Episode 60 – Oral Manifestations of Systemic Conditions: Part 1

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Introduction

Many systemic conditions involve the tissues of the head and neck, with signs and symptoms sometimes presenting in the oral cavity first. Tissues of the lips, tongue, gingiva, mucosal surfaces, dentition, and bone can be involved. Therefore, a detailed examination of the head, neck, and oral cavity is important to reveal findings indicating an underlying systemic condition to allow for early diagnosis and treatment. Systemic conditions that may exhibit oral manifestations include gastrointestinal, hematologic, and nutritional disorders. [1]

Gastrointestinal disorders

The gastrointestinal (GI) tract consists of the oral cavity, pharynx, esophagus, stomach, small intestine, and colon (large intestine). The oral cavity is often involved in conditions affecting the GI tract, such as ulcerative colitis, Crohn's disease, celiac disease, and gastroesophageal reflux disease.

Ulcerative colitis

- Ulcerative colitis is a chronic inflammatory bowel and ulcerative disease.
- Symptoms include flare-ups of bloody diarrhea, abdominal cramps, and fever.
- Inflammation is usually restricted to the mucosa and submucosa of the rectum and colon and is characterized by periods of exacerbation and remission.
- Etiology is not known.
- Treatment is aimed at controlling inflammation, reducing symptoms, and replacing lost fluids and nutrients. [2] [3] [4] [5]

Several oral manifestations have been associated with ulcerative colitis and may be related to disease severity. Oral signs may include:

- Aphthous ulcerations which are the most common oral sign affecting up to 4-20% of individuals. [5] Ulcers generally coincide with disease exacerbation, but can occur without intestinal disease activity. Ulcers can be painful, usually healing within a couple of weeks, but new ulcers may develop causing extended periods of ulceration.
- Tongue coating.
- Pyostomatitis vegetans is a rare chronic mucocutaneous ulcerative disorder involving multiple small white or yellow raised pustules with an erythematous and edematous base. Lesions can rupture easily and coalesce to form linear or 'snail-track' ulcers (i.e., fissured lesion with raised edges). Almost all areas of the mouth

can be involved, most frequently the labial gingiva, and labial and buccal mucosa, though the tongue and floor of the mouth can be affected. Pain and burning symptoms may be minor to severe. Its oral presence may precede GI symptoms by months or years.
- Periodontitis has been shown to be of higher prevalence among individuals with ulcerative colitis compared to control groups.
- Glossitis, cheilitis, stomatitis, mucosal ulcers, and gingival inflammation, which are usually a result of nutritional deficiencies (e.g., iron, folate, B12) from the intestinal involvement and/or as a side effect of medications used to treat the condition (e.g., aminosalicylates). Symptoms such as halitosis, acidic taste, and taste change may also be related to medication use. [4] [5] [6] [7] [8] [9] [10]

Crohn's disease
- Crohn's disease is an inflammatory bowel disease that can involve the entire GI tract (i.e., from oral cavity to the anus).
- Symptoms may include diarrhea (sometimes bloody), constipation, abdominal pain, fever, loss of appetite, and weight loss.
- Etiology is not known. Diet and stress may aggravate the disease. Research suggests hereditary, genetic, and environmental factors contribute to disease development.
- Treatment is aimed at relieving symptoms and reducing inflammation. [3] [4] [5] [11]

Crohn's disease may present with intraoral involvement which may:
- Occur in up to 50% of individuals and more frequently in young males. [4]
- Precede intestinal involvement.
- Assist with diagnosis of the condition.
- Indicate the severity of the systemic disease and degree of intestinal impairment. However, oral lesions noted after disease diagnosis and management may not indicate recurrent disease, but adverse effects of treatment. [3] [4] [5] [11]

Certain oral manifestations can be classified as:
- Specific lesions which show evidence of noncaseating granulomatous[1] change during histologic examination; or
- Nonspecific lesions which show no granulomatous change and may be related to nutritional deficiency (e.g., from chronic diarrhea, nutrient malabsorption, decreased food intake, etc.) or adverse reactions of drug therapy. [9]

Specific lesions
Specific lesions may include:
- Diffuse lip and mucosal swelling which is one of the most common and obvious presentations. Swelling is usually persistent, firm on palpation, painless, and

[1] Granulomas form in response to chronic inflammation in an attempt to prevent spread of an infectious agent the body cannot eradicate. A granuloma whose centre has undergone caseous necrosis (whitish, cheese-like debris) is a caseating granuloma (e.g., typically occurs in tuberculosis). A noncaseating granuloma does not have central caseating necrosis (e.g., occurs in diseases such as Crohn's disease and sarcoidosis).

frequently involves the lips and buccal mucosa. Swelling may extend to the perioral area and involve other parts of the face. Lip swelling can be symmetrical or localized. It can involve both lips but usually only one lip is involved (prevalence between upper and lower lip involvement is similar). Chronic lip swelling can lead to vertical lip fissuring.

