ABSTRACT

In current modern medicine, a multitude of diseases have an impact on oral health care services. Oral manifestations in many systemic diseases may be the only evidence or the first sign of such medical conditions. In some other diseases these oral lesions are concurrently accompanied by other medical symptoms. Therefore, familiarity of both physicians and dentists with such manifestations will assist them for early diagnosis and better treatment of the disease. This paper reviews the oral manifestations of systemic conditions in a new way based on their etiology, organ involvement and a new classification i.e., the most common (> 30%), less common (10-30 %) and rare (<10%) diseases.

Keywords: Oral manifestations; Systemic diseases; Oral Health; Diagnosis

Introduction

The oral cavity is an important anatomical location with a role in many critical physiologic processes, such as digestion, respiration and speech. Oral cavity can act as a mirror, which has the potential to reflect the human body’s internal condition. As dentists are concerned with primary diagnosis and treatment of oral diseases, and involved with the non – surgical medical aspects of dentistry to provide optimal health, they have responsibility in recognition of the interaction of oral and systematic health, integration of medical and oral health care and management of medical aspects of those medically compromised patients who need dental procedures. Therefore, they should participate in the treatment of these patients as an active member of teamwork in close association with physicians, to provide medical and dental needs of such patients. Accordingly, many systemic diseases have manifestations in the oro facial regions. Sometimes, the oral lesions of some systemic diseases are the only evidence of the disease. Diseases such as lichen planus, pemphigus vulgaris, herpetic infections and squamous cell carcinoma, may only show oral signs and symptoms. In many other systemic conditions such as koplik’s spots in measles, oral lesions may precede the other manifestations of the disorder. Sometimes, in some disorders such as systemic lupus erythematosus, oral ulcers will appear either simultaneously with the cutaneous lesions or after skin manifestations. Furthermore, in some other diseases, such as vesiculobullous disorders, the oral lesions are similar to the other lesions of the disease and in abnormalities such as malabsorption, oral lesions will be caused by secondary effects of the systemic changes due to the underlying condition and so the resultant oral lesion has different patterns than other lesions of the systemic disease.

In this article, which is kind of unique in its content, we review those systemic diseases, which show orofacial manifestations in a novel way. We start from those systemic conditions with more than 30% prevalence of oral manifestations termed “the most common systemic diseases with oral lesions”. After that we review the less common systemic diseases with 10-30% oral lesions; and end with the ones with rare (less than 10%) oral manifestations respectively (Table 1-3). It is for sure that other researchers have reviewed before oral manifestations of systemic diseases. But to the best of our knowledge, oral manifestations of systemic conditions have not been covered in this way. In many articles, oral manifestations of medical conditions are described according to the type of specific medical diseases such as infectious, dermatologic or hematologic diseases etc.

It is obvious that there are many diseases such as vesiculobullous, dermatological, infectious and others with oral lesions as the only evidence of the disease, but as mentioned before, according to the classification of diseases used in this article, and due to the limitation of the content, we had to skip the names of those diseases. Therefore, according to the tables 1-3, a brief description of the following diseases with explanation of their oral lesions will be presented here.

Systemic disorders with the most common oral manifestations (Table 1):

Sjogren’s syndrome: This common chronic autoimmune disease is characterized by persistent oral and ocular dryness. Involvement of multiple organs may be seen. The oral dryness seen in this disorder is often the main characteristic and can be very severe causing functional disturbances in speaking, eating, taste perception, and swallowing. Also it can evoke pain from mucosal atrophy, candidiasis, rampant caries especially on the smooth surfaces of teeth, difficulty in wearing dentures and bacterial sialadenitis. About 2-5% of these patients may develop mucosal associated lymphoid tissue lymphomas (MALT). Physicians should advise the patients to visit their dentist every 4 months for evaluation of the dental states and prophylaxis programs with fluoride and recommend the use of sugar-free lozenges and xylitol chewing gums to enhance salivary flow. Behcet’s syndrome: The triad of recurring oral, genital and ocular ulcers describes Behcet’s syndrome. The most prominent feature of this multisystemic and lethal disease is the recurrent aphthous like oral ulcers. Aphthous ulcers are round, symmetrical and shallow. No tissue tag is present, which helps to distinguish them from vesiculobullous diseases. A zone of erythema surrounds the whitish base (fibrinous exudates) of the ulceration.
the ulcer. These ulcers mostly affect the soft palate and oropharynx. The cardiovascular, gastrointestinal, musculoskeletal and central nervous systems can also be affected in this disease so early diagnosis and referral of a patient with frequent oral aphthous ulcer is very important.\textsuperscript{19,20}

