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Review

THE MOST FREQUENT ORAL MANIFESTATIONS IN THE COURSE OF DISEASES, SYNDROMES, AND PATHOLOGIES OF OTHER ORGANS AND SYSTEMS: AN OVERVIEW-PART 1

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ABSTRACT

Various pathological conditions manifest in the oral cavity and can be an epiphenomenon of systemic diseases, therapies, syndromes, or pathologies affecting other organs and systems. The recognition of oral lesions or manifestations related to systemic conditions is helpful for early diagnosis, leading to a better response to treatments and improved prognostic standards. Mucosal, osseous, articular, and glandular manifestations are described in the context of systemic diseases and therapies, categorized by organs, systems, and apparatuses.

KEYWORDS: *oral lesions, mucosal lesions, systemic diseases*

INTRODUCTION

The involvement of the oral cavity in pathologies and diseases affecting other organs or systems is fairly common. Clinicians must carefully observe early signs and record symptoms in the oral mucosa, teeth, salivary glands, or temporomandibular joint to guide or complete the diagnostic procedure. The inspection of the oral cavity holds significant importance as a crucial phase of the comprehensive objective examination, not only for dental patients but also for patients affected by seemingly unrelated pathologies (1, 2).

This article describes the most prevalent oral manifestations of diseases, syndromes, and pathologies of organs and systems different from the oral cavity (3). Also, the oral complications due to systemic therapies were treated. While not claiming to be exhaustive, we intend to draw the clinician's attention to the most common and typical pathological manifestations that affect the oral cavity, convinced that the oral cavity can be a privileged window for assessing an individual's overall health.

Neurological and psychiatric manifestations

Branches of several cranial nerves innervate the oral cavity, salivary glands, and temporomandibular joint, including a) the trigeminal nerve (V pair), b) the facial nerve (VII pair), c) the glossopharyngeal nerve (IX pair), and d)

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the hypoglossal nerve (XII pair) (4). Pathologies affecting the central and peripheral nervous systems can lead to motor and sensory impairments within the oral cavity (5).

One example is Huntington's disease, which presents a wide array of signs and symptoms. These can include dysphagia, dysarthria, difficulties with mastication, compromised oral health, and choreiform movements affecting the tongue and other orofacial muscles. In cases of stroke, motor and sensory disturbances related to oral motricity can also be observed, depending on the extent of hypoxic damage at the central level (6).

Multiple sclerosis often manifests with trigeminal neuralgia, trigeminal sensory neuropathy, and facial palsy as the three most common orofacial symptoms (7). Trigeminal neuralgia can even be the initial manifestation of the disease in 0.3% of cases (8). Chronic neurodegenerative diseases, such as Alzheimer's and dementia, are associated with cognitive decline, which often correlates with deterioration in oral health. Lower DMFT values characterize severe cases of these conditions, compromised chewing and swallowing disorders, and an increased risk of mortality, physical frailty, functional disability, hospitalization, falls, and decreased quality of life. Oral pain, specifically, is linked to physical frailty (9. 10).

Burning mouth syndrome (BMS) is frequently accompanied by depression and varying degrees of distress (11, 12). The presence of dynias in multiple mucosal sites (13), higher prevalence in females, and its occurrence during peri-postmenopausal ages suggest a peripheral neuropathy triggered by stress, hormonal changes, or emotional stimuli (14). Eating disorders, such as anorexia nervosa and bulimia, often exhibit oral features, including tooth erosion, dental caries, changes in salivary quantity and quality, xerostomia, gingival and periodontal diseases, and oral mucosal lesions such as palatal erythema and ulcers (15).

Oral manifestations in cardiovascular diseases

Cardiovascular diseases (CVDs), including conditions such as coronary artery disease, stroke, and heart failure, are significant causes of morbidity and mortality worldwide. In recent decades, emerging evidence has indicated a potential association between CVDs and oral health.

Focal infections within the oral cavity can potentially initiate endocarditis and myocarditis through the hematogenous dissemination of bacteria or their toxins. Necrotic roots, apical granulomas, cysts, dental caries, and periodontal pockets can act as reservoirs for cardiac infections or elicit an immune response that exhibits cross-reactivity with valvular and endocardial antigens (antigenic mimicry) (16-19). Furthermore, chronic inflammation resulting from periodontal diseases can contribute to systemic inflammation, leading to endothelial dysfunction, atherosclerosis, and an increased risk of cardiovascular adverse events (20).

