Spectrum of orocutaneous disease associations

Immune-mediated conditions

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Learning objectives
After completing this learning activity, participants should be able to recognize the important and close relationship between the skin and the mucosal tissues inclusive of GI disorders and inflammatory disorders; recognize and differentiate the mucosal manifestations of multiple dermatologic conditions; and describe the pathophysiology of how oral disease may potentially manifest on the skin, and vice versa.

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There are a number of diseases that manifest both on the skin and the oral mucosa, and therefore the importance for dermatologists in clinical practice to be aware of these associations is paramount. In the following continuing medical education series, we outline orocutaneous disease associations with both immunologic and inflammatory etiologies. (J Am Acad Dermatol 2017;77:795-806.)

Key words: chronic ulcerative stomatitis; Crohn's disease; immune-mediated conditions; linear immunoglobulin A bullous dermatosis; lupus erythematosus; mucous membrane pemphigoid; oral cavity; orocutaneous disease; paraneoplastic pemphigus; pemphigus vulgaris; rheumatoid arthritis; scleroderma.

ORAL ANATOMY

The normal anatomy of the oral cavity is comprised of the lips anteriorly, the cheeks laterally, the floor of the mouth inferiorly, the oropharynx posteriorly, and the palate superiorly. It includes the lips, gingivae, teeth, hard palate, cheek mucosa, and tongue (Fig 1). The lip has an interior wet vermilion and is lined with a stratified squamous, nonkeratinized epithelium together with an outer dry vermilion, separated from each other by the red line. The outer dry lip

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is composed of stratified squamous, keratinized epithelium. The cheeks are lined by mucosa that is nonkeratinized, although in some places it can be parakeratinized. The gingivae and hard and soft palates are lined with a keratinized stratified squamous epithelium (masticatory mucosa).

GRANULOMATOSIS WITH POLYANGIITIS

Key points

- **Granulomatosis with polyangiitis, formerly known as Wegener granulomatosis, is a systemic immune-mediated condition characterized by the presence of antineutrophilic cytoplasmic antibodies**
- **Hyperplastic gingivitis with the appearance of overripe strawberries is characteristic of this disease**
- **Granulomatosis with polyangiitis is responsive to a 2-phase treatment plan beginning with a remission induction phase followed by a maintenance phase**

Etiology

Granulomatosis with polyangiitis (GPA) is a systemic, immune-mediated process characterized by the presence of circulating antineutrophil cytoplasmic autoantibodies.[1-6] Antineutrophil cytoplasmic autoantibodies target proteinase 3 and myeloperoxidase, causing neutrophil activation and degranulation.[7-9] While all ages can be affected, patients are most commonly affected in the sixth and seventh decades of life.[6] The cause of GPA is unknown, although a genetic predisposition relating to human leukocyte antigen (HLA)-DPB1*0401, the α1-antitrypsin gene *SERPINA*, or the proteinase 3 gene *PRTN3* together with exposure to environmental or infectious agents has been suggested.[10,11]

Oral manifestations

The oral cavity is affected in ≤62% of patients with GPA, with 5% to 6% of patients citing oral lesions as a presenting complaint.[8] Hyperplastic gingivitis of the upper anterior gingiva is most common and characteristically resembles overripe strawberries.[10,12] Other oral manifestations can include painful ulcerations of the palatal or gingival mucosa, tooth mobility, poor healing after tooth extraction, cranial nerve palsies, and parotid gland swelling.[1,6,8,10,13] Table I shows the differential diagnosis of GPA.[14]

Cutaneous manifestations

Up to 50% of patients present with nonspecific cutaneous manifestations, including palpable purpura, subcutaneous nodules, pustules, vesicles, or petechiae commonly involving the extremities.[10,12] Alopecia can occur during active disease because of vasculitis of the scalp.[10]

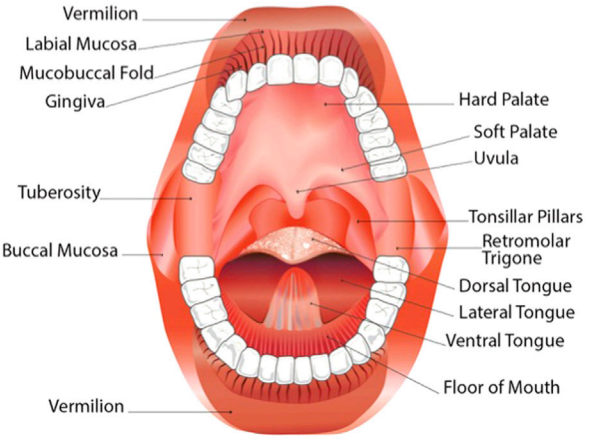

Fig 1. Normal oral anatomy.

Table I. Differential diagnosis of granulomatosis with polyangiitis

Differential diagnosis
Vasculitides: Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis
Granulomatous disease: sarcoidosis, Crohn's disease
Systemic lupus erythematosus
Nasal natural killer/T-cell lymphoma
Langerhans cell histiocytosis
Lymphomatoid granulomatosis
Blood dyscrasias: leukemia, lymphoma
Granulomatous infectious disease: tuberculosis, deep mycoses
Drug-induced gingival changes

Treatment

Treatment is divided into remission induction and maintenance phases.[4,6,7,15] The criterion standard GPA therapy combines prednisone and cyclophosphamide and typically brings symptoms under control within a week.[7,8,15] Intralesional steroid injections may relieve gingival symptoms.[1] Azathioprine and methotrexate are the principal agents of the maintenance therapy regimen.[2,6,7,16]

PEMPHIGUS VULGARIS

Key points

- **Pemphigus vulgaris is an immune-mediated disorder characterized by immunoglobulin G autoantibody production against desmoglein-1 and -3 desmosome antigens**