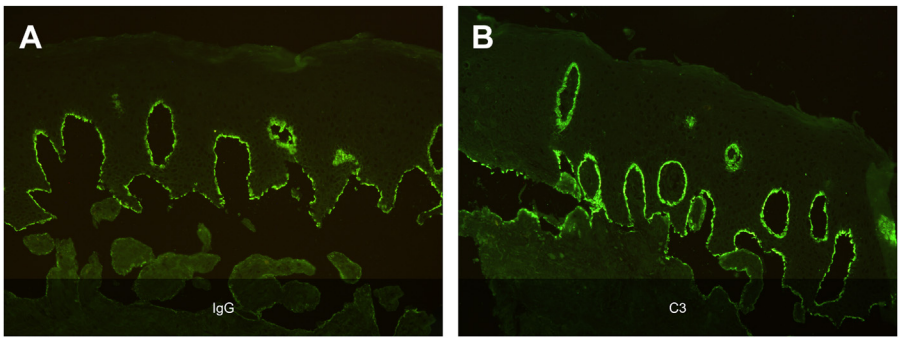

Fig. 20. Direct immunofluorescence microscopy reveals a linear band of IgG (*A*) and C3 (*B*) deposition at the basement membrane zone.

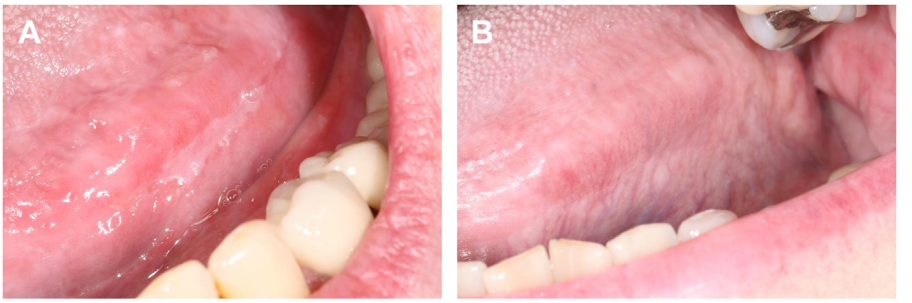

Fig. 21. (*A*) Large ulceration of the left lateral border of the tongue. (*B*) Same lesion after corticosteroids therapy. The ulceration healed completely.

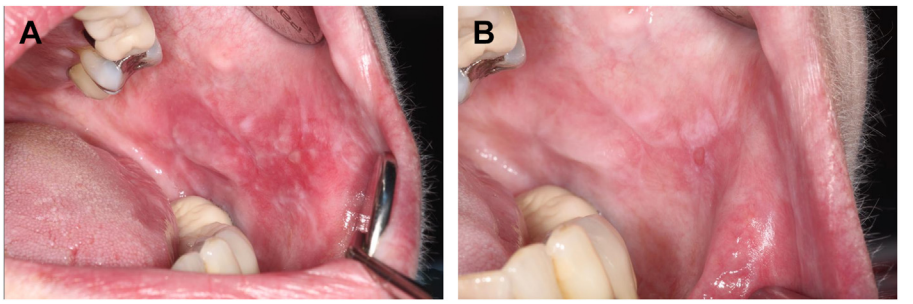

Fig. 22. (*A*) Diffuse and ill-defined erosions of the left buccal mucosa. (*B*) Near resolution of lesions after corticosteroids treatment.

Box 1
Medications most implicated in drug-induced bullous pemphigoid

Alogliptin
Anagliptin
Aspirin
Biostim
D-Penicillamine
Enalapril
Erlotinib
Etanercept
Everolimus
Furosemide
Ibuprofen
Levofloxacin
Linagliptin
Nivolumab
Pembrolizumab
Phenacetin
Psoralens with UVA
Rifampicin
Serratiopeptidase
Sirolimus
Sitagliptin
Tetanus toxoid
Tiobutarit
Vildagliptin

attached gingiva is the most frequently involved intraoral site, although the soft palate, buccal mucosa, and floor of the mouth may be affected as well.[3,29] In contrast to PV, the Nikolsky's sign is usually negative in BP.[25]

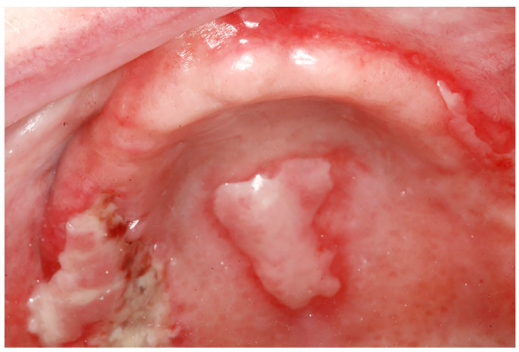

Fig. 23. Large, irregular bullae and shallow ulcerations involving the palate and the alveolar ridge.

