REVIEW ARTICLE

Systemic Disease Manifestations in the Oral Cavity

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The oral cavity is the window to the body and is often the area where systemic disease first presents itself. The various tissues including lips, tongue, gingiva, mucosal surfaces, dentition and bone are involved in the presentation of disease state. This review introduces an organized structure for the oral examination as well as presenting signs in various parts of the oral cavity. The review is not all inclusive however does address some of the most common, as well as a few of the more rare, disease states seen in both adults and children. A chart is included at the end of the article outlining the various disease states included as well as the area of the oral cavity in which they can be manifested.

INTRODUCTION

The oral cavity reflects the overall status of the body including hydration, and other organs.[1] Signs of systemic disease are often manifested in the oral cavity before the systemic disease itself is suspected. Some changes seen in the oral cavity are disease specific while others may simply increase the clinician's level of suspicion. A well-planned pattern for examination of the oral cavity will help ensure that no areas are unexamined. The progression utilized in this article is examination of the color and pigmentation of the mucosa, inspection of the mucosal surfaces and palate for lesions, evaluation of the tongue, the gingival surfaces and lastly the dentition. Attention must also be paid to the bony structures of mandible and maxilla when completing the physical examination.

Bacteria in the oral cavity can enter the blood stream through small abrasions or trauma due to food, brushing and flossing the teeth, self-inflicted trauma such as biting the tongue or lips or by the use of toothpicks. The bacteria may also be aspirated into the respiratory system leading to pulmonary infections such as pneumonia. The inflammatory response caused by periodontal disease can complicate already existing diseases such as diabetes, heart or kidney disease and also lead to problems with orthopedic implants such as infections or failure.

The most significant diseases indicated as having an oral systemic connection are cardiovascular disease, pulmonary disease, diabetes, orthopedic implant failure and kidney disease. Problems encountered in fetal development have also been associated with oral manifestations. Oral bacteria and periodontal disease are suspected of being contributing factors to the worsening of chronic disease states.

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This article is not designed to be all-inclusive but rather to outline a systemic approach to identification of systemic disease as it presents within the oral cavity.

ORAL MUCOSA

The lips are the portal to the oral cavity. They reflect systemic changes through their tissue structure, color and hydration status. One of the most common viral infections of the oral mucosa is Herpes simplex virus (HSV-1) that leads to herpes labialis or primary herpetic gingivostomatitis. The virus lies dormant in the sensory ganglia and can be reactivated secondary to immunosuppression, stress or trauma. Dry, cracking lips may also be seen in patients with diabetes mellitus. Thin receding lips may be seen in patients with vitamin deficiencies that will be discussed later.

Changes in the color or pigmentation of the oral mucosa may well be the most easily identified change and is a starting point for evaluation. Mucosal pallor can be present with anemia however it can be so subtle that it is difficult to appreciate. Systemic diseases, such as Addison's disease, may change the pigmentation and may be the first indication of primary adrenal insufficiency.[2] (Figure 1) Systemic diseases such as McCune-Albright syndrome, Peutz-Jeghers syndrome and neurofibromatosis type 1 are also accompanied by changes in the melanin pigmentation of the oral cavity. Chronic liver disease can produce changes in the pigmentation of the oral cavity. Serum bilirubin levels greater than 2 – 3 times baseline will produce a yellow color in the thin mucosa of the sublingual are and the soft palate. Changes in oral pigmentation can also occur without relationship to disease such as ethnic related, tobacco-related, dietary intake related and medication-related pigmentation.

The mucosa should be inspected for hydration status as well as any lesions or growths. Ulcerated areas or aphthous lesions are commonly known as canker sores and can develop secondary