**Erythema multiform (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN):** EM is an acute, self-limited hypersensitivity reaction that affects the skin and mucosal surfaces. The prevalence of the oral lesions ranges from 23 to 70\% of patients with recurrent EM. Lips are the most common affected sites. The pathognomonic lesions of EM are the serosanguinous lesions on the lips, which make the lips swollen and bloodstained. Widespread ulcerations affect the oral mucosa. Buccal mucosa, tongue, and labial mucosa are the most commonly intra oral affected sites. These lesions are managed symptomatically. Anti-viral drugs help reduce the recurrences of EM associated with herpes simplex infections.\textsuperscript{5,21}

TEN/SJS are also hypersensitivity reactions that are more severe than EM. There is always skin involvement in TEN/SJS. Extensive oral ulcers and hemorrhagic crusts on the lips are the typical oral lesions of TEN/SJS. High dose systemic corticosteroids used for the systemic condition, also regresses the oral ulcers.\textsuperscript{5,21}

**Diabetes:** In poorly controlled diabetes as an endocrine disorder, gingivitis and severe periodontitis is very common. These inflammatory conditions have a two-way relationship with diabetes. Greater attachment loss (periodontitis) is seen in poorly controlled glycemic individuals. Also studies have shown that treating the periodontal disease can improve the glycemic control of diabetic patients.\textsuperscript{14,22,23} Furthermore, virulent orofacial infections, candidiasis in the form of angular cheilits (painful fissures at the corners of mouth), xerostomia due to dehydration, sialosis (swelling of the salivary glands which is usually bilateral and painless), lichen planus (may be related to the drugs used) and burning mouth syndrome are common.\textsuperscript{3,18} Delayed wound healing, generalized atrophy of the tongue papilla and taste dysfunction are also features of poor glycemic control.\textsuperscript{3}

**Addison disease:** This disease is caused by autoantibodies against the adrenal cortex, leading to failure of cortisol and aldosterone secretion. In more than 75\% of the patients, hyperpigmentation of the oral mucosa especially the gingiva can be detected.\textsuperscript{8} But this feature is not specific and other conditions such as physiologic pigmentation, medication or tobacco induced pigmentation, neurofibromatosis type1, McCune-Albright syndrome and Peutz-Jeghers syndrome can also manifest with diffuse oral pigmentation.\textsuperscript{4}

**HIV/AIDS:** AIDS or “acquired immune deficiency syndrome” is caused by the human immunodeficiency virus (HIV). In brief the oral manifestations of AIDS are candidiasis or thrush (94\%), Viral infections (23%) such as herpes simplex, herpes zoster, cytomegalovirus, “hairy leukoplaquia” (white plaques at the lateral borders of the tongue that cannot be wiped away) which is caused by Epstein-Barr virus (14\%), periodontal disease and necrotizing gingivostomatitis (16\%), neoplasms i.e., Kaposi sarcoma, lymphoma (12\%), aphthae (12\%) and salivary gland swelling and xerostomia (2.4\%).\textsuperscript{3,9,15,16}

**Primary Immunodeficiency disorders:** These disorders include...
B-cell defects (e.g. selective IgA deficiency, hypogammaglobulinemia, Job’s syndrome), T-cell defects (e.g. chronic mucocutaneous candidiasis, DiGeorge’s syndrome), combined immunodeficiency disorders (e.g. severe combined immunodeficiency, ataxia-telangiectasia, Wiskott-Aldrich syndrome) and phagocyte deficiencies. Oral and craniofacial pathology are not observed in primary B-cell defects.18 The exception is Job’s syndrome (hyperimmunoglobulinemia E syndrome) which manifests with oral candidiasis (up to 83%), midline defect of the tongue and delayed resorption and exfoliation of the primary teeth.24 The most common presenting oral complaint in patients with T-cell defects are chronic oral candidiasis and herpes simplex virus infections. Combined Immunodeficiency disorders manifest with aphthous-like ulcers, oral candidiasis and HSV infections in the oral cavity.16 Patients with phagocytic cell defects show oral ulcers and candidal infections. Also periodontitis is seen commonly in inherited neutropenia.16,24