Symptoms such as angina and myocardial infarction can manifest as referred oral pain or discomfort, emphasizing the importance of considering cardiovascular causes in patients experiencing such manifestations (21). The pharmacological treatment of hypertension, peripheral vascular disease, and angina pectoris may induce oral signs and symptoms. For example, the use of calcium channel blockers (CCBs) can lead to a condition known as Drug-Induced Gingival Overgrowth (DIGO) (22). The most prevalent CCB associated with DIGO is nifedipine, with a prevalence exceeding 20%. Other CCBs may also contribute to this condition, including diltiazem, felodipine, amlodipine, and isradipine (23). Gingival enlargement typically occurs within 1 to 3 months after starting treatment. Initially, it presents as a firm, nodular enlargement in the interdental papillae, gradually extending to the buccal and lingual margins. Anterior teeth are commonly affected, with the extension reaching the buccal aspect (24). Histologically, DIGO exhibits mixed inflammatory and fibrotic characteristics (25, 26).

Another consequence of cardiovascular treatment is Acquired Angioedema, which can arise from the use of angiotensin-converting enzyme (ACE) inhibitors. Clinically, it manifests as non-pitting, non-itching submucosal swelling, primarily affecting the oral cavity's extremities, such as the lips (27). Angioedema predominantly affects the tongue in women, individuals of African descent, and smokers. It typically manifests within the first month of initiating therapy in approximately 50% of cases (28).

A dry mouth, characterized by xerostomia (a symptom) and hyposalivation (a sign), is also a common side effect of various medications, including antihypertensives and diuretics (29). The prevalence of dry mouth increases with age due to atrophic glandular degeneration, affecting up to 30% of individuals over 65, particularly women (30). Polypharmacy, which is prevalent among older individuals, further contributes to the incidence of this condition (31). There is a therapeutic association between drugs used for cardiovascular diseases and over 400 classes of xerogenic drugs (32).

Oral manifestations in chronic renal failure

Oral manifestations are often observed in the advanced stages of Chronic Renal Failure (CRF), characterized by a significant reduction in glomerular filtration rate. Soft and hard tissue can be involved in the manifestation of CRF, presenting a wide range of clinical and symptomatic features. These manifestations can also be a consequence of the therapies the patients undergo. Moreover, changes in bacterial microflora are observed in these patients (33).

Regarding soft tissue involvement, Uremic Stomatitis is commonly observed and often localized on the lingual surface. It can present in four clinical variants: membranous-erythematosus, ulcerative, hemorrhagic, and hyperkeratotic. This condition is caused by an increase in serum nitrogenous waste products. The ulcerative variant is the most common, while the hyperkeratotic variant is the rarest.

Tissue Dystrophy, which is more prone to bacterial infection, can occur due to small bleeding events. Necrotic Pseudomembranous Gingivostomatitis may be observed in patients with unexpected increases in serum nitrogen levels. Xerostomia, characterized by reduced salivary flow, is present in 28-59% of patients with end-stage renal disease cases. Hyposalivation can lead to various sequelae, including a higher susceptibility to cervical caries, candidiasis, atrophic and chapped lips, and dry, pale labial mucosa. Spontaneous Gingival Bleeding may occur during CRF as a result of bacteremia. Bacterial toxins induce platelet dysfunction, exacerbated by renal anemia and anticoagulant therapies. Furthermore, endothelial dysfunction worsened by dyslipidemia leads to the development of Petechiae and Bruising in these patients (34, 35).

Regarding hard tissue involvement, Enamel Renal Syndrome (ERS) is a genetic condition characterized by enamel hypoplasia and nephrolithiasis. Both deciduous and permanent teeth can be affected, with tooth surfaces appearing rough or smooth and yellow-brown in color. Pulp stones may be present in the pulp chambers. Increased concentrations of volatile sulfur compounds due to microbiological degradation can lead to Halitosis, especially when blood urea levels exceed 55 mg/dl. There is also an increase in tartar levels. Another oral manifestation of CRF is the chronic kidney disease mineral and bone disorder syndrome (CKD-MBD), resulting from several metabolic disorders. Skeletal manifestations include osteitis fibrosa and osteomalacia, which show an excess of osteoid bone with a high risk of fractures, as well as adynamic and mixed bone disease. Expansive jaw lesions may appear radiographically as a radiolucent area due to the loss of bone trabeculae and reduction of the cortex. Other manifestations include temporomandibular joint defects, delayed eruption, and periodontal calcifications due to altered calcium-phosphorus products (36-38).