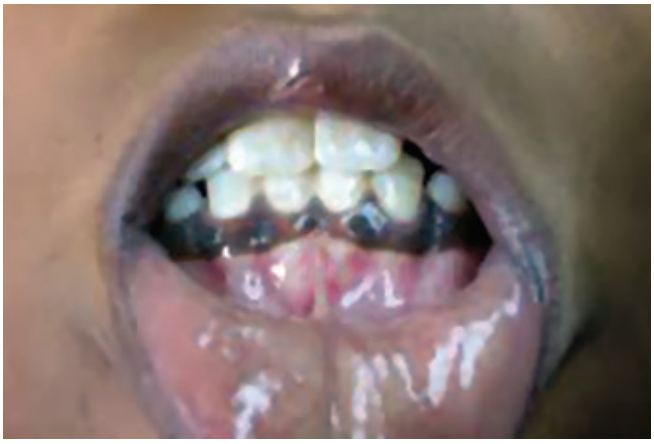

Figure 1: Addison's disease oral manifestation

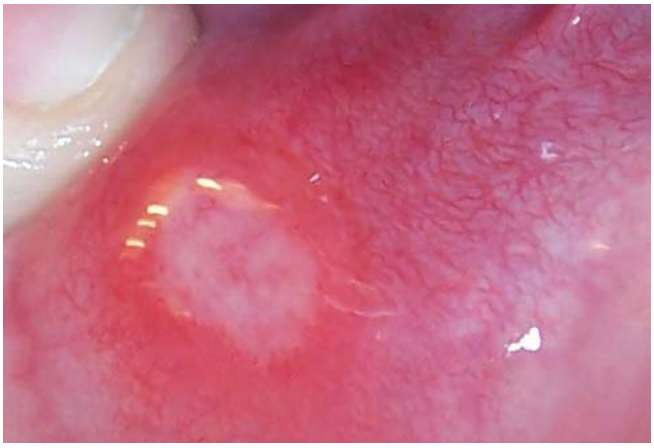

Figure 2: Aphthous ulcer

to trauma. Aphthous lesions may also develop secondary to medications such as non-steroidal anti-inflammatory agents (NSAIDs), nicorandil and angiotensin converting enzyme (ACE) inhibitors although any drug has the potential to cause an aphthous type reaction in the mouth. Use of bisphosphonates has also led to development of ulcers in the oral cavity.

Systemic lupus erythematosus (SLE) presents with oral manifestations in up to 45% of the patients. Oral discoid lesions can vary markedly however the most common presentation is that of a well-demarcated area of erythema with either atrophy or ulceration surrounded by radiating striae. Patients with SLE and discoid lupus can also present with variations of the above lesion such as honeycomb plaques, raised keratotic plaques or non-specific erythema and chelitis. Purpura, petechiae and ulcers are also commonly seen along with lesions on the vermillion border of the lip similar to the discoid lesions seen on other sun-exposed areas of skin. The oral mucosal lesions seen in SLE typically resolve with systemic immunosuppressive treatment although oral preparations of topical corticosteroids can be used to treat smaller intraoral lesions. Similar lesions can be identified in patients with erosive lichen planus.[3]

In Europe and Asia there is an association between hepatitis C and oral lichen planus. This remains controversial in the United States where no significant correlation between the two diseases has been demonstrated.[1]

Blisters inside the oral cavity can be associated with pemphigus. Benign mucus membrane pemphigoid manifests with diffuse painful blisters that may cause ulceration and scarring. The blisters are often difficult to see as they rupture and ulcerate easily. Once systemic therapy is initiated the oral lesions resolve but may take longer to respond than the dermal lesions.

Crohn's disease patients may present with diffuse mucosal swelling and cobble stoning of the oral mucosa. There may also be aphthous-type ulcers, fibrous tissue tags, polyps, nodules, linear ulcerations or mucogingivitis within the oral cavity. (Figure 2) The aphthous ulcers affect 4 to 20 percent of the patients with ulcerative colitis.[4] Pyostomatitisis is often seen in patients with either inflammatory bowel disease or Crohn's disease. The characteristic ulcers are yellowish and serpentine pustules on an erythematous base and are known more commonly as "snail track" ulcers. Systemic treatment for the intestinal disease will lead to resolution of the oral lesions although persistent ulcers may require topical treatment with steroid preparations formulated for use in the oral cavity. Intralesional injections of triamcinolone acetonide (Kenalog®) may be required for persistent focal-type mucosal swelling.