- Cobblestoning of the buccal mucosa usually consists of firm normal colour plaques separated by mild depressions or fissures, which may alternate with mucosal folds of normal epithelium. It may be painful and interfere with eating and speaking.
- Mucosal tags (epithelial tags or folds) are small, localized, white or normal colour swellings often presenting in the vestibule and retromolar area, and are often asymptomatic.
- Linear ulcerations are usually located in the buccal vestibule and may have hyperplastic margins. These persistent ulcers are deep and may be confused with aphthous ulcers.
- Mucogingivitis may affect the entire gingiva including up to the mucogingival margin. The gingiva may become edematous and hyperplastic, and may be associated with ulceration.
- Granulomatous cheilitis is swelling of the lip due to granulomatous inflammation. It is a rare condition with onset usually seen in young adulthood. [4] [5] [9]

Nonspecific lesions

Nonspecific lesions are more common than specific lesions. They may be painful, impairing oral selfcare, oral function (e.g., speaking, eating, etc.), and quality of life. [9]

Nonspecific lesions may include:

- Aphthous ulcers which are one of the most common lesions associated with Crohn's disease, occurring in about 20-30% of individuals. [5] They are painful shallow round to oval shaped lesions with an erythematous border and are clinically indistinguishable from classic aphthae. Their onset is usually sudden and may occur with or precede intestinal disease activity. Their association with disease flare-ups is not clear.
- Pyostomatitis vegetans can occur in Crohn's disease, but is more frequent in ulcerative colitis.
- Angular cheilitis is where the commissures and adjacent skin have recurrent fissures and indurated erythematous plaques not necessarily related to candida infection.
- Periodontal disease has been reported. Several studies have reported a prevalence of periodontitis among individuals with Crohn's disease compared to controls. Gingival bleeding is also common and occurs in approximately 20% of individuals. [9] Periodontitis in the primary dentition may suggest Crohn's disease and may precede intestinal symptoms.
- Dental caries has been reported at higher prevalence rates in individuals with Crohn's disease compared to controls. Studies have shown higher levels of *Lactobacillus* and *Streptococcus mutans*, dental plaque, and refined carbohydrate intake in individuals with Crohn's disease.
- Other nonspecific oral findings include glossitis due to nutritional deficiencies, gingival hyperplasia, lichen planus, halitosis, dysphagia, odynophagia, dysgeusia,

hyposialia, minor salivary gland enlargement, submandibular lymphadenopathy, candidiasis, and perioral erythema with scaling (flaking skin). [4] [5] [8] [9] [12] [13]

Celiac disease

- Celiac disease is a hereditary autoimmune disease that occurs in genetically predisposed individuals, with a higher frequency in females.
- Ingestion of gluten results in mucosal inflammation and small intestine villi damage leading to nutrient malabsorption.
- There is no cure. Management is by strict adherence to a gluten-free diet.
- Symptoms in adults may include diarrhea, undernutrition, loss of appetite, abdominal bloating and discomfort, nausea, vomiting, constipation, and weight loss. Approximately 50% of adults have no digestive symptoms at time of diagnosis. [5]
- Symptoms in children may include abdominal bloating, nausea, vomiting, chronic diarrhea, constipation, gas, failure to grow, and bulky, pale, very foul-smelling stools.
- Both children and adults can develop anemia (iron-deficiency anemia in children, folate-deficiency anemia in adults) leading to fatigue and weakness.
- Approximately 10-15% develop dermatitis herpetiformis, a chronic skin condition caused by a reaction to gluten ingestion characterized by extremely itchy bumps or blisters that appear on the forearms near the elbows, knees, torso, buttocks, and along the hairline. The bumps and blisters resemble herpes lesions, but are not caused by the herpes virus. [5] [9] [14] [15] [16] [17]

Several oral manifestations have been associated with celiac disease, such as:

