The diagnosis of aggressive CGCG carries important prognostic implications, which should be mentioned in a diagnostic pathology report. Clinical features of tooth resorption, tooth displacement, and osseous cortical perforation remain the hallmark of this variant. To this, we can potentially add histomorphologic aspects, such as 160 giant cells or more per 25 HPFs, 6 stromal mitoses or more per 25 HPFs, and increased vascular density.

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CLINICAL PATHOLOGIC CONFERENCE CASE 5: BILATERAL EROSIVE LESIONS IN A 49-YEAR-OLD FEMALE

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Clinical Presentation: A 49-year-old Cuban female was referred by her general dentist for evaluation and treatment of what the clinician believed to be extremely painful major aphthous ulcerations of 2 months' duration. The patient's medical history was significant for gastric reflux, constipation, diabetes, and depression; she also indicated a history of fever, chills, and night sweats. The patient's surgical history revealed a previous cholecystectomy and hysterectomy with bilateral salpingo-oophorectomy. She initially was seen by a rheumatologist and an otolaryngologist, who had prescribed antifungal medications. When the patient's condition did not improve after 2 weeks of antifungal therapy, incisional biopsy was performed. The histopathologic report was nonspecific, describing ulcerative squamous mucosa with prominent granulation tissue (original slides unavailable). The patient then began a course of prednisone and fluocinonide cream, which provided no relief. After no improvement, the patient was referred to the oral pathology clinic.

Clinical examination revealed diffuse ulcerations involving the right and left buccal mucosa, lateral and ventral surfaces of the tongue, and upper and lower labial mucosa (Figure 1). The ulcerations exhibited irregular, erythematous borders with faint white striae radiating toward the periphery in focal areas. A positive Nikolsky sign was noted upon slight manipulation. Two incisional biopsies were performed: one from the left lateral tongue and the other from the left buccal mucosa.

Differential Diagnosis: The complete list of ulcerative conditions affecting the oral cavity is exhaustive; however, supporting clinical information allowed us to substantially narrow our differential diagnosis to chronic ulcerative conditions affecting the oral cavity with a positive Nikolsky sign.[1] Our differential diagnosis included 3 broad classifications of disease: (1) immune-mediated *subepithelial* blistering diseases (IMSEBD), (2) erosive conditions that demonstrate *intraepithelial* separation, and (3) paraneoplastic pemphigus (PNP), which bridges the 2 categories. Had the patient not exhibited a positive Nikolsky sign on clinical examination, more common entities, such as erosive lichen planus (LP) or lichenoid drug reaction, would have been strongly considered. Additionally, the patient was on no known medications to attribute the changes to a mucosal drug reaction.

"IMSEBD" is a term introduced by Chan et al.[2] and encompasses several entities affecting the dermal–epidermal junction, including bullous pemphigoid; mucous membrane pemphigoid (MMP); pemphigoid gestationis; anti-p200-, anti-p105-, and anti-p450 pemphigoid; linear IgA disease; epidermolysis bullosa acquisita (EBA); bullous systemic lupus erythematosus; bullous LP; and lichen planus pemphigoides (LPP).[2-4] These entities demonstrate

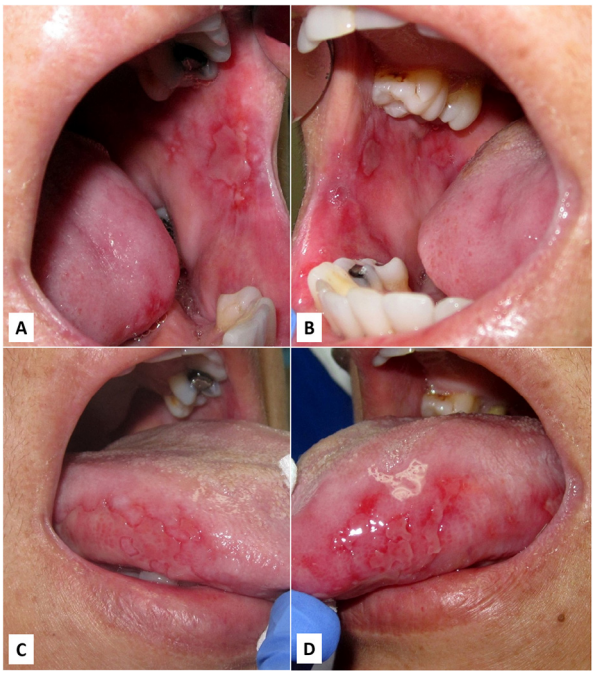

Fig. 1. Initial clinical presentation demonstrating numerous ulcerative lesions of the buccal mucosa and tongue. The ulcers exhibit irregular borders with an erythematous periphery. Vague white striae are present in some foci. **A,** Left buccal mucosa. **B,** Right buccal mucosa. **C,** Right lateral tongue. **D,** Left lateral tongue.

significant clinical and histopathologic overlap and often are only separated on the basis of direct immunofluorescence (DIF) or indirect immunofluorescence (IIF) antibody studies, salt-split testing, and/or molecular biochemical techniques, such as enzyme-linked immunosorbent assay (ELISA). Although included in this broad category, bullous pemphigoid tends not to have a positive Nikolsky sign and is quite rare in the oral cavity[4]; thus, it was excluded from our differential diagnosis in this case.