Recurrent, painful aphthous-like ulcers involving the soft palate and oropharynx are often seen in Behçet syndrome. The oral lesions are the most common presentation seen initially in the disease. (Figure 3)

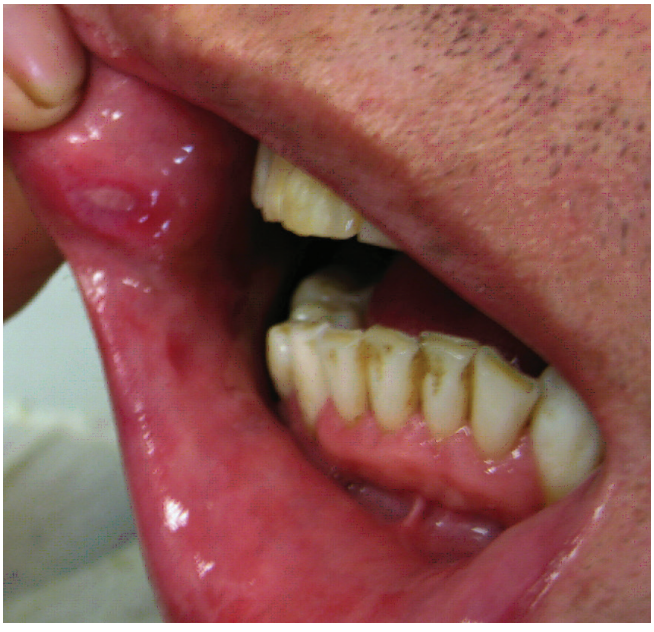

Figure 3: Behcet's disease

Stress is seen in everyday life and may be the only source for painful oral apthous ulcers. There are many theories on the origination of these lesions from trauma due to nighttime bruxism to increased acid production and reflux that are also associated with increased stress.

TONGUE

Examination of the tongue should include the dorsal and ventral surfaces as well as the lateral borders. The dorsal surface of the tongue may appear smooth and devoid of lingual papillae and is described as atrophic glossitis. This is a non-specific finding that can be associated with anemia or vitamin B complex deficiency. Patients may complain of burning pain, tenderness and erythema.

Many disease present with findings on the mucosal surfaces as well as the tongue and such is the case with ulcerative colitis. The oral lesions include not only the aphthous ulcers but also lesions similar to pyoderma gangrenosum have been reported on the tongue. These lesions can show progressive necrosis and deep ulceration. Flares of the lingular lesions as well as the aphthous ulcers can be correlated with exacerbations of the gastrointestinal complaints.

Iron deficiency anemia is one of the most common types of anemia that may present with glossitis. Pernicious anemia is another type of anemia resulting from poor absorption of cobalamin (vitamin B12) presenting with burning and pain of the tongue. It also presents with erythematous spots on the ventral surface of the tongue called "magenta tongue".

Migratory glossitis or erythema migrans is a common finding that is commonly called "geographic tongue" that affects 2% of the population.[5] It presents with non-indurated lesions on the dorsal surface of the tongue that range in color from red to white. The sites can change over a period of time in contrast to atrophic glossitis in which the site or sites do not change.

Plummer-Vinson syndrome, or Paterson-Kelly syndrome, is an iron deficiency anemia that generally presents in women of Scandinavian descent. The oral complications include glossitis, dysphagia, and esophageal webs. Another often seen complication are spoon shaped nails or koilionychia. The significance of the condition is that it is premalignant and related to a high frequency of oral and esophageal squamous cell carcinoma.[6]

Kawasaki disease has replaced rheumatic fever as the primary cause of childhood heart disease in the United States and children younger than 5 years are most commonly affected. Patients present acutely with erythema of the hands and feet, fever, oral erythema, rash and associated temperature greater than 38.5°C (101.3°F) for 5 days. Oral findings include ulceration in the oral cavity, swelling of papillae on the surface of the tongue (strawberry tongue) and intense erythema of the mucosal surfaces. The lips are cracked, cherry red, swollen, and hemorrhagic due to the long-standing high-grade fevers.

