

Oral mucosal changes associated with primary diseases in other body systems

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1 | INTRODUCTION

The oral cavity may be the first site of mucosal changes that may represent local mucosal disease and systemic conditions or be part of a broader systemic involvement. Although oral tissues may not be the primary morbidity-determining or mortality-determining organ, they may negatively impact on oral function and quality of life. Oral manifestations may therefore lead to a diagnosis of the underlying systemic disease. The objective of this chapter is to review mucosal changes in systemic diseases in order to facilitate the clinical detection of these oral manifestations and, accordingly, to provide appropriate advice to patients. The diseases were classified according to the organ system involved (Box 1). Due to the extensive scope of conditions, the chapter presents a concise review and will focus on oral mucosal and gingival changes in a systematic approach.

2 | WHITE BLOOD CELL LINEAGE DISORDERS

The white blood cell disorders are a group of diseases causing an increased risk of infection and impacting the healing of tissue wounds. The white blood cell count may be reduced or elevated, or within normal limits with inadequate function. Furthermore, anticancer treatment of hematologic conditions may affect white blood cell count and function. This is particularly relevant in patients following chemotherapy and hematopoietic stem cell transplantation. For the purpose of the review, the disorders of the white blood cell lineage

will be described separately, although they often occur concomitantly with deficiency of the red blood cell lineage and platelets, especially when the bone marrow is the source of the disorder. The main white blood cell diseases will be reviewed, followed by a description of all the oral mucosal manifestations.

The leukemias are malignant neoplasms of the white blood cells involving bone marrow, circulating white blood cells and organs rich in this cellular lineage, such as spleen and lymph nodes. Malignant transformation usually occurs at the pluripotent stem cell level, although it sometimes involves a committed stem cell line with a limited capacity for further cellular differentiation. Abnormal proliferation, clonal expansion and diminished apoptosis (programmed cell death) may lead to the replacement of normal blood elements by malignant cells.

Lymphomas are a heterogeneous group of neoplasms arising in the reticuloendothelial and lymphatic systems. The major types are Hodgkin lymphoma and non-Hodgkin lymphoma.¹ Lymphomas were once thought to be distinct from leukemias. However, better understanding of cell markers and improved evaluation show that there may be overlap between these malignancies. Multiple myeloma is the most common primary malignant neoplasm found in bone arising from hematopoietic derivation and occurs mostly in older adults. Multiple myeloma may first be identified as a single lesion or a few lesions called plasmacytomas. However, the distinction between isolated lesions and wider involvement including the marrow can be difficult. Multiple myeloma may become multicentric, affecting the bone marrow in many parts of the body, with diagnosis usually confirmed on bone marrow biopsy. Imaging studies may show sharply

BOX 1 Body systems and diseases that manifest in mucosal/gingival changes. Numbering follows the order of the topics in this review.

System	Diseases covered in this review	Mucosal/gingival changes related to:
1. White blood cell lineage disorders	<ul style="list-style-type: none"> • Leukemia • lymphoma • multiple myeloma • nonmalignant white blood cell diseases 	<ol style="list-style-type: none"> 1. Neutropenia 2. Proliferation of white blood cells 3. White blood cell dysfunction 4. White blood cell disorders, other 5. Pancytopenia
2. Red blood cell lineage disorders	<ul style="list-style-type: none"> • Polycythemia vera • anemia (including nutritional deficiencies, thalassemia, sickle cell disease) 	<ol style="list-style-type: none"> 1. Polycythemia vera 2. Anemia (including nutritional deficiencies, thalassemia, sickle cell disease)
3. Bleeding disorders	<ul style="list-style-type: none"> • Platelets (thrombocytopenia and qualitative defects) • coagulopathies • damage to blood vessel wall 	<ol style="list-style-type: none"> 1. Bleeding disorders
4. Pancytopenia	<ul style="list-style-type: none"> • Aplastic anemia • Fanconi anemia 	<ol style="list-style-type: none"> 1. Aplastic anemia 2. Fanconi anemia
5. Oral mucosal complications secondary to hematologic cancer treatment	<ul style="list-style-type: none"> • Chemotherapy and radiotherapy • hematopoietic stem cell transplantation • targeted therapy 	<ol style="list-style-type: none"> 1. Mucositis 2. Graft vs host disease 3. Targeted therapy adverse effect
6. Liver disease	<ul style="list-style-type: none"> • Primary liver diseases <ul style="list-style-type: none"> ○ hepatitis C ○ alcohol-induced ○ drug toxicity ○ autoimmune hepatitis ○ biliary cirrhosis • diseases associated with hepatitis • liver transplant 	<ol style="list-style-type: none"> 1. Primary liver disease 2. Diseases associated with hepatitis 3. Complications of liver transplant
7. Kidney diseases	<ul style="list-style-type: none"> • Kidney failure • kidney transplantation 	<ol style="list-style-type: none"> 1. Kidney failure 2. Kidney transplantation
8. Connective tissue diseases	<ul style="list-style-type: none"> • Lupus erythematosus • scleroderma • Sjögren syndrome 	<ol style="list-style-type: none"> 1. Lupus erythematosus 2. Scleroderma 3. Sjögren syndrome
9. Endocrine diseases	<ul style="list-style-type: none"> • Diabetes mellitus • adrenal insufficiency • multiple endocrine neoplasia syndrome • syndrome of inappropriate antidiuretic hormone secretion 	<ol style="list-style-type: none"> 1. Diabetes mellitus 2. Rare endocrine diseases with oral mucosal manifestation
10. Pulmonary diseases	<ul style="list-style-type: none"> • Asthma • chronic obstructive pulmonary disease 	<ol style="list-style-type: none"> 1. Asthma and chronic obstructive pulmonary disease
11. Immunologic diseases	<ul style="list-style-type: none"> • Angioedema • Behçet disease • autoimmune inflammatory diseases <ul style="list-style-type: none"> ○ periodic fever, aphthous-stomatitis, pharyngitis, adenitis ○ familial Mediterranean fever ○ hyperimmunoglobulinemia D periodic fever syndrome ○ tumor necrosis factor receptor-associated periodic syndrome ○ pyogenic sterile arthritis, pyoderma gangrenosum acne 	<ol style="list-style-type: none"> 1. Behçet disease and inflammatory syndromes
12. Nutritional deficiencies	<ul style="list-style-type: none"> • Various nutritional deficiencies 	<ol style="list-style-type: none"> 1. Vitamin A (retinol) deficiency 2. Vitamin B12 (riboflavin) deficiency 3. Vitamin B3 (niacin) deficiency 4. Vitamin B6 (pyridoxine) deficiency 5. Vitamin B7 (biotin) deficiency 6. Vitamin C (ascorbic acid) deficiency 7. Vitamin K (phylloquinone) deficiency 8. Iron, vitamin B9 (folate), vitamin B12

