

# Oral Manifestations of Systemic Disease

ANGELA C. CHI, DMD; BRAD W. NEVILLE, DDS; JOE W. KRAYER, DDS; and WANDA C. GONSALVES, MD  
*Medical University of South Carolina, Charleston, South Carolina*

Careful examination of the oral cavity may reveal findings indicative of an underlying systemic condition, and allow for early diagnosis and treatment. Examination should include evaluation for mucosal changes, periodontal inflammation and bleeding, and general condition of the teeth. Oral findings of anemia may include mucosal pallor, atrophic glossitis, and candidiasis. Oral ulceration may be found in patients with lupus erythematosus, pemphigus vulgaris, or Crohn disease. Additional oral manifestations of lupus erythematosus may include honeycomb plaques (silvery white, scarred plaques); raised keratotic plaques (verrucous lupus erythematosus); and nonspecific erythema, purpura, petechiae, and cheilitis. Additional oral findings in patients with Crohn disease may include diffuse mucosal swelling, cobblestone mucosa, and localized mucogingivitis. Diffuse melanin pigmentation may be an early manifestation of Addison disease. Severe periodontal inflammation or bleeding should prompt investigation of conditions such as diabetes mellitus, human immunodeficiency virus infection, thrombocytopenia, and leukemia. In patients with gastroesophageal reflux disease, bulimia, or anorexia, exposure of tooth enamel to acidic gastric contents may cause irreversible dental erosion. Severe erosion may require dental restorative treatment. In patients with pemphigus vulgaris, thrombocytopenia, or Crohn disease, oral changes may be the first sign of disease. (*Am Fam Physician*. 2010;82(11):1381-1388. Copyright © 2010 American Academy of Family Physicians.)

In 2000, the U.S. Surgeon General's report *Oral Health in America* highlighted numerous ways in which oral and general health are linked.<sup>1</sup> Oral examination can reveal signs and symptoms of immunologic diseases, endocrinopathies, hematologic conditions, systemic infections, and nutritional disorders. In addition, several studies have reported associations between periodontal disease and diabetes mellitus, heart disease, stroke, and adverse pregnancy outcomes.<sup>2-4</sup> Identifying these oral findings may allow for early diagnosis and treatment. Family physicians should be familiar with the relationship between systemic and oral health, and be prepared to coordinate care with dental or medical subspecialists as indicated.

This article provides a guide for recognizing the oral manifestations of select systemic diseases. A number of oral manifestations of systemic disease have been covered previously<sup>5,6</sup>; therefore, a detailed discussion of these findings is not provided here. However, for comprehensiveness, salient features of these findings are included in *Table 1*, with a summary of the conditions and associated

oral manifestations discussed in this article. For each category of oral finding, the conditions are presented in order of the frequency in which oral manifestations are encountered, from the most to least common.

## Mucosal Changes

### MUCOSAL PALLOR AND ATROPHY

Oral findings in patients with anemia may include mucosal pallor, atrophic glossitis, and candidiasis. Oral mucosal pallor may be difficult to appreciate.<sup>7</sup> Atrophic glossitis appears as complete or patchy baldness of the tongue caused by atrophy of the lingual papillae (*Figure 1*). Atrophic glossitis is a nonspecific finding that can occur in association with iron deficiency anemia, pernicious anemia/vitamin B complex deficiencies, and various other conditions. Atrophy can be observed most easily on the dorsal tongue, although other sites may be affected. Burning, pain, tenderness, and erythema also may be present. Candidiasis may be a concurrent finding or an alternative cause of erythema, burning, and atrophy. In addition, some patients may present with angular cheilitis (a lip infection

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**Table 1. Oral Manifestations of Select Systemic Conditions**