Oral candidiasis can also present with the complaint of burning and atrophic glossitis. Oral candidiasis may also present with white plaques in the oral cavity. Angular cheilitis presents with fissures and crusting in the corners of the mouth due to causative organisms such as *Candida albicans or Staphylococcus aureus*. (Figure 4)

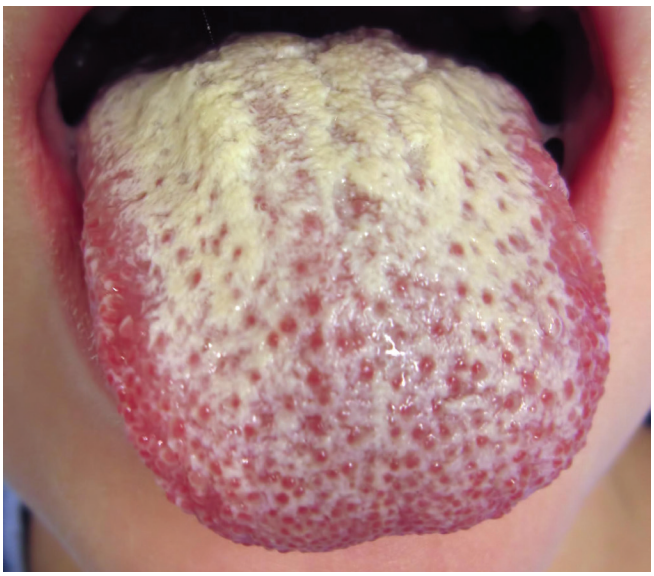

Figure 4: Tongue with candidiasis

Sarcoidosis is a multisystem granulomatous disease with distinct and specific oral manifestations including painless ulcerations of the tongue. They may be keratotic in appearance and have a brown-red or purple discoloration. Lesions of the jaw are reported in approximately 25% of the patients with sarcoidosis.

Leukemia may present in childhood with gingival hypertrophy, petechiae on the palate along with ecchymoses. Oral findings may be the only presenting symptom for patients with leukemia.

GINGIVA

Gingival inflammation and bleeding are associated with many systemic diseases such as diabetes mellitus, HIV (human immunodeficiency virus), thrombocytopenia, Wegener granulomatosis and leukemia. (Figure 5) Periodontal disease in the diabetic patient, when controlled, may improve the overall glycemic control.

A linear band of erythema along the free gingival margin is seen in HIV patients. Necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis can also be seen in the

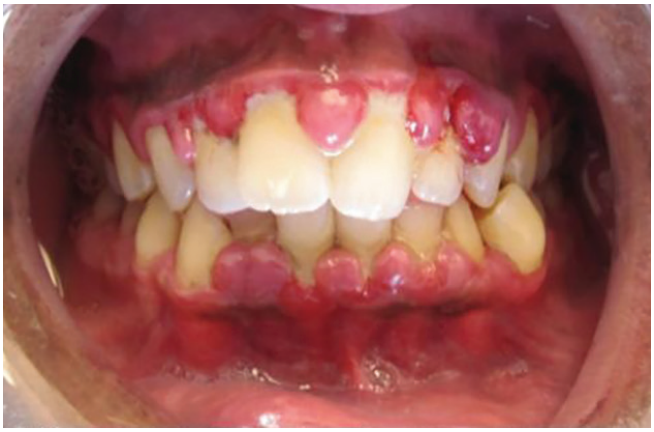

Figure 5: Gingival hyperplasia

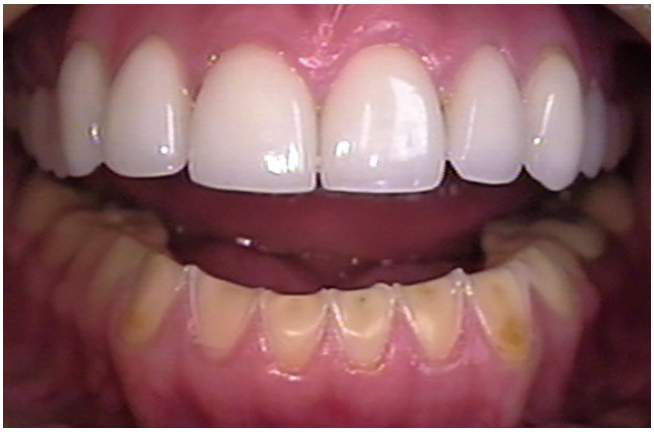

Figure 6: Dental erosions

HIV patient. These conditions present with ulceration and necrosis of the interdental papillae, loss of the supporting bone, gingival bleeding, swelling and often spontaneous hemorrhage. Control of the underlying infection though the use of systemic antibiotics and oral antiseptics will help prevent dental loss.