- Delayed tooth eruption, reduced salivary flow, recurrent aphthous stomatitis, angular cheilitis, and enamel defects (e.g., enamel hypoplasia) in the primary and permanent dentition of children.
- Enamel hypoplasia occurs mostly in the permanent teeth; symmetrically and chronologically in all quadrants; and in the maxillary and mandibular incisors and molars. Teeth may be discoloured with white, yellow, or brown spots. Other defects may include poor enamel formation, pitting or banding of teeth, and mottled or translucent-looking teeth. It has been hypothesized calcium malabsorption and immunological issues may hinder amelogenesis. However, there is no consensus on the process behind the association of enamel hypoplasia and celiac disease.
- Enamel defects are not often seen in adults as celiac symptoms may have developed later in life or severely affected teeth may have been restored or extracted.
- Recurrent aphthous stomatitis which may be a result of hematinic[2] deficiency with untreated celiac disease.
- Atrophic glossitis, characterized by a red, smooth, shiny tongue and glossodynia (i.e., painful or burning sensation in the tongue). These signs and symptoms are likely to be secondary to anemia and hematinic deficiencies rather than caused by the disease itself.

[2] Hematinic is a substance essential for the proper formation of components of the blood. Iron, folate, and vitamin B12 deficiency are the most common hematinic deficiencies, which have been associated with some common oral mucosal diseases, such as recurrent aphthous stomatitis and atrophic glossitis.

- Decreased salivary flow rates have been reported in the active phase of the disease, resulting in xerostomia and glossodynia. Saliva flow alterations may increase risk of oral mucosal infections and dental caries.
- Incidence of squamous cell carcinoma of the oropharynx increases in individuals with celiac disease. However, adherence to a gluten-free diet can significantly reduce the risk of cancer.
- Higher caries rates possibly due to increased susceptibility of the hypoplastic enamel and alterations in salivary flow rates.
- Dermatitis herpetiformis lesions seen on the skin can also affect the oral mucosa (e.g., tongue, buccal mucosa, alveolar ridge). The lesions manifest as erythematous-purpuric macules, erosions, ulcers, and vesicles. Clinically, it is difficult to differentiate it from other blistering diseases (e.g., pemphigus,[3] pemphigoid), so histological and immunofluorescence studies are necessary. [5] [15] [18] [19] [20]

Gastroesophageal reflux disease

- Gastroesophageal reflux disease (GERD) is the recurrent regurgitation of gastric contents that causes damage to the esophageal mucosa and structures of the oral cavity. Both adults and children can be affected.
- GERD may be caused by weakening of the lower esophageal sphincter.
- Risk factors for GERD include delayed gastric emptying, obesity, hiatal hernia, pregnancy, and connective tissue disorders (e.g., scleroderma).
- Acid reflux can be aggravated by smoking and consuming large meals, food before bed, fatty foods, coffee, or alcohol.
- Symptoms may include heartburn, chronic cough, sore throat, globus (lump in the throat), dysphagia, and odynophagia.
- GERD may lead to erosive esophagitis, Barrett esophagus, and esophageal adenocarcinoma if left untreated.
- Treatment may include life style modifications (e.g., maintaining healthy weight, smoking cessation, avoiding trigger foods, etc.), medications (over-the-counter or prescription) to reduce or block stomach acid production, and/or surgery. [4] [5] [21]

Oral conditions associated with GERD may include:

- Dental erosion which is one of the most common oral manifestations of GERD. It is caused from chronic exposure to acidic gastric fluids (pH of 1-2). Lingual surfaces of the maxillary teeth are most commonly affected. The severity can range from mild enamel loss to severe dentin exposure depending on the frequency and quantity of acid exposure, and duration of the disease. Newly exposed dentin is usually smooth and shiny, while previously exposed dentin may be stained. Dentin exposure increases tooth sensitivity to temperature changes.
- Nonspecific oral burning sensation, mucosal erosions and ulcerations, palatal erythema, and hypersalivation.
- Halitosis has been reported in symptomatic GERD possibly due to the diminished function of the lower esophageal sphincter allowing the flow of gases and gastric contents into the esophagus and oral cavity.

[3] Refer to Episode 30 for additional information on oral pemphigus.