<i>Clinical presentation</i>	<i>Associated condition*</i>	<i>Oral manifestation</i>	<i>Comments</i>
Mucosal pallor and atrophy	Anemia	Mucosal pallor; atrophic glossitis; candidiasis (including angular cheilitis); mucosal burning, pain, or tenderness; erythema	Oral mucosal pallor may be difficult to appreciate
Oral lesions (including ulcerative, erosive, or white lesions; swelling; erythema)	Lichen planus	Erosive: diffuse erythema and painful ulceration with peripheral radiating striae Reticular: white lacy striae, especially on bilateral buccal mucosa	In symptomatic patients, oral lesions may be treated with a topical corticosteroid gel or rinse
	Lupus erythematosus	Oral discoid lesions, honeycomb plaques, raised keratotic plaques, erythema, purpura, petechiae, irregularly shaped ulcers, cheilitis	In discoid lupus erythematosus, oral lesions seldom occur in the absence of skin lesions
	Benign mucous membrane pemphigoid	Diffuse and painful oral ulceration, scarring	Intact blister formation occasionally may be seen intraorally (before rupture and ulceration)
	Pemphigus vulgaris	Diffuse and painful oral ulceration, positive Nikolsky sign	Oral lesions often are the first manifestation of disease and may precede the onset of skin lesions After initiating systemic therapy, oral lesions may take longer to resolve compared with extraoral lesions
	Crohn disease	Diffuse mucosal swelling; cobblestone mucosa; localized mucogingivitis; deep linear ulceration; fibrous tissue tags, polyps, or nodules; pyostomatitis vegetans ("snail track" ulcers on an erythematous base); possible aphthous-like ulcers	Oral lesions usually resolve with systemic treatment of underlying intestinal disease, although persistent ulcers may require application of topical corticosteroids, and persistent swelling may respond to intralesional injection of triamcinolone acetonide (Kenalog)
	Behçet syndrome	Recurrent, painful aphthous-like ulcers, usually numerous and especially involving the soft palate and oropharynx	Oral lesions are the most common lesions associated with Behçet syndrome and may be the first manifestation of disease
Change in mucosal pigmentation	Addison disease	Diffuse melanin pigmentation, candidiasis (in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome)	Differential diagnosis for diffuse oral melanin pigmentation also includes ethnic pigmentation, tobacco-related pigmentation, medication-related pigmentation, neurofibromatosis 1, McCune-Albright syndrome, and Peutz-Jeghers syndrome
Periodontal bleeding and inflammation	Diabetes mellitus	Gingivitis, periodontitis, candidiasis, generalized atrophy of the tongue papillae, taste dysfunction, salivary dysfunction, burning mouth syndrome, delayed wound healing	Patients with diabetes and associated periodontal disease may experience improved glycemic control with periodontal treatment
	HIV-associated periodontal disease	Linear gingival erythema: linear band of erythema along the free gingival margin Necrotizing ulcerative gingivitis: ulceration and necrosis of gingival interdental papillae, gingival bleeding and pain, halitosis Necrotizing ulcerative periodontitis: gingival ulceration, necrosis, rapid loss of periodontal attachment, edema, pain, spontaneous hemorrhage	In addition to these atypical forms of periodontal disease, patients with HIV also may exhibit more conventional forms of gingivitis and periodontitis

*continued*

*HIV = human immunodeficiency virus.*

\*—Listed in order of most to least commonly encountered within each clinical presentation.

**Table 1. Oral Manifestations of Select Systemic Conditions** (continued)

Clinical presentation	Associated condition*	Oral manifestation	Comments
Periodontal bleeding and inflammation	Thrombocytopenia	Petechiae, purpura, ecchymosis, hemorrhagic bullae, hematomas	Hemorrhage may occur with minor trauma or spontaneously
	Leukemia	Mucosal bleeding, ulceration, petechiae, and diffuse or localized gingival enlargement; secondary infections (e.g., candidiasis, herpes simplex virus infection, periodontal bone loss)	Gingival infiltration by leukemic cells occurs most often in acute monocytic leukemia and acute myelomonocytic leukemia
Dental erosion	Gastroesophageal reflux disease	Water brush, xerostomia, burning sensation, halitosis, palatal erythema, dental erosion	Dental erosion may require dental restorative treatment Other oral findings usually will resolve with medical management of gastroesophageal reflux disease
	Bulimia and anorexia	Dental erosion, xerostomia, increased caries rate, sialadenosis (especially bilateral parotid enlargement)	Dental erosion may require dental restorative treatment Xerostomia and sialadenosis usually resolve on normalization of nutritional status; sialogogues may help

\*—Listed in order of most to least commonly encountered within each clinical presentation.

caused by *Candida albicans* or *Staphylococcus aureus*), which appears as erythema, fissuring, and crusting at the corners of the mouth.

**ORAL LESIONS**

In addition to ulcerative or erosive lesions, white lesions or nonspecific erythema may be indicative of systemic disease.