Cyclical Neutropenia (CN): CN is a chronic autosomal dominant disorder characterized by a periodic defect in neutrophil production. In the intervals of 19-21 days a reduction of neutrophils from normal to neutropenic levels, which lasts 3-6 days, is seen. Oral ulcers, abscesses and severe periodontitis are among the most common manifestations of this rare disorder.25,26 Monthly subcutaneous injection of Pegfilgrastim 6mg (G-CSF) is a new method of treatment advised for these patients.26

Anemia: Anemia or reduction in hemoglobin concentration is due to the failure of the rate of red blood cell production matching the rate of destruction.27 In severe iron deficiency anemia the first oral manifestation is atrophic glossitis (42%); the flattening of the tongue papilla which leaves a red and bald tongue. Mucosal pallor (33%), burning mouth (8%) oral candidiasis and angular cheilitis (58%) also can be seen.28 In severe cases of iron deficiency anemia or Plummer-Vinson syndrome, dysphagia and occasionally hyperkeratosis lesions of the oral mucosa are added to these complications. Recurrent aphthous ulcers are mostly seen in vitamin B12 and folate deficiency.24,28 In aplastic anemia oral lesions are common and multiple hemorrhages of the orofacial region can be the first clinical signs of the disease. Fungal and viral infections are also common.28

Thalassemia: Thalassemia is a group of inherited hemolytic anemia. The most common orofacial manifestations are maxillary enlargement, bossing of the skull and prominent molar eminence (chipmunk face). This usually results in increased over jet (space between the maxillary and mandibular anterior in horizontal dimension) and spacing of the maxillary teeth.1

Chronic Kidney disease: Chronic renal failure is the progressive decline in renal function due to a reduction in glomerular filtration rate. The medications used for the treatment of this disorder (cyclosporine, calcium channel blockers) can induce gingival enlargement. Other oral manifestations which can be seen in 90% of the patients are bad taste and malodor, xerostomia, periodontitis, uremic stomatitis, oral infections, delayed eruption of teeth in children and bone lesions related to defects of calcium metabolism and secondary hyperparathyroidism.10

Rheumatoid Arthritis (RA): RA is a chronic inflammatory disease of the synovial joints, which can occasionally be accompanied by extra articular manifestations. Secondary sjogren’s syndrome may be seen in up to 50% of the cases.18,31 Temporomandibular joint symptoms are uncommon but radiological changes such as condylar erosions are seen frequently.18

Systemic sclerosis (Scleroderma): A connective tissue disorder characterized by thickening and fibrosis of the skin. The exces colagen deposits of this syndrome in most patients affect the orofacial tissues resulting in restricted facial movement, pinched nose and fish-mouth (limited mouth opening). Multiple telangiectasia can be detected on the lips, hard palate and tongue. In 30% of the patients chicken tongue (tongue stiffness) and resorption of the mandibular angle and coronoid process may be seen. Although the widening of the periodontal ligaments of teeth is uncommon, but it is a characteristic feature of the syndrome. Secondary sjogren’s syndrome also can develop.18,32

Chronic GVHD: Graft versus host disease is a hypersensitivity reaction seen in patients receiving allogeneic hematopoietic cell transplantation. Oral lesions are common and reported in 81.8% of the patients in one study. Extensive and disabling lichenoid reactions, salivary gland dysfunction and reduced mouth opening are the common features of disease.33

Systemic disorders with less common oral manifestations (table 2): Inflammatory bowel disease(IBD): IBD is a chronic, relapsing, inflammatory disorder involving any segment of the gastrointestinal tract from mouth to anus and has two forms; Crohn's disease and ulcerative colitis.34 Oral lesions of Crohn’s disease has been seen in 0.5-20% of the affected individuals.35 Orofacial swelling of the facial soft tissues, lips and buccal mucosa (cobblestoned form) is painless, firm and persistent. Aphthous-like ulcerations in the depth of the buccal vestibule are usually deep and linear and tissue tags surround these ulcers.35 Oral lesions of ulcerative colitis are less common.7 Pyostomatitis Vegetans are “serpentine pustules” that have a “snail tract” pattern and can occur on multiple oral sites, sparing the dorsum of the tongue.3,7 Severity of oral lesions usually reflects the severity of the bowel disease.7