DIAGNOSIS AND HISTOPATHOLOGIC FEATURES

BP diagnosis relies on the clinical findings, histologic and immunopathologic evaluations.[23–25] A biopsy must be taken from perilesional mucosa for an accurate diagnosis similar to the other entities discussed above.

Histopathologic examination of perilesional tissue demonstrates a subepithelial separation with a superficial perivascular inflammatory infiltrate and numerous eosinophils (**Fig. 24**).[3] The presence of eosinophils, especially within the bulla may provide a clue for diagnosing BP (see **Fig. 24**C). DIF studies are imperative to confirm the diagnosis. The DIF will highlight the deposition of IgG and complement C3 in a linear homogeneous pattern at the basement membrane zone similar to that seen in BMMP.[7,23–25]

Circulating autoantibodies in patients' serum are typically detected in 50% to 90% of cases using IIF assay. ELISA is also a useful diagnostic tool for BP with 89% sensitivity and 98% specificity. Several case series have shown that anti-BP180 IgG levels correlate with disease severity and could be used as a predictive marker for relapse.[30]

TREATMENT AND PROGNOSIS

BP treatment and prognosis depend on the extent of involvement and severity of the disease. However, the standard treatment is corticosteroids.[23–25] For mild disease where less than 20% of body surface area is affected, high-potency topical corticosteroids such as clobetasol propionate may be used. Combining topical corticosteroids with nicotinamide and tetracycline antibiotics (ie, doxycycline) has shown promising results in multiple cases. Systemic corticosteroids, such as prednisone at a dose of 0.5 to 1.0 mg/kg per day are reserved for more severe and extensive cases unless contraindicated.[23–25,29] Immunosuppressant therapies such as azathioprine, mycophenolate mofetil, methotrexate, and cyclophosphamide are used when systemic corticosteroids fail to control the disease. In refractory cases, intravenous immunoglobulin therapy, rituximab, or omalizumab can be used.[23–25]

Drug-induced BP cases are often self-limited and resolve spontaneously after discontinuation of the offending medication(s). Treatments are available to help relieve the symptoms and maintain quality of life.[27,28]

The disease typically has a chronic clinical course with unpredictable exacerbations. A

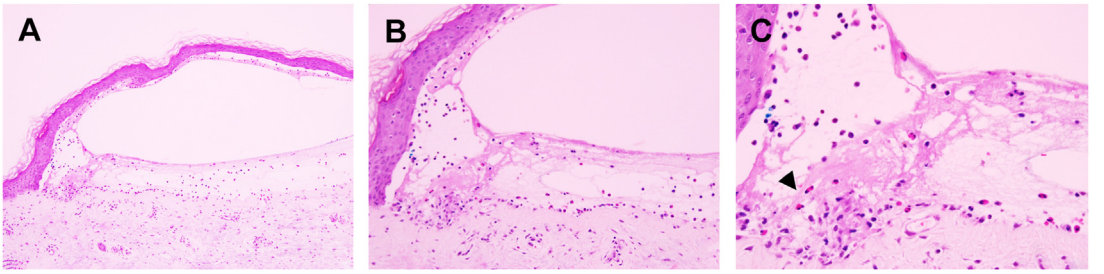

Fig. 24. Light microscopic examination reveals (*A*, *B*) a subepidermal blister with mild superficial inflammatory cell infiltrate. (*C*) Prominent eosinophils (*arrowhead*), a characteristic for bullous pemphigoid. (*Courtesy of* Dr Vladimir Vincek)

relapse rate of 30%-50% is observed within the first year. The mortality rate is relatively high in BP approximately 10% to 40%, mainly because it is a disease of the elderly. In addition, treatment-related adverse effects are associated with increased mortality. BP patients are susceptible to microbial infections such as varicella-zoster virus, staphylococcal, streptococcal infections, and sepsis. Patients need to avoid trauma and maintain good hygiene to prevent complications.[23–25,29]

EPIDERMOLYSIS BULLOSA ACQUISITA

Epidermolysis bullosa acquisita (EBA) is the rarest of the vesiculobullous autoimmune conditions. It is mediated by autoantibodies directed against type VII collagen, a major element of the anchoring fibrils at the stromal-epithelial junction. The estimated annual incidence of EBA is 1 case per million population., Approximately 9.6% of EBA cases have been associated with other conditions such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, and thyroiditis. Affected individuals may have a genetic susceptibility to developing EBA.[31–36]