*Lupus erythematosus.* The reported frequency of oral lesions ranges from 8 to 45 percent in patients with systemic lupus erythematosus and from 4 to 25 percent in patients with discoid lupus erythematosus.<sup>8</sup> Descriptions of oral lesions in lupus erythematosus vary greatly. The classic presentation is the oral discoid lesion, characterized by a well-demarcated zone of erythema, atrophy, or ulceration surrounded by white, radiating striae. These lesions appear similar to those found in patients with erosive lichen planus.<sup>6</sup> Variations include honeycomb plaques (silvery white, scarred plaques), raised keratotic plaques (verrucous lupus erythematosus; *Figure 2*), and nonspecific erythema<sup>9</sup> (*Figure 3*). Purpura, petechiae, or irregularly shaped ulcers also are possible. Discoid lesions like those typically found elsewhere on sun-exposed skin may be found on the lip vermillion. Cheilitis may be evident as well.<sup>10</sup>

Oral lesions in patients with systemic lupus erythematosus typically resolve with systemic immunosuppressive



**Figure 1.** Atrophic glossitis in a patient with pernicious anemia. Mucosal atrophy appears as smooth, bald areas devoid of lingual papillae on the dorsal tongue.

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**Figure 2.** Keratotic, rough-surfaced plaque (verrucous lupus erythematosus) in a patient with discoid lupus erythematosus. Note the adjacent nonspecific erythema on the palatal mucosa.



**Figure 3.** Discrete red and white plaque on the hard palate in a patient with discoid lupus erythematosus.

therapy. For patients with limited skin or oral mucosal disease, topical corticosteroids or systemic antimalarial drugs are appropriate.<sup>11</sup>

*Pemphigus vulgaris.* Oral lesions are the initial manifestation in 50 to 80 percent of patients with pemphigus vulgaris, and may precede skin lesions by one year or more.<sup>12</sup> Patients typically experience painful, diffuse oral ulceration (*Figure 4*). It is difficult to observe intact blisters intraorally because the lesions rupture easily. However, a positive Nikolsky sign (i.e., blister formation on normal-appearing mucosa or skin with application of firm lateral pressure) may be elicited. Extraoral findings may include cutaneous blisters, crusted skin erosions, and bilateral conjunctivitis. The differential diagnosis for chronic, multifocal oral ulceration includes other systemic immune-mediated conditions, such as erosive lichen planus and benign mucus membrane pemphigoid (*Table 1*).

Oral lesions usually resolve with systemic immunosuppressive therapy, but may be slower to resolve compared with extraoral lesions.

*Crohn disease.* The reported prevalence of oral lesions in Crohn disease ranges from 0.5 to 20 percent.<sup>13,14</sup> Oral lesions may precede abdominal symptoms and do not necessarily correlate with intestinal disease activity<sup>15,16</sup> (*Table 1*). Descriptions of oral lesions in Crohn disease vary widely. Some characteristic abnormalities include diffuse swelling, cobblestone appearance of the mucosa, localized mucogingivitis, and deep linear ulceration. The swelling usually is persistent, firm, and painless, and tends to involve the lips, buccal mucosa, and facial soft tissues. The deep linear ulcers often occur at the depth of the buccal vestibule and may be surrounded by hyperplastic margins (*Figure 5*). Secondary fibrosis



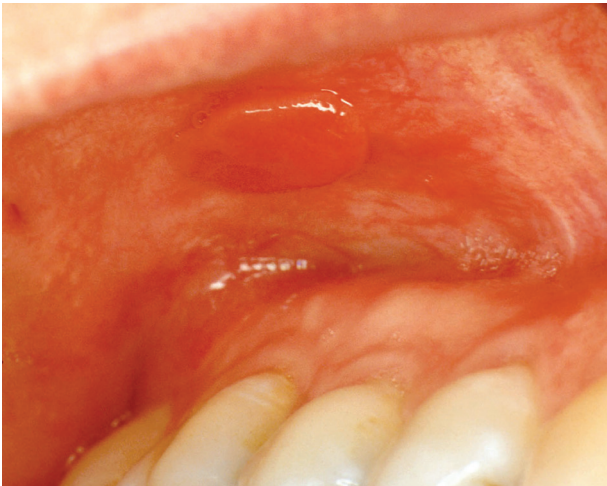
**Figure 4.** Diffuse ulceration of the buccal mucosa in a patient with pemphigus vulgaris.



**Figure 5.** Linear ulceration at the depth of the left mandibular buccal vestibule in a patient with Crohn disease.

can produce tissue tags, polyps, or nodules (*Figure 6*). An uncommon presentation is pyostomatitis vegetans, characterized by serpentine pustules that coalesce in a “snail track” pattern.