Patients with thrombocytopenia may demonstrate petechiae, purpura or ecchymosis in the oral cavity. Minor trauma from dentition or food may cause spontaneous hemorrhage. Control of the systemic illness with restoration of a normal platelet count will help control the oral symptomatology.

Acute monocytic and acute myelomonocytic leukemias demonstrate gingival infiltration by leukemic cells leading to mucosal bleeding, ulceration and petechiae. "Strawberry gingivitis" is pathognomonic finding in Wegener's granulomatosis. Usually the buccal surfaces of the gingiva are affected and the lesions are confined to the attached gingival border. There may also be underlying alveolar bone loss and increased tooth mobility.[5]

Non-Hodgkin's lymphoma usually arises in lymph nodes and tends to grow as solid masses. They usually present as a non-painful mass that has been enlarging for months. One of the initial complaints may be that a denture no longer fits correctly and the mass may initially be mistaken for a palatal torus. In the oral cavity, lymphoma usually appears as extranodal disease developing within bone or soft tissues. There may or may not be ulceration of the lesions but they are usually boggy masses in the buccal vestibule, posterior hard palate or gingival tissues.

Gingival hyperplasia can be seen with many medications such as phenytoin, calcium channel blockers and cyclosporine. The affect is primarily on the anterior gingival which can interfere with mastication and speech. Tooth eruption can often be delayed by pressure of the hypertrophic gingival tissue. Stopping the offending medication usually leads to resolution of the hyperplasia however gingival reduction may be necessary in severe cases.

DENTITION

Dental surfaces should be examined for unusual findings of erosion. (Figure 6) Gastroesophageal reflux disease (GERD) with accompanying water brash may cause erosion of the dental surfaces especially on the lingual surfaces of the teeth. Reduction of the pH in the oral cavity below 5.5 can occur with regurgitation of gastric contents and this reduction leads to destruction of the dental enamel.[1] Erosion is most commonly seen on the palatal surfaces of the maxillary dentition. Erosion of the enamel exposes the underlying dentin, which is a softer, more yellow material that is more susceptible to dental carries. The extent of erosion depends on the frequency and the quantity of exposure along with the duration of disease.

Bulimia and anorexia nervosa also produce changes in the dentition due to the frequent purging. Bulimic patients may also have evidence of self-induced trauma to the soft tissues of the oral cavity and posterior pharynx. Anorexic patients, as well as bulimic patients, may be at increased risk for dental caries due to their decreased salivary production and xerostomia although one study did not find a distinct correlation.[7]

Increased dental caries can also be seen in endocrine disorders such as Sjogren Sydrome related to the low salivary volume which decreases the ability of the saliva to dilute the dietary sugars.

Tetracycline exposure during the dental development of the fetus or a child before the age of 8 can cause yellow, brown or grey band formations in the enamel of the teeth. Oral iron preparations in the liquid form can cause grey staining in the enamel that can be removed by professional dental cleaning. Overdose of oral fluoride can result in a white lacy appearance to the incisors and molars however if the overdose is severe pitting of the enamel may occur.

Stress is another systemic condition that can cause great impact on the dental surfaces. Bruxism, grinding or clenching of the teeth subconsciously due to a high level of stress or worry, can cause chipping or fractures in the dental enamel.