Lupus erythematosus: This multisystemic autoimmune disease can affect the oral mucosa in its cutaneous form (Discoid LE) and its systemic form (SLE). Manifestations include ulcerations (7-40%), erythematous areas, erosions and red and white lesions similar to oral lichen planus.36-38 Locations more frequently affected are buccal mucosa, hard palate and lower lip.18 Rhodus et al. report the following manifestations in SLE patients: Xerostomia (100%), angular cheilitis (87%), glossodynia (87.5%), mucositis (81.3%), periodontitis (93%).37

Von Willebrand disease and Haemophilia: The two most
Table 2: Systemic disorders with less common oral manifestations

<table>
<thead>
<tr>
<th>Disease</th>
<th>Category</th>
<th>Sex Predilection</th>
<th>Age</th>
<th>Main oral finding</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coeliac Disease (gluten-sensitive enteropathy)</td>
<td>Autoimmune GI tract disorder</td>
<td>-</td>
<td>Any age</td>
<td>Enamel defects, Aphthous like ulcers</td>
<td>Incisors</td>
</tr>
<tr>
<td>Leukemia (AML)**</td>
<td>Hematologic malignancy</td>
<td>-</td>
<td>Over 40</td>
<td>Gingival swelling, bleeding and ulceration, Chloroma (localized mass of leukemic cells)</td>
<td>Gingiva, Interdental papilla</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Neuromuscular disorder</td>
<td>F</td>
<td>20-45</td>
<td>Trigeminal Neuralgia, Paresthesia</td>
<td>Perioral muscles</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>Psychopathologic disorder</td>
<td>F</td>
<td>14-25</td>
<td>Sialosis, Enamel erosions</td>
<td>Parotid gland, Palatal aspect of anteriors</td>
</tr>
<tr>
<td>Measles</td>
<td>Infectious Disease</td>
<td>-</td>
<td>childhood</td>
<td>Koplik’s spots</td>
<td>Buccal Mucosa, Lower Lip</td>
</tr>
</tbody>
</table>

common hereditary coagulation abnormalities manifest as bleeding episodes from mucous membranes, excessive hemorrhage after dental treatment and additional mucosal purpura, in the oral cavity.18,28 Bleeding over long periods of time can turn the teeth brown by depositing hemosiderin and blood products.29 The most common sites of bleeding are as follows: gingiva 64%, labial frenum 60%, tongue 23%, buccal mucosa 17%, dental pulp 13%. Minor oral bleeding from gingiva and dental pulp can be controlled by local measures, while major bleeding episodes require factor replacement.39,40

Pregnancy: Gingivitis is the most common oral finding in gravid women. “Pregnancy epulides” or pyogenic granuloma, which is a localized hyperplastic response of gingival tissue, exists in approximately 1% of pregnant women. It is mostly found in the labial aspect of the interdental papilla. No pain exists but bleeding on brushing is common.41 Oral hygiene instructions and plaque control programs should be planned for pregnant women because periodontitis which follows gingivitis increases the risk of low-birth weight babies.42

Coeliac disease (gluten-sensitive enteropathy): Coeliac disease or celiac disease (CD) is a rare inherited abnormality resulting from inflammatory injury to the mucosa of the small intestine after the ingestion of wheat gluten. It can present at any age. Enamel defects are the most common oral lesions associated with CD (20%). The incisors are more frequently involved.43,44 If left untreated this disease can show aphthous-like ulcers, because of foliate or iron deficiency anemia.45,46 Atrophic glossitis and delayed tooth eruption has also been reported. Even in the absence of gastrointestinal symptoms patients with generalized dental enamel defects should be further evaluated for CD.44

Leukemia: This malignancy is the result of the proliferation of a clone of abnormal hematopoietic cells.47 Gingival swelling, bleeding and ulceration can be detected in up to 30% of patients with acute myeloblastic leukemia, but it is less frequent in the chronic forms of the disease. Persistent bleeding after extraction, mucosal purpura, mucosal pallor, fungal and viral infections, oral ulcers, and lymphadenopathy can also be seen.18 Gingival hyperplasia due to infiltration of the interdental papilla with leukemic cells is also a feature.48 Cancer therapy can produce oral ulcers and mucositis.18

