

Oral Manifestations of Systemic Diseases

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Abstract

Many systemic diseases have oral manifestations. The oral cavity might well be thought of as the window to the body because oral manifestations accompany many systemic diseases. These oral manifestations must be properly recognized if the patient is to receive appropriate diagnosis and referral for treatment. We have reviewed a series of recent articles and summarized known and newly described oral manifestations of several systemic diseases. The lesions of the oral mucosa, tongue, gingiva, dentition, periodontium, salivary glands, facial skeleton, extraoral skin and other related structures caused by some of the more common systemic diseases are highlighted.

Key Words: Oral manifestations, anemia, leukemia, rheumatology, neoplasm, metastasis, diabetes mellitus, uremia, Crohn's disease, endocrinology.

Hematologic Diseases

Anemia

Iron deficiency anemia is the most common hematologic disorder (1). Oral manifestations include atrophic glossitis, mucosal pallor, and angular cheilitis. Atrophic glossitis, flattening of the tongue papillae, resulting in a smooth and erythematous tongue may mimic migratory glossitis. Migratory glossitis, also known as geographic tongue, is a condition of unknown etiology that affects 1B2% of the population. It results in lesions on the tongue that are erythematous, non-indurated, atrophic, and bordered by a slightly elevated, distinct rim that varies in color from gray to white. In atrophic glossitis, these areas do not have a white keratotic border and they increase in size rather than changing position. In more severe cases, the tongue may be tender. Angular cheilitis, occurring at the commissures of the lips, is caused by *Candida albicans* infection (2) resulting in reddening and cracking, and some level of discomfort. The manifestations of Plummer-Vinson syndrome also include dysphagia due to pharyngoesophageal ulcerations. Oral complications seen with sickle cell anemia include mandibular salmonella osteomyelitis which results in areas of osteoporosis and erosion followed by osteosclerosis. Anesthesia or paresthesia of the mandibular nerve, and asymptomatic pulpal necrosis may also occur (3). These conditions are exacerbated when marrow proliferation is intense. Associated dentofacial deformities are characterized radiographically by areas of decreased densities and coarse trabecular pattern most easily seen between the root apices of the teeth and the inferior border of the mandible. Osteosclerosis may follow thrombosis and infarction.

Leukemia

Oral complications of leukemia frequently include gingival hypertrophy, petechiae, ecchymosis, mucosal ulcers, and hemorrhage (4). Less frequently, mental nerve neuropathy, called "numb chin syndrome," may be the presenting complaint (5). Palatal ulcerations and necrosis may herald the presence of mucormycosis of the nasal cavity and the paranasal sinuses (6). Sixteen per cent and 8% of children with acute leukemia are reported to have gingivitis and mucositis respectively (7). Bacterial infections of the oral cavity, which may be a source of septicemia, are also common in these patients and must be recognized early and treated aggressively. Treatment of leukemia with chemotherapeutic agents can result in reactivation of herpes simplex virus (HSV) leading to oral mucositis. Oral mucositis can also occur from chemotherapy without an HSV component, since thinning of the surface layer of mucosa and/or bone marrow suppression allows for opportunistic organisms to invade the mucosa (Fig. 1).

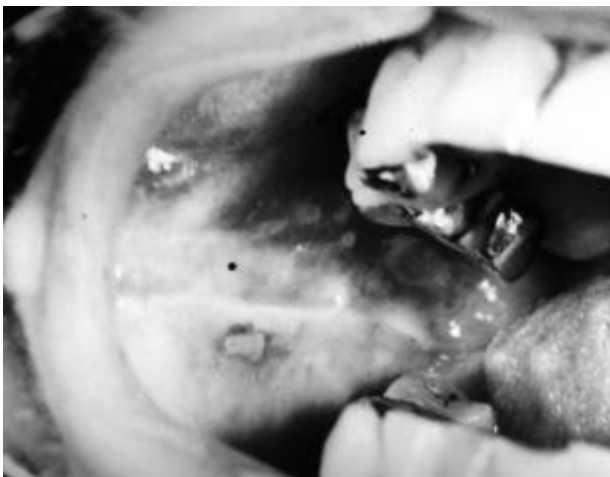


Fig. 1. Buccal mucosa mucositis with ulceration secondary to chemotherapy.