- Xerostomia may be an adverse side effect of medications to treat GERD (e.g., proton pump inhibitors), rather than it being caused by GERD itself. [4] [5]

Hematologic disorders

Hematologic malignancies and blood cell dyscrasias are a diverse group of diseases with many systemic sequelae. The hard and soft tissues of the head and neck, including the oral cavity can be involved and may frequently represent the first clinical manifestation of these disorders. Also, several complications from chemotherapeutic therapy for these diseases may affect the oral cavity. [4]

White blood cell disorders

Leukemia

- Leukemia is a white blood cell (WBC)[4] malignancy resulting in an increased number of circulating immature or abnormal leukocytes. Leukemias are classified as acute or chronic and the type of WBC primarily affected (i.e., lymphoid or myeloid).
- Etiology of leukemia is not known. However, it seems to develop from a combination of genetic and environmental factors.
- Overgrowth of leukemic cells in the bone marrow replaces the hematopoietic stem cells,[5] which subsequently reduces the number of normal circulating blood cells. This can lead to individuals developing anemia, neutropenia, leukopenia, and thrombocytopenia.
- Symptoms depend on the type of leukemia and may include, flu-like symptoms, fatigue, frequent or serious infections, delayed wound healing, lymphadenopathy, splenomegaly or hepatomegaly, weight loss, bleeding or bruising, petechiae[6], bone and/or joint pain (caused by malignant bone marrow expansion), and excessive sweating (especially at night).
- Approximately 65% of individuals exhibit oral manifestations and are more common in acute than in chronic leukemias. [22] Oral manifestations may include:
    - Pale oral mucosa and ulcerative necrotic lesions. Ulcerations commonly involve the gingival and palate and appear deep and punched out with a greyish white necrotic base.
    - Petechiae, ecchymosis[7] and gingival bleeding are attributed to thrombocytopenia due to suppression of normal bone marrow. Gingival bleeding is more common in acute leukemia.
    - Gingival hyperplasia is caused by infiltration of leukemic cells. Gingival enlargement can be severe and is usually generalized. It can involve the interdental papillae and marginal and attached gingiva, and may cover the entire crowns of teeth. The gingiva can appear edematous, pale red to deep purple in colour, and hemorrhagic. Gingival hyperplasia is more common in acute than chronic leukemia.

[4] Refer to Episodes 44 & 45 for additional information on white blood cells and the immune system.
[5] Hematopoietic stem cells, also called blood stem cells, can develop into RBCs, WBCs, or platelets.
[6] Petechiae are caused by submucosal hemorrhage and appear as multiple small red spots.
[7] Ecchymosis is a submucosal hemorrhage that appears as large diffuse red macules with irregular margins.

- Necrotizing ulcerative gingivitis (due to non-functioning WBCs); toothache (due to invasion of pulp by leukemic cells); tooth mobility as a result of necrosis of the periodontal ligament; and periodontal bone loss.
- Impaired immune function in leukemia can lead to various secondary oral infections (e.g., candidiasis, herpes simplex virus infection).
- Chemotherapeutic drugs used to treat leukemias may cause mucositis. Many are often immunosuppressive drugs, which increase the risk for secondary oral viral, fungal, and bacterial infections. [4] [22] [23] [24]

Lymphoma

- Lymphoma is a broad term for cancer of the lymphatic system (i.e., lymph nodes, spleen, thymus gland, bone marrow, tonsils). There are several types of lymphoma. Two main sub-types are Hodgkin lymphoma and non-Hodgkin lymphoma.
- Symptoms may include swollen lymph nodes (e.g., in neck, armpits, groin), fever, persistent fatigue, night sweats, unexplained weight loss, shortness of breath, and itchy skin.
- Etiology is not known.
- Certain subtypes of non-Hodgkin lymphomas (e.g., cutaneous T-cell lymphoma, Burkitt lymphoma, AIDS-associated lymphoma) are commonly associated with oral manifestations.
- In non-Hodgkin lymphomas usually the lymphoid tissues of the Waldeyer's ring[8] are affected, although palatal and buccal mucosal involvement is possible. Lymphomas in the oral cavity are usually painless, soft masses, with or without traumatic ulceration.
- Cutaneous T-cell lymphoma is a malignant proliferation of T cells, which frequently involves the skin and sometimes the oral cavity. Oral manifestations may include ulcerated plaques or solid tumours on the gingiva, palate, or tongue. Oral lesions represent advanced disease and poor prognosis.
- Burkitt lymphoma is an aggressive B-cell lymphoma and generally presents as a rapidly enlarging mass, often involving the head and neck. The oropharynx, maxilla, and mandible are common sites of soft tissue and bone destruction, which may lead to painful loosening of teeth and paresthesia of the face.
- Lymphoma in HIV-positive individuals is considered an AIDS-defining illness. AIDS-associated lymphomas may present with masses or ulcers involving the gingiva, palate, tonsils, tongue, and mandible. Oral involvement occurs in approximately 3% of AIDS-associated lymphoma. [4] [25]

Cyclic neutropenia

- Cyclic neutropenia is a rare syndrome of recurrent neutropenia. Periods of neutropenia usually last 3-5 days, with episodes returning every 3 weeks.
- It is caused by an inherited or sporadic mutation in the neutrophil elastase gene (*ELANE*).
- Symptoms may include fever, malaise, mucosal ulcerations, recurrent infections, and occasional abdominal discomfort. Individuals with cyclic neutropenia are

[8] The Waldeyer's ring is a ring of lymphoid tissue in the throat made up of the tonsils, adenoids, and other lymphoid tissue.

generally well between episodes. Symptom onset usually occurs in childhood and may improve approaching adulthood.