CLINICAL FEATURES

EBA rarely occurs in childhood, and it typically affects older adults, with an average age of 50 years and an equal gender distribution.[31–35,37] EBA is characterized by the development of blisters and bullae on the skin and mucous membranes. Mucosal involvement is seen in one-fourth of EBA cases. Oral mucosa is the most frequently affected mucosal site, followed by ocular, genital, esophageal, tracheal, and anal mucosae (**Fig. 25**). Ocular and tracheal involvement may lead to blindness and life-threatening respiratory complications, respectively, due to scarring. Atrophic scarring, hypopigmentation, onychodystrophy (nail dystrophy), anonychia, and hand deformities may also occur (**Fig. 26**).[31–35,37,38]

Depending on EBA subtype, oral lesions can be subclinical, chronic, or severe. Usually, oral lesions are described as widespread painful blisters, erosions, and scarring that can affect any oral mucosal surfaces. In severe cases, scarring may result in ankyloglossia and trismus. Gingival involvement may manifest as gingivitis or severe periodontal disease with significant alveolar bone loss, and teeth mobility (**Fig. 27**).[38,39]

DIAGNOSIS AND HISTOPATHOLOGIC FEATURES

The International Bullous Disease Group proposed nine diagnostic criteria with a minimum of three required for EBA diagnosis (**Box 2**).[38] EBA diagnosis is established by the clinical findings, histologic and immunopathologic evaluations.[34,38] A biopsy must be taken from perilesional mucosa for an accurate diagnosis and ulcerated and eroded areas should be avoided as mentioned earlier.

Histopathologic examination of a perilesional tissue demonstrates a subepithelial/subepidermal separation with scattered inflammatory cell infiltrate (**Fig. 28**).[31–35,37,38] DIF studies are imperative

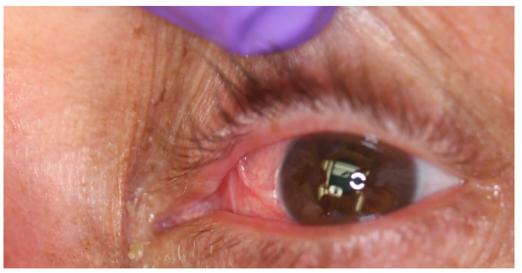

Fig. 25. Ocular involvement in epidermolysis bullosa acquisita may be mistaken for pemphigoid.

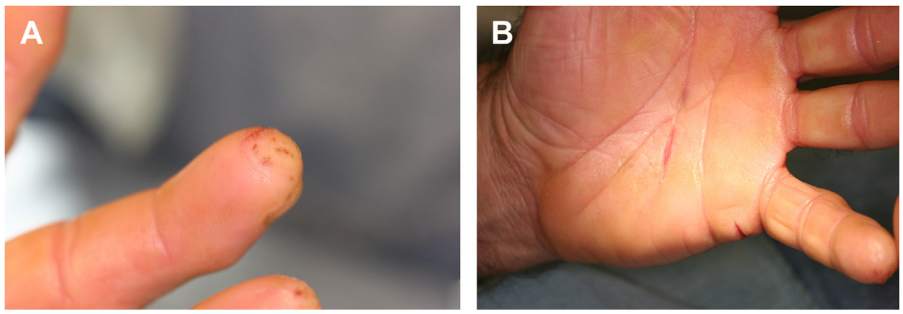

Fig. 26. Ulcerations of the fingertips (*A*) and palm (*B*).

to confirm the diagnosis. DIF highlights the deposition of IgG, complement C3, and IgA in a linear homogeneous pattern at the basement membrane zone, like that seen in BP and BMMP. However, a u-serration shaped pattern on DIF is exclusively seen in EBA and bullous systemic lupus erythematosus. This pattern differentiates EBA from pemphigoid spectrum diseases.[31–35,37,38]

IIF study on salt-split skin is a useful diagnostic tool for distinguishing EBA from BP. An artificial bulla is induced on incubated perilesional skin biopsy sample in a concentrated salt solution. When fluorescein-conjugated anti-human IgG antibodies serum is applied on the salt-split skin, in EBA cases, IgG autoantibodies will be localized to the dermal side (floor of the bulla), corresponding to collagen VII presence. This discriminates BP, where immunoreactants are localized at the epidermal side (roof of the bulla).[34,38,40]

TREATMENT AND PROGNOSIS

EBA treatment remains challenging due to the paucity of randomized controlled trials and the rarity of the disease, with most therapeutic recommendations based on small case series within the literature.