Multiple Myeloma

When multiple myeloma involves the oral cavity, it is usually a late secondary manifestation of lesions within the jaws, most often the mandible. These lesions cause swelling of the jaws, pain, numbness, mobility of teeth, and pathologic fractures (8). Punched out lesions of the skull and jaw are characteristic radiographic findings. The incidence of jaw involvement in multiple myeloma averages about 15% (9B13). Since multiple myeloma results in immunosuppression, a variety of infections may be present, including oral hairy leukoplakia and candidiasis (14, 15). Amyloid deposits in the tongue can lead to macroglossia (16).

Rheumatological Diseases

Sjogren's Syndrome

Sjogren's syndrome (SS) patients frequently present with xerostomia and parotid gland enlargement (17). SS is often associated with rheumatoid arthritis. In one study (18), 88% of the patients with SS had abnormal submandibular/sublingual salivary flow, and 55% had abnormal parotid flow. Enlargement of the parotid or submandibular gland is apparent in 35% of patients with SS (19). Xerostomia can be associated with fissured tongue, depapillation and redness of the tongue, cheilitis, and candidiasis (Fig. 2).



Fig. 2. Characteristic fissuring of tongue and loss of papillae as seen in xerostomia.

Swallowing and speaking may become difficult due to persistent xerostomia. Bacterial parotitis, which is usually accompanied by fever and purulent discharge from the gland, may also occur. There is an increase in dental caries, especially around the cervical region of the teeth (20). It is important to recognize SS quickly and refer the patient to a dentist since dental caries can progress rapidly (21). Diagnosis is usually confirmed by labial minor salivary gland biopsy. Histologically, there is a periductal lymphocytic infiltrate.

Scleroderma (Progressive Systemic Sclerosis)

Scleroderma is a chronic disease characterized by diffuse sclerosis of the skin, gastrointestinal tract, heart muscle, lungs, and kidney (22). The lips of a patient with scleroderma may appear to be pursed due to constriction of the mouth aperture, thus making it difficult to open the mouth.

Stomatognathic function, denoting the mouth and jaws collectively, is also difficult. Esophageal fibrosis leads to lower esophageal sphincter hypotension and gastroesophageal reflux in 75% of scleroderma patients (23). Symptoms include dysphagia and heartburn. The oral mucosa appears pale and feels rigid. Multiple telangiectasias may be present (24). The tongue can lose mobility and become smooth in appearance as the palatal rugae flatten. Salivary hypofunction can also be present, although usually to a lesser degree than in Sjogren's syndrome. Radiographically, the periodontal ligament space is often thickened.

Lupus Erythematosus (LE)

Lupus erythematosus occurs as discoid lupus erythematosus (DLE) and systemic lupus erythematosus (SLE) (25). Oral lesions occur in 25-50% of patients with DLE versus 7-26% of patients with SLE (26, 27). In DLE, these lesions usually begin as an irregular whitish area that extends peripherally (Fig. 3).



Fig. 3. Buccal mucosa exhibiting irregular white areas of ulceration as seen in discoid lupus erythematosus.

As they extend, the central area may become red and ulcerated while the border remains elevated and hyperkeratotic. Oral lesions of lichen planus are similar to those of DLE both clinically and histologically (28). Strict histologic criteria must be applied to distinguish one from the other (28).

Oral or nasopharyngeal ulceration is recognized as a major diagnostic manifestation of SLE by the American Rheumatism Association Committee on Diagnostic and Therapeutic Criteria (29). These ulcerations are generally painless and often involve the palate (26). Purpuric lesions such as ecchymoses and petechiae may also occur. In up to 30% of patients with SLE, salivary gland involvement may occur concomitantly, leading to secondary Sjogren's syndrome and severe xerostomia (30).