- Oral manifestations occur in >90% of individuals [4] and may include:
    - Recurrent ulcers (similar to aphthous stomatitis) which are very common, vary in size, and may be found on the buccal mucosa, lips, tongue, and pharynx. The ulcers usually occur during periods of neutropenia and resolve within 1-2 days once neutrophil counts rebound.
    - Recurrent gingivitis, which is generally worse during periods of neutropenia, but can persist even if the neutrophil count is within normal limits. Recurrent gingivitis may lead to periodontitis. [4] [26] [27]

Langerhans cell histiocytosis

- Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X, is a rare condition characterized by abnormal production of histiocytes[9] and eosinophils.[10]
- LCH may manifest as solid, localized tumours or as multiorgan disease.
- LCH is more common in pediatric populations.
- Etiology is not known.
- The most common form of LCH is an eosinophilic granuloma, which presents as localized, lytic bone lesions and is usually benign. Oral swellings or ulcerations resulting from maxillary or mandibular bone involvement are common with this form.
- In multiorgan disease, oral ulcerations may develop on the gingiva or palate, along with a necrotizing gingivitis. [4]

Letterer-Siwe disease and Hand-Schüller-Christian disease are 2 other forms of LCH that may be associated with oral manifestations.

- Letterer-Siwe disease is most common in infants and is highly aggressive. Oral symptoms include large ulcerations, ecchymosis, gingivitis, and periodontitis with subsequent tooth loss.
- Hand-Schüller-Christian disease is more localized, with oral lesions similar to those in Letterer-Siwe disease. Oral findings may be the primary manifestation of Hand-Schüller-Christian disease and include irregular ulcerations of the hard palate, gingival inflammation, difficulty in chewing, and halitosis. [4]

Multiple myeloma

- Multiple myeloma is a cancer characterized by excessive proliferation and improper function of plasma cells (type of WBC)[11], resulting in bone destruction and displacement of healthy blood cells.
- Plasma cells are produced and mainly reside in bone marrow. Excessive plasma cells may eventually form a single tumour (i.e., solitary plasmacytoma) or several tumours (i.e., multiple myeloma) in various sites of the body, especially bone marrow. Plasma cells produce immunoglobulin M (IgM), a type of antibody and a key

[9] Histiocytes are nonmotile macrophages (type of WBC) that reside in tissues, especially connective tissue.
[10] Eosinophils are a type of WBC that circulate in the blood and is responsible for combating parasites.
[11] Refer to Episodes 44 & 45 for additional information on plasma cells.

component of humoral immunity[12] (also called antibody-mediated immunity). Overproduction of plasma cells results in abnormally high levels monoclonal proteins (M proteins) within the blood and urine.
- Symptoms of multiple myeloma may include bone pain (especially in spine and ribs); low levels of circulating red blood cells (anemia) resulting in weakness, fatigue, and pallor; reduced kidney function; and increased susceptibility to infections.
- Etiology is not known.
- Oral manifestations may include osteolytic (bone) lesions, with about 30% of individuals experiencing mandibular involvement, which is associated with swelling, pain, paresthesia, and tooth loss. Approximately 14% of individuals have oral manifestations, which may include gingivitis, periodontitis, and dome-shaped masses that tend to ulcerate. Thrombocytopenia secondary to hematopoietic suppression can result in ecchymosis and gingival bleeding. [4] [28] [29]

Mastocytosis
- Mastocytosis is a rare disorder characterized by abnormal accumulation and activation of mast cells[13] in the skin, bone marrow, and internal organs (gastrointestinal tract, liver, spleen, lymph nodes).
- Pathologic proliferation of mast cells results in a wide range of symptoms (mild to life-threatening). Symptoms are mainly due to the release of chemicals (e.g., histamine, heparin, cytokines) from the mast cells and thus produce symptoms associated with an allergic reaction, although a true allergic trigger may not be identified.
- Symptoms may include headache, urticaria, diarrhea, flushing, and anaphylaxis.
- Mastocytosis is usually caused by a mutation in the *KIT* gene and is typically not inherited. Mastocytosis can affect both children and adults.
- Mast cell infiltration of the salivary glands can result in a Sjögren-like syndrome, characterized by xerostomia and associated complications. While oral manifestations are rare compared to involvement of long bones or ribs, painful osteolytic lesions of the maxilla or mandible have been reported. [4] [30] [31]