The most common IMSEBD of the oral cavity is MMP (also known as *cicatricial pemphigoid*). MMP can affect patients of a wide age range, but traditionally it affects middle-aged to older adults and demonstrates a female predominance.[5-7] The most common oral site is the gingiva, which is involved in 94% of patients with MMP.[8,9] Ocular lesions are of great importance because up to 40% of patients with MMP in the oral cavity also have, or will develop, ocular manifestations.[4] Eye lesions typically involve the conjunctiva and may demonstrate significant scarring, leading to major complications, including blindness.[4,5] Other sites, including the subglottis, larynx, esophagus, nose, penis, vulva, and anal mucosa, may be involved in MMP.[4] MMP is usually confirmed with DIF, where C3, immunoglobulin G (IgG), and occasionally IgA are deposited at the basement membrane zone. It may be distinguished from EBA by salt-split testing.[6] Although our patient demonstrated the appropriate age and gender for MMP, she did not show gingival lesions or extraoral manifestations; thus, MMP was included in our differential diagnoses because commonality but was not at the top of the list because of the specific locations affected.

Pemphigoid gestationis is an IMSEBD occurring during or around the time of pregnancy[10]; therefore, it could easily be eliminated from our differential diagnosis because our patient was not pregnant. Other IMSEBDs, including linear IgA disease, EBA, bullous systemic lupus erythematosus, and anti-p200-, anti-p105-, and anti-p450 pemphigoid, occur predominantly on skin. If they occur in the oral cavity, skin involvement is usually present first.[6,10,11] Our patient did not have extraoral lesions; thus, these entities were lower on our list of differential diagnoses.

Another IMSEBD, LPP, is a poorly understood condition, with variable features of both LP and LPP. Patients typically present with disease in the fourth to fifth decades, and the disease demonstrates a slight male predilection.[12] LPP most commonly occurs as bullae that develop over pre-existing LP, especially on the extremities.[12] A recent review in 2015 identified 27 cases from the literature of oral LPP.[13] Of these 27 cases, only 1 case demonstrated oral involvement without cutaneous manifestations. The histopathology of LPP shows overlapping features of both LP and pemphigoid (colloid bodies, lymphocytic band in the superficial lamina propria, basal cell degeneration, subepithelial clefting) but demonstrates features most compatible with pemphigoid on DIF (linear deposits of C3 and IgG, as well as occasional IgM and IgA, along the basement membrane zone). Although it would be very rare, this entity deserves merit on our list of differential diagnoses because of the patient age and clinical appearance, as our patient exhibited slight white striae at the periphery of the erosive areas. Another similar entity, bullous lichen planus, is extremely rare and demonstrates clinical features of both LP and LPP as well; however, histopathologic and immunofluorescence studies were compatible with LP, rather than LPP.[3,14-17]

The second category of disease in our differential diagnosis was an autoimmune, intraepithelial separation disease, that is, pemphigus. Pemphigus is an autoantibody response targeted toward the intercellular keratinocyte adhesion molecules (desmosomes). It is broken down into 2 broad categories: pemphigus vulgaris (PV) and pemphigus foliaceus (PF), with pemphigus vegetans, erythematosus, and IgA pemphigus representing subcategories or variants of pemphigus.[18] PV is the only entity within this category that tends to affect the mucosa, with or without cutaneous involvement; the other categories occur most often on skin. The reason is that PV autoantibodies recognize desmoglein 3 and often desmoglein 1; however, PF autoantibodies usually recognize only desmoglein 1. Desmoglein 1 and desmoglein 3 are both expressed in the oral mucosa, but desmoglein1 is expressed at a much lower level than desmoglein3 in the oral mucosa.[6,19,20]

PV is a potentially life-threatening autoimmune disease that requires swift and accurate diagnosis because treatment often entails aggressive immunosuppression.[21] It is the most common form of pemphigus in the United States, and it usually has a clinical onset in patients between ages 50 and 60 years.[18] PV demonstrates a female predilection and can be mucosal-dominant, mucocutaneous, or cutaneous, with the types corresponding to type of antidesmoglein antibody present.[18,22] The mouth is affected in 70% to 90% of PV cases, with areas most frequently subjected to trauma being the most common sites of occurrence (e.g., labial mucosa, tongue, buccal mucosa, palate).[8] The age group and sites of involvement put PV high on our list of differential diagnoses.

Finally, we included PNP on our differential diagnosis because it can exhibit both intraepithelial and subepithelial separation, the latter being associated with interface dermatitis. PNP is a rare blistering condition that often indicates the presence of an underlying benign or malignant neoplasm. It most commonly affects patients ages 45 to 70 years, although it can affect a wide age range.[18,22] PNP is most often associated with lymphoreticular disease, although many other associations have been described.[6,11] Clinically, PNP demonstrates extreme variability, but the most consistent and