Systemic corticosteroids are used as the first line for EBA treatment. Depending on the severity and

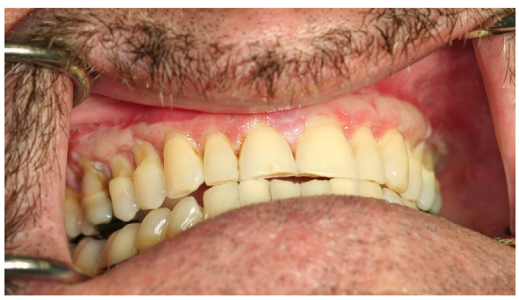

Fig. 27. Epidermolysis bullosa acquisita manifests as a periodontal disease with significant alveolar bone loss.

Box 2
International bullous disease group diagnostic criteria for the diagnosis of epidermolysis bullosa acquisita

1. A bullous disorder within the defined clinical spectrum, *and*
2. Histopathology demonstrating a subepidermal or subepithelial blister (*Optional*)
3. Positive DIF* microscopy of perilesional tissue with linear deposition of IgG, C3, IgA, and/or IgM at the basement membrane zone, *and*
4. Detection of circulating anti-collagen VII autoantibodies by immunoblotting, ELISA**, and/or IIF*** microscopy on collagen VII expressing human cells, *OR*
5. Labeling anchoring fibrils by indirect immunoelectron microscopy or negative IIF*** microscopy on collagen VII deficient skin

For seronegative patients, diagnosis is confirmed if criteria (1) *AND* (3) are present *AND* 1 or more of the following:

6. Presence of "u-serration" patterns on DIF* microscopy, *OR*
7. Direct immunoelectron microscopy of perilesional skin exhibiting immune deposits within anchoring fibrils zone ± sublamina densa zone, *OR*
8. Fluorescent overlay antigen mapping analysis showing in vivo bound immune deposits below the basal keratinocyte membrane, lamina lucida, and lamina densa components, *OR*
9. $^{+}$Deposition of autoantibodies to the dermal side on DIF* and/or IIF*** on salt-split skin test

**Direct immunofluorescence; **Enzyme-linked immunosorbent assay; ***Indirect immunofluorescence; + Can be used as an alternative to criteria (4) through (8)*

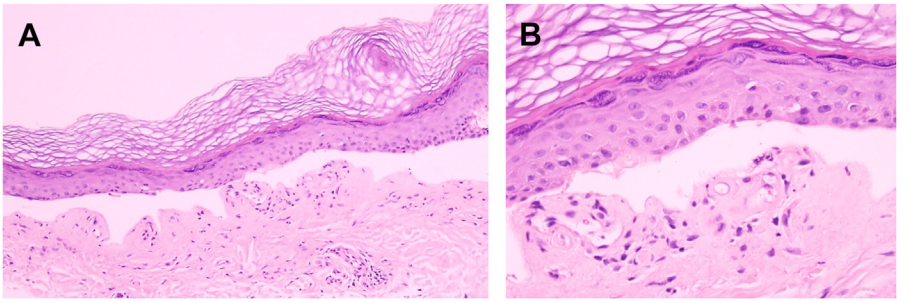

Fig. 28. (*A*, *B*) Light microscopic examination of a perilesional tissue demonstrates a subepidermal separation with scant inflammatory cell infiltrate. (*Courtesy of* Vladimir Vincek, MD, PhD, Gainesville, FL)

extent of the disease the initial dosage ranges from 0.5 to 2.0 mg/kg/d. Systemic corticosteroids in combination with steroid-sparing immunosuppressant therapies including dapsone, azathioprine, colchicine, cyclosporine, cyclophosphamide, methotrexate, and mycophenolate mofetil have been widely used in EBA treatment with variable success results.[31–35,37–39,41] Rituximab and high-dose intravenous Immunoglobulin have shown to be effective in EBA treatments, especially in recalcitrant cases. Despite advancements in therapy, patients may experience relapses during treatment.[41]

CLINICS CARE POINTS

- If a vesiculobullous disease is suspected the biopsy must be from unaffected, perilesional tissue
- Oral lesions in PV are the most difficult to treat and are the first to show and the last to go.
- PV starts in the oral cavity over 50% of the time and early treatment before it gets to the skin is essential
- The clinical finding of intact, persistent, blood-filled blisters is highly diagnostic of BMMP.
- Once BMMP lesions progress and especially if they involve other mucous membranes, the eyes, or the skin, then systemic therapy and referral to dermatology and/or ophthalmology is indicated.
- Bullous pemphigoid is predominantly a skin disorder with lesser oral involvement

DISCLOSURE

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