In kidney transplant (KT) recipients, DIGO can be induced by immunosuppressive drugs such as cyclosporine. Studies have shown that patients with severe DIGO may present this manifestation even before transplantation, and children and adolescents seem to be more predisposed than adults. Clinically, DIGO initially appears as soft and hyperemic nodules at the level of the papillae, extending buccally, lingually/palatal, and in a coronal direction. It appears pink, firm, and resistant to palpation, often covering up to ½ of the crown of the labial face of the upper and lower anterior teeth. Compared to cyclosporine, tacrolimus can induce partial or total regression of the lesion. Sporadically, GH may occur in patients who take cyclosporine from the beginning of therapy. Gingival hyperplasia is also associated with calcium channel blockers in patients undergoing dialysis or pre-dialysis (39).

Oral Candidiasis is present in kidney transplant recipients, with an incidence ranging from 4% to 43%. *Candida dubliniensis* and *Candida famata* have been found in many cases. Suburral Tongue can occur in 22% of KT recipients and presents as a yellowish-white superficial layer on the back of the tongue. Oral Hairy Leukoplakia (OHL) can be observed in transplant recipients in 8%-11% of cases. It is a painless, irregular white spot with prominent folds that cannot be scraped off. It usually appears on one or both lingual borders and sometimes on the posterior aspect of the tongue. This condition may be due to the reactivation of the Epstein-Barr virus following immunosuppression. Candida Albicans may also be associated with OHL. Finally, KT recipients following immunosuppression have a higher frequency of developing malignant lesions, with Kaposi's Sarcoma representing 5.7%-11% of cases. It is an angiogenic tumor of viral etiology caused by human herpes virus-8 (HHV8). Clinically, it can present as a macular, plaque, or nodular form, often localized on the palate or gingiva (40, 41).

Oral manifestations in hematological diseases

Hematological diseases, also known as blood disorders, encompass a wide range of conditions that affect the blood, blood-forming tissues, and the immune system. These diseases can significantly impact individual health and quality of life. Oral cavity involvement is frequent and, in some cases, the site of the first manifestations.

Iron deficiency anemia is the most common hematological disorder. It may manifest in the orofacial region as a burning sensation (in 76% of cases) and numbness of the oral mucosa, atrophic glossitis, taste dysfunction, recurrent aphthous ulcers, dry mouth, and oral lichen planus (in 33.3% of cases), as well as lingual varicosities. If the atrophy

extends to the mucous membranes of the upper aerodigestive tract, it predisposes individuals to develop squamous cell carcinomas, a condition known as Plummer-Vinson Syndrome (42, 43).

In patients affected by pernicious anemia, patients may present with Hunter's Glossitis (or Moeller-Hunter), characterized by atrophy of the filiform papillae with a smooth and erythematous appearance involving more than 50% of the dorsum of the tongue. Atrophic oral candidiasis, angular cheilitis, and recurrent aphthous ulcers may also be present. The symptomatology is characterized by glossodynia, burning, xerostomia, and lingual paresthesia. These signs often appear before symptomatic anemia, and one characteristic of this phase of pre-anemia is the so-called "magenta tongue" (44). During folate deficiency anemia, the same clinical manifestations are present in pernicious anemia without neurological implications (45).

In sickle cell anemia, the jaw bones are involved in most cases. This involvement is marked by an expansion of the marrow spaces due to compensatory hyperplasia of the marrow. Radiographically, there is a reduction in bone trabeculation, which leads to various sequelae. In less severe cases, there is an increase in mid-facial growth, potentially resulting in interincisal diastema and paresthesia or anesthesia of the mental nerve.

In more severe cases, complications can include osteomyelitis, osteosclerosis, ischemic infarction, or osteonecrosis of the mandibular bone. The mandible is more affected than the maxilla because it has less blood circulation. The only observable manifestation at the soft tissue level is pale or yellowish mucosa resulting from hemolytic jaundice (46).

In cases of Homozygous β-thalassemia (Cooley's Anemia), skeletal abnormalities are primarily evident in childhood. Patients often exhibit maxillary bone protrusion due to compensatory marrow hyperplasia, usually called the "squirrel face." The mandibular bone is less affected due to its thicker cortex, which resists marrow expansion. Patients may also present with anterior-superior diastemas, malocclusions, tooth discolorations, and tooth dislocations, which can have shorter roots and crowns (47). The oral mucosa frequently displays characteristic pallor.