Platelet disorders

Thrombocytopenia
- Thrombocytopenia is a condition caused by a low number of platelets (thrombocytes) in the blood, resulting in increased bruising, petechiae, and bleeding from mild trauma. Severe thrombocytopenia may result in an increased risk of spontaneous bleeding. The normal range for platelets is 150,000-300,000 platelets per microliter of blood. Thrombocytopenia is a platelet count of <150,000/mm^3.
- Thrombocytopenia can be caused by certain cancers (e.g., leukemia), cancer treatments (e.g., chemotherapy, radiation therapy), medications, infections (e.g., hepatitis C), and autoimmune diseases (e.g., immune thrombocytopenic purpura). It is rarely inherited.
- Oral manifestations may include:

[12] Refer to Episode 45 for additional information on humoral immunity.
[13] Mast cells are granulocytes (type of WBC) that play a vital role in immune responses, especially allergy and anaphylaxis.

- Petechiae and ecchymosis on the buccal mucosa and soft palate.
- Gingival bleeding is common and often spontaneous.
- In severe thrombocytopenia, hemorrhagic bullae appear as deep red, purple, or black blisters which may be seen on mucosal surfaces. [4] [32] [33] [34]

Red blood cell disorders

Anemias

- Common anemias associated with oral manifestations include iron-deficiency anemia and megaloblastic anemia secondary to vitamin B12 deficiency.
- Megaloblastic anemia (or macrocytic anemia) is a condition where the bone marrow produces unusually large, structurally abnormal, immature RBCs (megaloblasts).
- Different types of megaloblastic anemia can be classified depending on the cause.
- Usually, megaloblastic anemias are caused by vitamin B12 or B9 (folate) deficiency (sometimes called vitamin-deficiency anemia). Vitamins B12 and B9 are essential in the production of RBCs.
- Causes of vitamin B12 deficiency may include insufficient dietary intake of B12 (e.g., due to vegetarian or vegan diet, malnutrition) or malabsorption (e.g., due to gastric surgery, inflammatory bowel disease, aging, certain medications that interfere with absorption, heavy alcohol consumption).
- Symptoms common to anemia may include fatigue, pallor, shortness of breath, lightheadedness, dizziness, headaches, chest pain, and arrhythmia or tachycardia.
- All forms of anemia can cause oral mucosal pallor. [4] [35] [36] [37] [38] [39] [40] [41]

Hemochromatosis

- Hemochromatosis is a disorder in which the body builds up too much iron in the skin, heart, liver, pancreas, pituitary gland, and joints. High levels of iron are toxic and can eventually cause organ damage.
- It may be caused by hereditary hemochromatosis, transfusion iron overload (directly associated with the number of blood transfusions), chronic hemolysis (destruction of RBCs), or excess dietary iron.
- Symptoms may include increased skin pigmentation, joint pain (commonly in the knuckle and first joint of the first 2 fingers), abdominal pain, fatigue, weakness, diabetes, weight loss, heart failure, liver failure, memory fog, and loss of sex drive.
- Increased skin pigmentation is often one of the first signs of the disease and may precede other features by many years. It can affect >90% of individuals and is most evident on sun-exposed skin, particularly on the face. Increased pigmentation causes the classic bronze or gray skin colour.
- Generally, hemochromatosis is treated with regularly scheduled phlebotomy (i.e., drawing a unit of blood at a time), which is the most direct and safe way to lower iron stores.
- Oral manifestations are observed in about 15-25% of individuals, with the majority presenting with blue-gray hyperpigmentation of the oral mucosa. Usually, the buccal mucosa and gingiva are affected, although some present with diffuse, homogenous pigmentation of the oral cavity. Histologic examination reveals iron mineral deposits. [4] [42] [43] [44] [45] [46] [47]

