Oral Manifestations of Autoimmune and Connective Tissue Disorders

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KEYWORDS

• Oral manifestations • Sjögren's syndrome • Rheumatoid arthritis • Pemphigus vulgaris
• Benign mucous membrane pemphigoid • Behçet disease • Sarcoidosis • Oral lichen planus

KEY POINTS

- Immune system malfunction is the underlying cause of symptoms in autoimmune, autoinflammatory and connective tissue disorders.
- Orofacial manifestations occur in these conditions either as a component of the disorder itself or as a consequence of the drugs used to treat the condition.
- The informed practitioner should be aware of the most common autoimmune, autoinflammatory and connective tissue disorders that present with oral manifestations.

Introduction

Blisters and vesicles are mucosal or skin reactions that involve dissection of intramucosal or epithelial cells. Within the group of blistering diseases, autoantibodies to integrins and adhesion molecules that maintain mucosal integrity may vary; however, clinically, it results in similar appearing lesions a differential diagnosis. Skin involvement may be found in several when compiling of these conditions with varying severity resulting in symptoms with a high morbidity, and rarely, mortality of the patient with the disease. The most common autoimmune/immune-mediated bullous diseases are presented. Our review is limited to those conditions presenting with oral manifestations: pemphigus vulgaris (PV), cicatricial pemphigoid or benign mucous membrane pemphigoid, lichen planus, and Behçet disease (BD). In the second half of this article, we review the most common connective tissue disorders that may present with oral manifestations that the well-informed oral health care provider may encounter in their patient population.

Autoimmune and autoinflammatory-related blistering and ulcerative diseases

Pemphigus vulgaris

Incidence, predilection, and genetics

Pemphigus disease (Table 1) is a rare and potentially life-threatening autoimmune blistering disease with an incidence of 0.1 to 0.5 in 100,000.[1] The most frequently occurring variant, PV represents about 70% to 80% of the cases and whose incidence varies from 0.76 to 16 cases per million per year depending on geographic location being studied. The disease is most commonly found in the Jewish population, particularly those of Ashkenazi origin, and Eastern countries such as Malaysia, China, and Japan, with a slight female predilection. Genetic association between HLA class II genes and observations of increased prevalence in certain ethnic groups illustrate a genetic predisposition. This, combined with exogenous factors (medications, viral infection, diet, etc.) and/or endogenous factors (stress) initiate autoimmune mechanisms leading to tissue damage.[2]

Clinical features

Clinically, PV almost always begins with multiple mucosal site involvement; frequently, those areas that are subjected to frictional trauma such as the gingiva, palate, buccal mucosa, and tongue (Fig. 1). Oral involvement can precede skin involvement by up to 1 year. Lesions begin as flaccid vesicles or bullae that rupture quickly, leaving behind painful shallow ulcerations that heal without scarring.

Diagnosis and histopathology

Histologic examination of perilesional or even normal-appearing mucosa shows a suprabasalar cleft leaving 1 to 2 layers of basal and suprabasal keratinocytes attached to the connective tissue papillae yielding a tombstonelike pattern (Fig. 2A). Round acantholytic (Tzanck) cells are often noted within the cleft. Antibodies against keratinocyte adhesion molecules (desmoglein [Dsg] 1 and 3, E-cadherin, desmoplakin, and alpha-9-acetylcholine) and desmosomes induce intraepithelial acantholysis resulting in blistering. Dsg 1 (primarily found in skin) and Dsg 3 (chiefly detected in mucosal epithelium) are the most important target antigens. Direct immunofluorescence (DIF) studies reveal binding of IgG, in the intracellular spaces between epithelial cells revealing a characteristic netlike pattern (see Fig. 2B). Recently, serum and salivary IgG

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Table 1 Autoantibodies in autoimmune blistering diseases

	Autoantigens	DIF immunoreactants
Pemphigus groups		
Pemphigus vulgaris	Desmoglein 3 and 1	IgG, IgM, C3
Pemphigus foliaceus	Desmoglein 1	
Paraneoplastic pemphigus	Desmoglein 1, and 3, periplakin, desmoplakin	IgG, IgM, C3
Pemphigoid groups		
Bullouspemphigoid	BP-AG 1, plectin, $\alpha 6\beta 4$ integrin	
Pemphigoid gestationis	BP-AG 2	
Mucous membrane pemphigoid	Collagen XVII/BP180, BP230, laminin 332, $\alpha 6\beta 4$ integrin	IgG, C3, IgA, IgM

and IgA antibodies to Dsg 3 have been suggested as a diagnostic alternative to biopsy.[3]