Rheumatoid Arthritis

The temporomandibular joint (TMJ) is often involved in rheumatoid arthritis (31). This is usually characterized by erosions in the condyle leading to a decreased range of motion of the mandible with pain upon movement. Oral dryness and salivary gland swelling can also be found in patients with rheumatoid arthritis. These patients can also develop secondary Sjogren's syndrome (32). Limited jaw function may necessitate TMJ reconstruction once the active disease is controlled. Prosthetic joints may provide an interim solution for those patients severely affected with rheumatoid arthritis.

Oncological Diseases

Metastatic Disease

Oral metastatic tumors can occur in the soft or hard tissues (33). They are uncommon, however, comprising only about 1% of oral malignant neoplasms. Tumors metastasize more often to the jaws than to oral soft tissue. Tumors of the jaw are usually detected when the patient presents with swelling, pain, paresthesia, or when they spread to the soft tissue. Overall, the most common primary site for metastases to the jaw is the breast, whereas the lung is the most common primary site for oral soft tissue metastases (34). In men, the lung is the most common primary site for both jaw and soft tissue metastases. The molar region of the mandible is the most common bony site for metastasis. In about 30% of cases, the oral metastatic lesion is the first indication of an undiscovered malignancy (34).

The early manifestation of metastases to the attached gingiva may resemble one of three more common hyperplastic reactive lesions of the gingiva and must be evaluated by biopsy. The peripheral ossifying fibroma generally presents as a small, well-demarcated, focal mass with a sessile or pedunculated base on the free margin of the gingiva (Fig. 4).



Fig. 4. Palatal peripheral ossifying fibroma originating between second maxillary premolar and first maxillary molar.

These pale pink to red lesions can be quite large (35) and can occur at any age (peak incidence is 20 years of age). The pyogenic tumor or "pregnancy tumor" which has a propensity to bleed, also occurs on the attached gingiva. This lesion is usually small (less than 1 cm in diameter), red, and ulcerated. Another small, well-demarcated, dark red focal mass attached to the gingiva with a sessile or pedunculated base is the peripheral giant cell granuloma (36). In summary, it is important to recognize that various tumors do metastasize rarely to the oral cavity.

Langerhans' Cell Histiocytosis (Histiocytosis X)

Langerhans' cell histiocytosis (LCH) represents a spectrum of clinical disorders ranging from a highly aggressive and frequently fatal leukemia-like disease affecting infants to a solitary lesion of bone (37). The presence of alveolar bone loss in young children with precocious exfoliation of primary teeth should suggest the possibility of LCH (38). LCH can also occur in adolescents and adults. Of the bones of the jaw, the mandible is the most frequently involved. The presenting signs usually include pain, swelling, ulceration, and loose teeth. Radiographically, the teeth often appear to be "floating in air" surrounded by large radiolucent regions. This is due to rapid alveolar bone loss. The term "eosinophilic granuloma of bone" is used when a solitary lesion is found, but multiple lesions may develop later (Fig. 5).



Fig. 5. Panoramic radiograph in this patient with Langerhans' cell histiocytosis showing multiple radiolucencies of the mandible.

Endocrine Disorders

Diabetes Mellitus

There are many oral manifestations of diabetes mellitus, some having been described as early as 1862. Generally, the symptoms are more severe, and the rate of their progression appears to be more rapid in those patients who have poorly controlled insulin-dependent diabetes (IDDM) than in those who are well-controlled with insulin or in those with non-insulin-dependent diabetes (NIDDM).

Studies indicate that age, duration of disease, and degree of metabolic control may play a more important role in the oral manifestations of diabetes rather than whether the type of disease is IDDM or NIDDM (39). About a third of diabetic patients complain of xerostomia, which may be due to an overall diminished flow of saliva and an increased salivary glucose level (40). Concomitant diffuse, nontender, bilateral enlargement of the parotid glands, called diabetic sialadenosis, may be seen in patients. This process may not be reversible, even after carbohydrate metabolism has been well controlled. Altered taste and burning mouth syndrome have also been reported in association with poorly controlled diabetes. Xerostomia may act as a predisposing factor in the development of oral infections. Dry and damaged mucosa is more susceptible to opportunistic infections by *Candida albicans* (40). Erythematous candidiasis presents as central papillary atrophy of the dorsal tongue

papillae and has been reported in up to 30% of diabetic patients. Mucormycosis and benign migratory glossitis have also been shown to have a higher incidence in IDDM than in the general population.