ALVEOLAR AND MANDIBULAR INVOLVEMENT

Multiple myeloma usually involves the oral cavity in the later stages of the disease.[5] Bone involvement predominantly of the mandible results in asymmetry of the jaw with swelling, numbness, mobility of the teeth and sometimes pathologic fractures. Multiple myeloma usually presents in the 6th to 7th decade with the initial complaint of bone pain. Jaw involvement is present in 30% of the cases where multiple "punched out" areas can be seen on x-ray.[4]

The most common form of Langerhans cell histiocytosis (LCH), or histiocytosis X, is esosinophilic granulomatous type usually seen in young adults. X-ray studies reveal radiolucent bone lesions in the flat bones such as the posterior jaw. The description of "floating teeth" is used to describe the findings due to the characteristic loss of alveolar bone. Mandibular fractures and displaced teeth are not uncommon with this type of disease. The form of the disease present in infants is referred to as Letterer-Siwe disease. Alveolar bone loss in young children with premature primary teeth loss should raise the suspicion of the possibility of LCH.[5]

As many as 50 to 70% of African Burkitt's lymphoma cases present with tumors in the jaws.[4] Male children are most often affected with the peak age of 7 years being the norm. The tumors cause facial swelling and proptosis. Marked tooth mobility may be present due to bone destruction with the most commonly affected area being the posterior segment of the maxilla. The destruction of bone may lead to early loss of teeth. Younger patients have more bone involvement than older patients.[4]

Metastatic spread to the tissues of the oral cavity and jaw is not uncommon. Breast cancer most often metastasizes to the jaw whereas lung cancer spreads to the soft tissues of the oral cavity. The most common site for spread in the oral cavity is the molar region of the mandible and in almost one-third of reported cases; the oral metastatic lesion is the initial finding of the undiscovered malignancy.[8]

VITAMIN AND MINERAL DEFICIENCIES

The final area of concern regarding systemic disease and oral manifestations is the relationship between vitamin and mineral deficiencies and disease of the oral cavity. Vitamin deficiencies can impact many groups of people such as those following fad diets, those with poor dietary intake due to fast food and junk foods, alcoholics, and those with eating disorders as described in above sections.

It is well known that vitamin A deficiency can lead to blindness in infancy and lead to night blindness in later life. Prolonged deficiency of Vitamin A will also lead to dryness of the oral mucosa and leukoplakia. The mucosa on the lips recedes into the oral cavity and lips are described as "retreating". Angular chelitis is also a common finding in patients with vitamin A deficiency.

Vitamin B12, also known as cobalamin, is utilized in the production of adenosine triphosphate (ATP) that is used as energy in our cells. Angular chelitis is a common sign of vitamin B12 deficiency however it is not specific and can be misleading. This deficiency can also lead to the tongue becoming swollen, dark red and atrophic.

Niacin (Vitamin B3) deficiency also produces changes in the tongue where it is swollen but later becomes atrophic, dark red and smooth. Erosions and aphthous ulcers also appear on the tongue and gingiva.

CONCLUSION

Abnormalities of the oral cavity are seen with many systemic diseases and are often the first signs of disease. Development of an adequate differential diagnosis based on the presenting signs and symptoms is of the highest priority. An early definitive diagnosis often depends on recognition of changes that may be quite subtle in presentation. The primary care physician should be aware of the oral manifestation of systemic disease and prepared to recognize the associated changes in order to initiate correct treatment with the highest standard of care.

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Table 1: Association Between Location in Oral Cavity and Systemic Disease

	Oral Mucosa	Tongue	Gingivia	Dentition	Alveolar Mandibular
Herpes Simplex (HSV1)	•				
Diabetes Mellitus	•		•		
Anemia	•	•			
Addison's Disease	•				
McCune-Albright	•				
Peuz-Jeghers	•				
Neurofibromatosis 1	•				
Chronic liver disease	•				
Aphthous lesions	•				
SLE	•				
Hepatitis C	•				
Pemphigus	•				
Crohn's Disease	•				
Ulcerative colitis		•			
Behcet's syndrome	•				
Kawasaki disease		•			
Angular chelitis	•	•			
Sarcoidosis		•			
Leukemia		•	•		
HIV			•		
Thrombocytopenia			•		
Wegener granulomatosis			•		
Non-Hodgkin Lymphoma			•		
Gastroesophageal Reflux Disease (GERD)				•	
Bulemia/anorexia				•	
Sjogren Syndrome				•	
Stress	•			•	
Multiple myeloma					•
Histiocytosis X					•
Burkitt's Lymphoma					•
Metastasis					•
Vitamin A deficiency	•				
Vitamin B12 deficiency		•			
Vitamin B3 deficiency		•			