Congenital erythropoietic porphyria

- Congenital erythropoietic porphyria (CEP) is a very rare inherited metabolic disorder affecting the synthesis of heme.[14] CEP causes porphyrins[15] to accumulate in the skin and other tissues. High levels of porphyrins can cause significant problems (e.g., they are photosensitizers and injure tissues when exposed to light).
- Clinical signs may be present from birth and can range from mild to severe. Signs may include:
    - Photosensitivity resulting in blisters, erosions, swelling, and scarring of skin exposed to light.
    - Excessive hair growth (hypertrichosis) in light-exposed areas.
    - Corneal scarring and eye inflammation.
    - Reddish urine.
    - Hemolytic anemia. Severe hemolytic anemia results in an enlarged spleen.
- Oral signs may include erythrodontia (red/brown discoloured teeth) which fluoresce when exposed to ultraviolet light. [4] [48] [49] [50] [51]

Sickle cell disease

- Sickle cell disease is a group of inherited disorders caused by mutations in the hemoglobin subunit beta (*HBB*) gene.[16] Individuals with this disease have atypical hemoglobin molecules called hemoglobin S, which can distort RBCs into a sickle or crescent shape. The sickle-shaped RBCs die prematurely, which can lead to anemia.
- Sickle cell disease is most common among individuals with ancestors from Africa, the Mediterranean, India, South America, Central America, and parts of the Caribbean.
- Signs and symptoms may include anemia, repeated infections, and periodic episodes of pain. Symptoms maybe mild to severe, varying from person to person, and usually begin in early childhood. Anemia can cause shortness of breath, fatigue, and delayed growth and development in children.
- Hemolysis may cause yellowing of the eyes and skin (jaundice). Sickle cells can damage the spleen, increasing susceptibility to infections. Episodes of pain can occur when sickled RBCs, which are stiff and inflexible, get stuck in small blood vessels depriving tissues and organs (e.g., lungs, kidneys, spleen, brain) of oxygen-rich blood, which can lead to organ damage, stroke, chest pain, etc. Pain can vary in intensity lasting for a few hours to a few days.
- Oral manifestations in sickle cell disease may vary.
    - The most common oral manifestations are pallor and jaundice of the oral mucosa due to anemia and hemolysis. Pallor of the gingiva may also be observed.
    - Although uncommon, osteomyelitis of the jaw has been reported in the maxilla and mandible.

[14] Heme is the iron-containing molecule that combines with globin proteins to form hemoglobin (the protein in RBCs that carries oxygen to cells throughout the body).
[15] Porphyrins are ring-shaped molecules with a reddish hue that undergo a series of chemical changes to produce heme.
[16] The *HBB* gene provides instructions for making one part of hemoglobin called beta-globin.

- Vascular occlusion in the maxillofacial region can occur in the narrow canals of major nerves supplying the maxilla and the mandible causing loss of sensation and neuropathy. The mental nerve and inferior alveolar nerve are especially vulnerable because they pass through narrow foramina and boney canals. As a result, individuals may experience numbness of the chin, lips, gingiva, mucosa, and teeth.
- Vascular occlusion of the dental pulp may cause pulpal necrosis without obvious etiology.
- Enamel hypoplasia, dentin hypoplasia, and delayed tooth eruption has been reported.
- Dental caries are also more common in individuals with sickle cell disease, possibly due to increased susceptibility to pathogens (e.g., *Streptococcus mutans*). Also, oral healthcare may be a secondary concern for many individuals trying to manage the disease. [4] [52] [53] [54]

Polycythemia vera

- Polycythemia vera is a rare type of slow developing blood cancer involving overproduction of blood cells in the bone marrow, especially RBCs. Overproduction of RBCs leads to abnormally high numbers of circulating RBCs within the blood. Consequently, the blood increases in volume and thickens, elevating risk of blood clots, which may prevent blood flow to vital organs.
- Polycythemia vera occurs when a gene mutation causes a problem with blood cell production. The cause of the gene mutation is unknown, but it is generally not inherited.
- Symptoms may include headaches, fatigue, weakness, dizziness, itchy skin (especially after a warm shower or bath), splenomegaly, unusual bleeding (e.g., nosebleeds), shortness of breath, blurred vision, tinnitus, and abnormal redness of the skin, especially on the face.
- Oral manifestations are less common and may include petechial hemorrhages, easy bruising, and gingival bleeding. A deep-red/purple hue may be present on the tongue, gingiva, and other mucosal surfaces. [4] [55] [56]

Nutritional disorders

Suboptimal nutritional intake can lead to chronic systemic diseases. It can also affect oral health by increasing the risk of dental caries, periodontal diseases, delayed healing, and impaired mucous membrane integrity.