Oral lesions usually resolve with systemic treatment of underlying intestinal disease. However, persistent ulcers



**Figure 6.** Erythematous, polypoid nodule of the superior buccal mucosa in a patient with Crohn disease.



**Figure 7.** Diffuse, ill-defined melanin pigmentation of the buccal mucosa in a patient with Addison disease. This patient also exhibited bronzing of the skin.

may require application of topical corticosteroids, and persistent swelling may respond to intralesional injection of triamcinolone acetonide (Kenalog).<sup>16-18</sup>

**CHANGES IN PIGMENTATION**

Hyperpigmentation of the oral mucosa (i.e., Addison disease) may be the first manifestation of primary adrenal insufficiency<sup>19</sup> (Figure 7). However, diffuse melanin pigmentation of the oral mucosa is a nonspecific finding, and numerous other conditions may be considered in the differential diagnosis (e.g., ethnic pigmentation, tobacco-related pigmentation, medication-related pigmentation, neurofibromatosis 1, McCune-Albright syndrome, Peutz-Jeghers syndrome).



**Figure 8.** Gingivitis with diffuse gingival erythema, swelling, and blunted interdental papillae in a patient with diabetes mellitus. Oral examination showed increased periodontal probing depths, and radiographic examination showed severe alveolar bone loss. These findings are indicative of underlying periodontitis.

Primary adrenal insufficiency may occur in association with the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome. In this condition, chronic mucocutaneous candidiasis develops in childhood in conjunction with hypoparathyroidism and other findings. In the oral cavity, candidiasis can present as pseudomembranous (white plaques that can be wiped away), hyperplastic (white plaques that cannot be wiped away), or erythematous.

**Periodontal Bleeding and Inflammation  
DIABETES**

There is a strong association between diabetes and periodontal diseases, including gingivitis (gingival inflammation) and periodontitis (inflammation and destruction of the periodontal ligament and alveolar bone that hold teeth in place; Figure 8). Notably, there is emerging evidence of a two-way relationship—diabetes can lead to poor periodontal health, and poor periodontal health can make it difficult to control diabetes.<sup>20</sup> Patients with poorly controlled diabetes experience significantly greater periodontal attachment loss compared with patients with well-controlled diabetes or those without diabetes.<sup>21,22</sup> In addition, treatment for periodontitis may improve glycemic control; however, further studies are needed to confirm these findings.<sup>23-28</sup> Furthermore, severe periodontal disease may be a strong predictor of various diabetic complications, including nephropathy, stroke, transient ischemic attack, angina, myocardial infarction, and heart failure.<sup>29,30</sup> The International Diabetes Federation recommends that primary care for diabetes should include annually inquiring about symptoms of gum disease

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(e.g., bleeding when brushing, swollen or red gingiva) and encouraging regular evaluation and treatment by a dental health professional.<sup>31</sup>

Additional oral or head and neck findings may include candidiasis, sialadenosis (bilateral noninflammatory enlargement of the parotid glands), generalized atrophy of the tongue papillae, taste dysfunction, salivary dysfunction, burning mouth syndrome, and delayed wound healing.

### THROMBOCYTOPENIA

In many cases, thrombocytopenia (platelet count usually less than  $50 \times 10^3$  per  $\mu\text{L}$  [ $50 \times 10^9$  per L]) may be detected initially because of oral lesion development. Minor trauma to the oral mucosa during routine function (such as chewing or swallowing) may produce various types of hemorrhagic lesions, including petechiae, purpura, ecchymosis, hemorrhagic bullae, and hematoma formation (*Figure 9*). In addition, gingival bleeding may result from minor trauma or occur spontaneously.

### LEUKEMIA

Oral manifestations of leukemia may include mucosal bleeding, ulceration, petechiae, and diffuse or localized gingival enlargement (*Figure 10*). Gingival infiltration by leukemic cells occurs most often in acute monocytic leukemia and acute myelomonocytic leukemia.<sup>32</sup> The gingiva may feel boggy and appear hemorrhagic with or without concurrent ulceration. Impaired immune function can lead to various secondary oral complications, such as candidiasis, herpes simplex virus infection, and periodontal bone loss.

Patients receiving treatment for leukemia may develop opportunistic infection and chemotherapy-related oral mucositis. Various preventive protocols (e.g., acyclovir [Zovirax], nystatin, chlorhexidine [Peridex], oral hygiene care) may be used to minimize these complications.<sup>33-38</sup>

### Dental Erosion

#### GASTROESOPHAGEAL REFLUX DISEASE

Potential oral findings in patients with gastroesophageal reflux disease include water brash (periodic increase in salivation), xerostomia (dry mouth), burning sensation, halitosis, palatal erythema, and dental erosion. The erosion pattern in patients with gastroesophageal reflux disease tends to favor the occlusal surfaces of the mandibular posterior teeth and the lingual surfaces of the maxillary anterior teeth (*Figure 11*). Affected teeth exhibit worn, shiny enamel; they may appear yellow and become sensitive to temperature changes as the