It has been well documented that there is a higher incidence of dental caries in patients with poorly controlled diabetes. This has been attributed to increased glucose levels in the saliva and crevicular fluid (41). Poor healing, xerostomia with subsequent increased accumulation of plaque and food debris, higher susceptibility to infections, and pronounced hyperplasia of attached gingiva all contribute to the increased incidence of periodontal disease in diabetics (40).

Hypoparathyroidism

Decreased secretion of parathyroid hormone (PTH) may occur following iatrogenic surgical removal of the parathyroid glands, as well as from autoimmune destruction of the parathyroid tissue. Rare syndromes such as DiGeorge syndrome and the endocrine-candidiasis syndrome may be associated with this condition (42). Hypocalcemia follows the loss of parathyroid hormone. Chvostek's sign, a significant finding associated with hypocalcemia, is characterized by twitching of the upper lip when the facial nerve is tapped just below the zygomatic process. A positive response suggests a latent degree of tetany. If the hypoparathyroidism develops early in life, during odontogenesis or tooth development, a pitting enamel hypoplasia and failure of tooth eruption may occur (43). The presence of persistent oral candidiasis in a young patient may signal the onset of endocrine-candidiasis syndrome. Hypoparathyroidism may be only one of several endocrine deficiencies associated with this condition.

Hyperparathyroidism

Loss of the lamina dura surrounding the roots of the teeth is an early manifestation of hyperparathyroidism, with alterations in the jaw trabecular pattern characteristically developing next. There is a decrease in trabecular density, and blurring of the normal pattern produces a "ground glass" appearance on the radiograph (44). With persistent disease, other osseous lesions develop, such as the so-called "brown tumor" of hyperparathyroidism. The name of this lesion is derived from the color of the gross tissue specimen, which is usually dark reddish-brown due to the abundant hemorrhage and hemosiderin deposition within the tumor. Radiographically, these lesions are unilocular or multilocular well-demarcated radiolucencies which commonly affect the mandible, clavicle, ribs and pelvis. They may be solitary, but more often are multiple. The long-standing lesions may produce significant cortical expansion. Histologically, the lesion is characterized by a proliferation of extremely vascular granulation tissue which serves as a background for numerous multi-nucleated osteoclast-type giant cells. This is identical to another lesion known as the central giant cell lesion of the jaws.

Hypercortisolism

Hypercortisolism, or Cushing's syndrome, results from a sustained increase in blood glucocorticoid levels. This can be due either to corticosteroid therapy or to endogenous overproduction from the adrenal gland(s). Excess adrenocorticotrophic hormone (ACTH) from a pituitary tumor also causes hypercortisolism and Cushing's disease. Fatty tissue deposition in the facial area is described as the characteristic "moon" facies. (45). The patient may also present with a variable degree of facial hirsutism. Pathological fractures of the mandible, maxilla or alveolar bone may occur

upon low impact trauma due to osteoporosis. Healing of fractures as well as healing of alveolar bone and soft tissues after dental extractions is also delayed.

Hypoadrenocorticism

Hypoadrenocorticism results from insufficient production of adrenal corticosteroid hormones caused by destruction of the adrenal cortex, a condition known as primary hypoadrenocorticism or Addison's disease. This is usually due to autoimmune destruction, but can also result from infection such as tuberculosis, metastatic tumor, amyloidosis, sarcoidosis or hemochromatosis. Secondary hypoadrenocorticism develops because of inadequate functioning of the pituitary gland. Orofacial manifestations include a "bronzing" hyperpigmentation of skin, especially predominant in sun-exposed areas and over pressure points. This is caused by increased levels of beta-lipotropin or adrenocorticotrophic hormone (ACTH), both of which can stimulate melanocytes. These skin changes are often preceded by oral mucosal melanosis (46). The diffuse or patchy brown macular pigmentation most commonly occurs on the buccal mucosa, but can also occur on the floor of the mouth, ventral tongue, and other areas of the oral mucosa.