Nutritional deficiencies may result from:

- Reduced nutrient intake due to inadequate diet, substance use disorder (alcohol and other drugs), or psychiatric conditions (e.g., anorexia nervosa, bulimia nervosa).
- Inability to absorb ingested vitamins and minerals due to pancreatic insufficiency, infectious agents, enzyme deficiencies, GI disease, systemic diseases, and intestinal resection or radiation.
- Increased host demand, such as pregnancy.
- Poor oral health which can alter food choices and negatively impact food intake. [4]

Water-soluble vitamins

Water-soluble vitamins include B vitamins and vitamin C. These vitamins need to be regularly replaced through dietary intake because they are stored in limited quantities in the body. Thus, hypervitaminosis of water-soluble vitamins is rare.

Oral manifestation of water-soluble vitamin deficiencies [4] [57]

Vitamin deficiency	Oral manifestations
Vitamin B2 (riboflavin)	• Erythema of pharyngeal and oral mucous membranes • Atrophic glossitis, often with a magenta hue • Glossodynia • Cheilosis • Angular cheilitis
Vitamin B3 (niacin, nicotinic acid) Deficiency is known as pellagra	• Mucosal edema • Cheilosis • Angular cheilitis • Bright red glossitis • Burning mouth • Gingival erythema • Dental caries
Vitamin B5 (pantothenic acid)	None known
Vitamin B6 (pyridoxine)	• Atrophic glossitis • Cheilosis • Angular stomatitis • Gingival erythema
Vitamin B7 (biotin, vitamin H)	None known
Vitamin B9 (folic acid)	• Atrophic glossitis with erythema and tongue swelling • Angular cheilitis • Glossodynia • Dysphagia • Recurrent aphthous stomatitis
Vitamin B12 (cobalamin)	• Generalized stomatitis • Taste disturbance • Red, atrophic, beefy, burning tongue with bald appearance due to loss of filiform papillae • Recurrent aphthous stomatitis
Vitamin C (L-ascorbic acid, ascorbic acid) Deficiency is known as scurvy	• Mucosal petechiae • Hemorrhagic gingivitis • Gingival bleeding • Gingival hypertrophy • Intraoral ulceration • Tooth mobility • Tooth loss • Impaired wound healing

Fat-soluble vitamins

The fat-soluble vitamins A, D, E, and K are readily stored in the body. Although reservoirs prevent against deficiencies, the risk of hypervitaminosis is increased.

Oral manifestations of fat-soluble vitamin deficiencies and toxicities [4] [58]

Vitamin deficiency / toxicity	Oral manifestations
Vitamin A (retinol) deficiency	• Xerostomia • Periodontal disease • Increased intraoral infection • Impaired tooth development in children
Vitamin A (retinol) toxicity	• Cheilitis • Gingivitis • Impaired healing
Vitamin D (calciferol, cholecalciferol, ergocalciferol) deficiency	• Loss of periodontal attachment • Recurrent aphthous stomatitis • Associated with higher risk of tooth defects, caries, tooth loss, gingival bleeding[17]
Vitamin D (calciferol, cholecalciferol, ergocalciferol) toxicity	None known
Vitamin E (tocopherol or alpha-tocopherol) deficiency	None known
Vitamin E (tocopherol or alpha-tocopherol) toxicity	None known
Vitamin K (phylloquinone) deficiency	• Submucosal hemorrhage • Gingival bleeding
Vitamin K (phylloquinone) toxicity	None known

Minerals

Minerals are crucial to numerous cellular functions and deficiencies have been associated with many systemic and oral conditions.

Oral manifestation of mineral deficiencies [4] [59]

Mineral deficiency	Oral manifestations
Iron	• Angular cheilitis • Atrophic glossitis • Glossodynia • Recurrent aphthous stomatitis
Zinc	• Burning mouth syndrome • Recurrent aphthous stomatitis • Perioral or intraoral erosions • Dysgeusia • Angular cheilitis • Impaired wound healing

[17] Refer to Episode 22 for additional information on vitamin D and oral health.

Take home messages

- The oral cavity may be one of the first sites affected by a systemic disease.
- Oral healthcare professionals play a key role in the early detection and referral of unidentified systemic disease with oral manifestations for timely diagnosis and treatment. This stresses the importance of thorough medical history updates; comprehensive intra- and extra-oral examinations; and being knowledgeable of oral conditions associated with systemic diseases and nutritional disorders.
- Oral healthcare professionals have the opportunity to collaborate with other health professionals such as physicians, nurse practitioners, medical specialists, and registered dieticians to help improve clients' systemic health, oral health, and quality of life.

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