**Figure 9.** Idiopathic purpura and hemorrhagic bullae on the palatal mucosa in a patient with thrombocytopenia.



**Figure 10.** Diffuse, hemorrhagic enlargement of the gingiva in a patient with acute monocytic leukemia.



**Figure 11.** Erosion of the enamel on the lingual surfaces of the maxillary anterior teeth in a patient with gastroesophageal reflux disease. The teeth appear yellowish from exposure of the underlying dentin. The erosion in this patient was so severe that pulpal exposure developed in the left maxillary central incisor and root canal therapy was performed. (Temporary restoration covers the endodontic access site.)

underlying dentin becomes exposed. Dental erosion is irreversible and may require dental restorative treatment depending on severity; other oral findings usually will resolve with medical management of gastroesophageal reflux disease.

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References	Comments
In patients with Crohn disease, oral lesions that persist despite systemic treatment of underlying intestinal disease may respond to topical or intralesionally injected corticosteroids.	C	16-18	Based on case series and usual practice
Treatment of periodontitis in patients with diabetes mellitus can lead to improved glycemic control.	B	23-28	Findings based on two RCTs, three meta-analyses, and one uncontrolled comparison study Improvement in glycemic control found in all studies, although not all reached statistical significance
Various preventive protocols (e.g., acyclovir [Zovirax], nystatin, chlorhexidine [Peridex], oral hygiene care) may be considered to minimize secondary oral opportunistic infection and chemotherapy-related oral mucositis in patients receiving treatment for leukemia.	B	33-38	Based on one meta-analysis of herpes simplex virus prevention with acyclovir; two meta-analyses of mucositis prevention with chlorhexidine; one RCT and one randomized crossover trial examining mucositis prevention with chlorhexidine and oral care; and one RCT examining mucositis and candidiasis prevention with chlorhexidine, oral hygiene care, iodopovidone, and nystatin

RCT = randomized controlled trial.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.



**Figure 12.** Erosion of the enamel on the lingual surfaces of the maxillary anterior teeth in a patient with bulimia. As the enamel thins, the teeth appear yellowish because of exposure of the underlying dentin.

### BULIMIA AND ANOREXIA

Potential oral or head and neck findings of bulimia and anorexia include dental erosion, xerostomia, increased rate of caries, and sialadenosis. Vomiting exposes teeth to acidic gastric contents, which leads to enamel erosion. The erosion pattern tends to involve the lingual surfaces of the maxillary anterior teeth (Figure 12) and, in severe cases, the buccal surfaces of the posterior mandibular teeth.<sup>39</sup> Patients may have dental sensitivity to cold or sweet stimuli. Xerostomia may be caused by medications often used by patients with bulimia or anorexia (e.g., antidepressants, diuretics, laxatives), as well as by vomiting and excessive exercise.<sup>40</sup> Because the buffering and cleansing properties of saliva are

important for prevention of tooth decay, xerostomia leads to increased caries risk. Additionally, sialadenosis affects approximately 25 percent of patients with bulimia; bilateral parotid enlargement is the most common presentation.<sup>41</sup>

Dental erosion is irreversible and may be addressed by dental restorative procedures. Xerostomia and sialadenosis usually resolve after normalization of nutritional status, although sialogogues may also be helpful.<sup>42</sup>

Figures 5, 6, and 12 provided by Michele C. Ravenel, DMD.

Figure 10 provided by Michael W. Tabor, DDS.

Figure 11 provided by John McDowell, DDS, MS.

### The Authors

ANGELA C. CHI, DMD, is an associate professor in the Department of Stomatology, Division of Oral Pathology, in the College of Dental Medicine at the Medical University of South Carolina in Charleston.

BRAD W. NEVILLE, DDS, is a distinguished university professor in the Department of Stomatology, Division of Oral Pathology, in the College of Dental Medicine at the Medical University of South Carolina.

JOE W. KRAYER, DDS, is an assistant professor in the Department of Stomatology, Division of Periodontics, in the College of Dental Medicine at the Medical University of South Carolina.

WANDA C. GONSALVES, MD, is an associate professor in the Department of Family Medicine in the College of Medicine at the Medical University of South Carolina.

Address correspondence to Angela C. Chi, DMD, Medical University of South Carolina, 173 Ashley Ave., MSC 507, Charleston, SC 29425 (e-mail: [chi@muscc.edu](mailto:chi@muscc.edu)). Reprints are not available from the authors.

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