Multiple sclerosis (MS): MS is a chronic, inflammatory disease of the central nervous system presenting with demyelinating lesions or plaques in the brain and the spinal cord. This disease can primarily manifest in the orofacial region with intermittent unilateral facial numbness or pain (mimicking trigeminal neuralgia), facial palsy or spasm, mild dysarthria (impaired ability to articulate words), Lhermitte sign, and monocular visual disturbances, such as partial loss of vision with pain or diplopia. Later in the course of disease facial paralysis may also occur in up to 25% of patients.46

Eating disorders: These are classified as psychopathologic disorders affecting patient relationship with food and her/his body, resulting in distorted eating habits. Anorexia nervosa and bulimia nervosa are included in this group of disorders. Oral lesions can be seen in many phases of the disease progression...
so they can play an important role in diagnosis, treatment and prognosis. Dental erosions on the palatal aspect of anterior teeth, swelling of the major salivary glands, mucosal changes due to metabolic alterations and anemia are frequently seen.47

Measles: Measles is a systemic infection caused by a paramyxovirus. Children are mostly affected. Oral manifestations are seen in 20% of cases. Koplik’s spots in the buccal mucosa (tiny, white plaque-like papules) are the most distinctive oral feature. Ulcers of the lips, acute necrotizing gingivostomatitis and perioral angular cheilitis are also reported. Maintaining a soft diet and oral rinse of chlorhexidine twice daily is sufficient for the management of the oral lesions.46

Systemic disorders with rare oral manifestations (Table 3):

**Lymphoma:** The neoplasm of the lymphoreticular system is divided into Hodgkin’s lymphoma (HL) and non-Hodgkin’s lymphoma (NHL). HL seldom involves the oral cavity. But 2-3% of the NHL may arise primarily in the oral cavity. Waldeyer’s ring is the most common site involved. The lesion is seen as a painless, erythematous swelling with surface ulceration. Jaw lesions can also be seen resulting in diffuse bone destruction.45

**Peptic ulcer disease:** Ulceration of the epithelial lining of the stomach or duodenum has rare oral manifestations such as aphthous stomatitis, glossitis and angular cheilitis due to iron deficiency anemia after chronic blood loss. Regurgitation of gastric acid leads to dental erosions. Vascular malformation of the lip is also reported.18

**Tuberculosis (TB):** TB is a chronic infectious granulomatous disease. Oral TB though uncommon (0.05-5%), can be seen secondary to the lung lesions or manifest as a primary lesion of the disease. Primary forms usually affect the gingiva and mucobuccal folds. The tongue is the most common site for the secondary lesions. The typical lesion of oral TB is an irregular, superficial, or deep, painful ulcer, which tends to increase slowly in size. Anti-TB medications will heal the oral lesions.49

**Metastases:** Metastasis of primary malignancies from elsewhere in the body are rare. 1% of oral malignant tumors are metastatic lesions from breast, prostate, and gastrointestinal tract. Posterior mandible is mostly involved with symptoms of pain, paresthesia, anesthessia, mobility of teeth and swelling. Bone destruction is visualized in dental radiographs. These lesions can be mistaken for dental disease.50

**Anxiety and stress:** An unpleasant emotional state, characterized by experience of fear and a rise in blood levels of “stress hormones”. Temporomandibular joint disorders due to parafunctional habits such as bruxism and clenching, cheek chewing, atypical facial pain and oral dysesthiasis such as burning mouth syndrome (BMS) are the orofacial manifestations.50

**Depression:** Depressive patients have a persistent low mood and negative thinking. Cancer phobia and oral dysesthiasia are seen. But BMS symptoms in depression are less common than anxiety disorder.18

Conclusion

Among different kinds of lesional manifestations of a vast variety of systemic diseases, oral manifestations comprise an important, if not a major, component of such diseases when it comes to proper diagnosis and treatment of such medical conditions. According to the relationship between oral and systemic diseases and due to the presence of the interaction between medical and dental fields, the importance of recognition of oral signs and symptoms of systemic conditions is a necessity because in many systemic diseases oral lesions are the only signs of the disease and, therefore, the diagnosis of such diseases can be confirmed by recognition of such oral manifestations. As a consequence, awareness, recognition and management of oral lesions accompanied in systemic conditions, is a necessity for all clinicians to provide delivery of high quality health care services.

This review can provide a better guide for dentists in particular to understand and recognize oral findings in such diseases and to give them a better clue to know when to examine the oral cavity and expect to see oral changes in certain patients.

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