Treatment considerations

Corticosteroids remain the most common treatment modality for this condition. When there are only oral lesions present, corticosteroids are applied topically in rinse or gel formulations. PV is a potentially life-threatening disease and, therefore, requires an early and more intensive therapeutic regimen than other autoimmune blistering diseases; if skin lesions are present, treatment consists of systemic steroids (pulse or continuous) and may be combined with adjuvant immunomodulatory or immunosuppressive medications, including azathioprine as first-line therapy. Other immunosuppressants may be considered if patients are unresponsive or experience significant side effects to first-line therapy (Table 2). More recently, anti—B-cell monoclonal antibodies have been used for the treatment of refractory cases with some success. Of these biologic agents, most is known about rituximab; however, other agents such as veltuzumab and ofatumumab either have been or are currently undergoing clinical trials. These agents seem to be well-tolerated with rare serious adverse events; however, patients are at increased risk

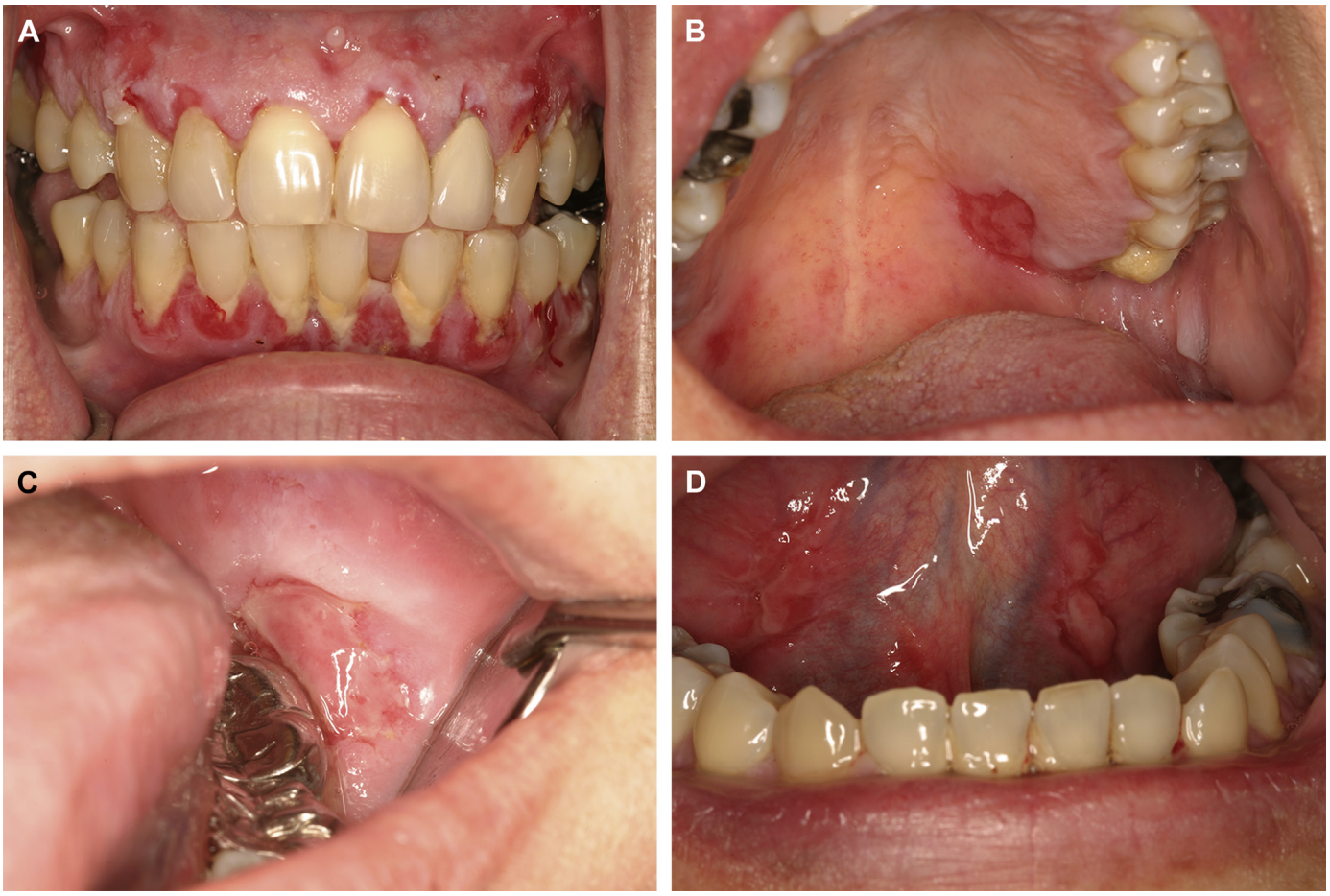

Fig. 1 Pemphigus vulgaris can affect the keratinized and nonkeratinized tissues of the oral cavity including the gingiva forming erosions often resembling desquamative gingivitis (*A*) hard palatal mucosa (*B*), buccal mucosa/vestibule, (*C*) and ventral tongue (*D*). When affecting the gingiva, patients may find it painful to brush their teeth effectively, causing plaque accumulation that exacerbates gingival inflammation and pain (*A*). (*Courtesy of* Michaell Huber, DDS, UT Health San Antonio, San Antonio, TX.)