Renal Disease

Uremic Stomatitis

Uremic stomatitis has become relatively rare, seen mostly in cases of undiagnosed and untreated chronic renal failure. Painful plaques and crusts are distributed predominantly on the buccal mucosa, the floor or dorsum of the tongue, and the floor of the mouth. The incidence has decreased because of readily available dialysis centers throughout the country. The most commonly accepted mechanism behind the development of uremic stomatitis is irritation and chemical injury of mucosa by ammonia or ammonium compounds formed by the hydrolysis of urea in saliva by urease. This occurs when the intraoral concentration of urea exceeds 30 mmol/L (47). Hemorrhagic diathesis from inhibited platelet aggregation may also play a role due to local hemorrhage, resulting in decreased vitality and viability of the affected tissues, thus allowing bacterial infection.

There are two predominant types of uremic stomatitis (47). In Type I, there is a generalized or localized erythema of the oral mucosa and a thick gray pseudomembranous exudate which does not leave a bleeding or ulcerated base when removed. Additional findings may include pain, burning, xerostomia, halitosis, gingival bleeding, dysgeusia, or candidal infection. Type II leaves ulceration if the pseudomembranous film is removed. This type may indicate a more severe form of stomatitis, secondary infection, anemia or underlying systemic hematologic disturbances caused by renal failure. Histologically, both types of uremic stomatitis show evidence of an intense inflammatory process with heavy polymorphonuclear leukocytic infiltration and necrosis of the oral mucosa. Bacterial colonization is most commonly associated with *Fusobacterium*, spirochetes, or *Candida*.

Gastrointestinal Diseases

Crohn's Disease

In 1969, oral manifestations of Crohn's disease were first described as being identical to those occurring in the intestinal mucosa. Histologically, these lesions feature non-necrotizing granulomas in the submucosa, composed of multinucleated Langerhans' giant cells, epithelioid cells, lymphocytes, and plasma cells. These granulomas may be of various sizes and depths in the submucosa and their

incidence varies from 10B99% (48, 49). Sometimes these granulomas can be found bulging into or within the lumina of lymphatics, a phenomenon known as “endovasal granulomatous lymphangitis” (49).

Clinically, these patients present with diffuse swelling of one or both lips with associated angular cheilitis, and “cobblestoning” of the buccal mucosa with hyperplastic rigid mucosa. Painful linear ulcerations in the buccal vestibule, painless localized swellings within the lips or face, tags attached to the buccal mucosa, fissuring on the midline of the lower lip, and erythematous edematous gingiva may be seen (50). The cervical lymph nodes may be firm and palpable as well. There is no direct time correlation between intestinal and oral lesions. Oral lesions have been documented to precede the intestinal lesions by years, and in some cases are the only manifestation of the disease. The oral lesions only respond to treatment with systemic steroids.

Ulcerative Colitis

Ulcerative colitis has been associated with destructive oral ulcerations resulting from immune-mediated vasculitis (51). These are similar to aphthous ulcers, but appear less frequently than lesions of Crohn's disease. Pyostomatitis vegetans is believed to be an oral manifestation of ulcerative colitis. These multiple painless intraepithelial microabscesses connect in linear or serpentine tracks mostly on the mucosa of lips, soft palate and ventral tongue. Pyostomatitis gangrenosum is the extreme variant with large, long-lasting and destructive ulcers which cause significant tissue scarring (52).

Conclusion

Systemic diseases often present with abnormalities of the structures of the mouth and jaws. Proper diagnosis is essential to initiate the correct treatment. The primary care physician and dentist must be familiar with these problems if their patients are to be well served. We have outlined several of the more common clinical entities in this review article.

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