In cases of cyclic neutropenia, recurrent aphthoid ulcers and rapidly progressive periodontal disease can be observed, especially in children and young adults. Neutropenic manifestations typically appear approximately every 21 days. Additionally, an atypical form of ulcerative gingivitis with gingival ecchymoses has been reported (48, 49).

Various signs may be observed in cases of qualitative and quantitative platelet deficits, including spontaneous petechiae (smaller than 3mm), purpura (3-10 mm), ecchymoses (larger than 3mm), hemorrhages, blood blisters that can spread to the oral mucosa, and excessive bleeding following trauma or extractions. Excessive gingival bleeding is also commonly reported after teeth brushing.

If the patient is affected by coagulation disorders, hemorrhages, and prolonged bleeding after routine dental procedures can also be observed. In Von Willebrand disease (the most common disorder), hemosiderin deposition can lead to the teeth appearing brown. In Hemophilia A and B, varying degrees of bleeding can occur following trauma, depending on the severity of the deficiency of factors VIII and IX, respectively.

Kaneda et al. identified gingiva as the site most commonly involved within the oral cavity, accounting for 64% of cases, followed by the pulp at 13%, tongue at 7.5%, lip at 7%, and palate at 2%. Rare instances of temporomandibular joint (TMJ) hemarthrosis and chronic hemophilic arthropathy have also been reported. Cases of gingival bleeding associated with swelling and ulceration in plasminogen deficiency have been documented, as well as the presence of fibrin pseudomembranes on the gums in cases of dysfunctional fibrinolysis (50).

Oral manifestations in genetic diseases

The tongue is the most frequently affected site in patients with lipoid proteinosis. However, many patients also experience involvement of multiple oral sites, including the floor of the mouth, lips, buccal mucosa, and palate. Oral lipoid proteinosis manifestations are caused by hyaline material deposits in the subepithelial connective tissue. Clinically, these manifestations appear as yellowish-white areas with thickening of the mucosa and a hard consistency resembling wood. Some patients may also exhibit a short lingual frenulum, restricting tongue movement. Additionally, gingival hyperplasia may occur more frequently in young individuals, while palatal involvement is typical in the elderly (51).

Dyskeratosis congenita presents a triad of symptoms: nail dystrophy, reticular skin hyperpigmentation, and oral leukoplakia, which shows a 35% risk of malignant transformation over 10-30 years. Recurrent blisters or aggregates may also be present, which, upon rupture, result in ulcerated and atrophic areas, particularly on the tongue and buccal mucosa (52).

In multiple hamartoma syndrome (Cowden's Syndrome), oral manifestations are present in approximately 80% of patients. Whitish or pink papules or nodules can be found on the gingiva, tongue, and buccal mucosa. These lesions can appear as isolated entities or fused, resembling a cobblestone-like appearance, typically on the gingiva. Other possible

oral manifestations include papillomatosis, fissuring, lobulations of the tongue, arched palate, caries, xerostomia, and periodontitis (53).

In patients with neurofibromatosis type 1, multiple or rarely isolated nodular neurofibromas can occur, particularly in children, affecting up to 72% of cases. These fibrous masses, located mainly on the tongue (26%), buccal mucosa (8%), labial mucosa (8%), oral floor, and palate (8%), appear as submucosal lesions without inflammation. Gingival localization (2%) can cause unilateral enlargement of the attached gingiva, extending to the interproximal area. This condition can lead to worsened periodontal health due to the impediment of oral hygiene. Some studies have reported macroglossia cases resulting from plexiform neurofibromas and enlarged fungiform papillae. These lesions have a 3%-5% risk of malignant degeneration. Deformities of the maxillary bones may also occur due to tumor localization in these areas or skeletal lesions caused by a generalized increase in osteoclast activity due to haploinsufficiency of the NF-1 gene (54).

Oral manifestations of Sturge-Weber syndrome can affect 38% of cases and result from facial capillary malformations. Angiomatous lesions are observed in the gingiva, tongue, palate, labial mucosa, and buccal mucosa. These lesions are usually unilateral and terminate abruptly at the midline. Gingival manifestations can range from slight hyperplasia to severe angiomatous proliferations, which blanch upon the application of pressure and may bleed following minor trauma. Furthermore, gingival enlargement can be attributed to the use of anticonvulsant drugs commonly prescribed for epileptic seizures in these patients. In some cases, macroglossia and maxillary bone hyperplasia have also been reported (55, 56).

In tuberous sclerosis (TSC) cases, oral manifestations often include fibromas. These fibromas are predominantly located in the anterior gingiva, with less frequent involvement of the labial mucosa, upper labial frenulum, palate, and tongue. Affected areas may exhibit confluent nodules smaller than 1 cm. Furthermore, enamel pits can be found on the labial surfaces of anterior teeth, including canines. This condition affects permanent dentition in 48-100% of cases, and some studies have also shown the involvement of deciduous dentition (57).

Patients with hereditary epidermolysis bullosa (EB) can exhibit various clinical manifestations depending on the specific form of the disease (simplex, junctional, dystrophic, Kindler). Blisters are commonly observed in patients with EB, often as a result of trauma, accompanied by erythema, atrophy, and ulcerations. Scarring can vary depending on the subtype and its variants. Microstomia, ankyloglossia, reduced gingival arches, and severe desquamative gingivitis are also commonly seen in these patients. Junctional EB can present various degrees of enamel abnormalities, ranging from pitting to generalized hypoplasia, which is not observed in the dystrophic variant (EDB). Recessive EDB is the most aggressive form of EB, as patients often struggle with oral hygiene, leading to high rates of dental caries. Malnutrition resulting from dysphagia can further contribute to reduced jaw growth, resulting in malocclusions and crowding. Periodontal disease is particularly prevalent in patients with EDB due to poor oral hygiene. Kindler syndrome, which involves a protein of the junctional epithelium, can also present with early-onset periodontitis (58, 59).

Focal palmoplantar and oral mucosa hyperkeratosis syndrome are characterized by focal painful hyperkeratosis primarily affecting the attached gingiva. This condition tends to occur in areas subjected to mechanical pressure or friction. At the gingival level, it often manifests as leukoplakia. Other sites in the oral cavity that can be involved include the palate, alveolar mucosa, lingual edges, retromolar mucosa, and buccal mucosa at the occlusal line. These areas are subject to mechanical stress during oral function (60).

Oral cavity and gastrointestinal diseases

The oral cavity serves as the initial segment of the gastrointestinal system, rendering it susceptible to involvement in gastrointestinal diseases. Crohn's disease, an inflammatory bowel disease of uncertain etiology, can affect any part of the gastrointestinal system, including the mouth (61). Oral manifestations of Crohn's disease may encompass aphthous stomatitis, mucosal tags, lip swelling, and pyostomatitis vegetans (62). Some studies have also reported additional oral changes in Crohn's patients, such as bilateral corrugated cobblestone changes in the buccal mucosa and erythematous gingival enlargement.

Ulcerative colitis, another form of inflammatory bowel disease, can also give rise to oral manifestations, with pyostomatitis vegetans being the most prominent. Pyostomatitis vegetans are elevated yellow-white circinate lesions that can affect multiple oral mucosal sites (63). Further oral abnormalities observed in ulcerative colitis include aphthous lesions, dental caries, and severe periodontitis (64). Gardner's syndrome, a genetic disorder characterized by intestinal polyps, multiple osteomas, and soft tissue tumors, can manifest in the oral cavity due to osteomas affecting various bones, including the jawbones (65). Celiac disease, a treatable gluten-induced condition, can exhibit oral manifestations, including recurrent aphthous stomatitis. It may also lead to enamel defects, delayed dental development, frequent caries, and lingual atrophy (66, 67).

Gastroesophageal reflux disease, resulting from the reflux of stomach contents into the esophagus or oral cavity, can cause oral alterations. Chronic exposure to acidic gastric content can result in irreversible dental erosion and irritation of the oral mucosa (68). Pseudo-lesions of the oral mucosa, such as hypertrophy of the lingual vallate papillae and lingual tonsils, may also occur due to chronic exposure to acidic gastric content (69).

Pediatric jaundice, characterized by elevated bilirubin levels in the circulation, can cause discoloration of the skin, eyes, and mucous membranes, including the oral mucosa. Neonatal jaundice is common, and although it often resolves, high serum bilirubin levels can become permanently trapped in dental hard tissues, leading to discoloration and structural alterations of enamel and dentin (70).

Peutz-Jeghers syndrome, a rare autosomal dominant disease often caused by a mutation in the serine/threonine kinase 11 gene, primarily affects the digestive system. It is associated with oral hyperpigmentation, which is considered a pseudo-lesion resulting from the hyperactivity of melanocytes, particularly involving the gums (71).

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