BOX 1 (Continued)

System	Diseases covered in this review	Mucosal/gingival changes related to:
13. Dermatologic diseases	<ul style="list-style-type: none"> • Mucocutaneous diseases • malignant acanthosis nigricans • sweet syndrome • Peutz-Jeghers syndrome • hereditary hemorrhagic teleangiectasia 	<ol style="list-style-type: none"> 1. Lichen planus 2. Pemphigus 3. Paraneoplastic pemphigus 4. Pemphigoid 5. Erythema multiforme 6. Other paraneoplastic syndromes with dermatologic manifestation
14. Vascular diseases	<ul style="list-style-type: none"> • Cyanotic heart diseases • polyarteritis nodosa • giant cell arteritis 	<ol style="list-style-type: none"> 1. Vascular diseases
15. Gastrointestinal diseases	<ul style="list-style-type: none"> • Celiac disease • Crohn's disease • ulcerative colitis • gastric regurgitation <ul style="list-style-type: none"> ○ acid reflux ○ pernicious anemia ○ Plummer-Vinson syndrome 	<ol style="list-style-type: none"> 1. Celiac disease 2. Crohn's disease 3. Ulcerative colitis 4. Gastric regurgitation
16. Other diseases	<ul style="list-style-type: none"> • Amyloidosis 	<ol style="list-style-type: none"> 1. Amyloidosis
17. Oral neoplasm		<ol style="list-style-type: none"> 1. Head and neck cancer 2. Complications of treatment for head and neck cancer

circumscribed lytic lesions or diffuse demineralization, including involving the jaw. Rarely, the lesion can appear as sclerotic or as diffuse osteopenia, especially in a vertebral body. Amyloidosis secondary to multiple myeloma is a common manifestation and will be reviewed below (see "Amyloidosis").

The spectrum of nonmalignant white blood cell diseases is very broad. This review will touch on granulocyte defects, including cyclic neutropenia, chronic granulomatous disease, Chediak-Higashi syndrome, leukocyte adhesion defect, Papillon-Lefevre syndrome, Job syndrome (hyperimmunoglobulinemia E) and Schwachman syndrome (lazy leukocyte syndrome). These diseases have similar oral manifestations. The oral mucosal complications will be categorized according to the white blood cell count (decreased/increased), white blood cell dysfunction and other complications.

2.1 | Neutropenia-related oral mucosal changes

2.1.1 | Infection

Oral infections with mucosal presentations are very common. Candidiasis is the most common, followed by herpes simplex virus infection (Figures 1 and 2).² In immuno-suppressed patients, these oral manifestations represent local infection due to a systemic predisposition and, like other infections in these patients, can have local, regional and systemic spread. Bacterial and fungal infections are also common. The onset is often rapid in immunocompromised individuals. The clinical presentation of candidiasis and viral infections is typical and can often be diagnosed clinically.³ Specifically,

candida infections commonly appear as white removable plaques, red patches on the palate or dorsum of the tongue, or redness at the angles of the mouth. The viral infections often manifest as small vesicles that rupture and may coalesce into larger ulcerative lesions, most often involving keratinized oral tissue. In contrast, bacterial infections can be a diagnostic challenge due to reduced clinical signs and symptoms that rely upon the presence of functional white blood cells that leads to signs and symptoms of infection. Less frequent oral infections include the deep fungal infections, such as aspergillosis, histoplasmosis, penicilliosis and mucormycosis, which have a poor prognosis and spreading necrosis is characteristic.⁴

2.1.2 | Impaired healing, oral ulcers and mucosal necrosis

Long-lasting oral ulcers may appear (Figure 3) and when no microbial pathogen is isolated from the ulcer it is diagnosed as a neutropenic ulcer. Such ulcers are relatively prevalent in the gingival tissues, probably because this area is prone to minor injuries while eating, brushing or flossing and the presence of a heavy bacterial biofilm.⁵ These painful ulcers vary in shape and tend to resolve when the white blood cell count returns to normal. Patients with a history of recurrent aphthous stomatitis (RAS) may experience periods of increased RAS activity. When the oral ulcer progresses into an extensive mucosal necrosis it is referred in the literature as *necrotizing stomatitis*. When no microbial pathogen is isolated in necrotizing stomatitis, the diagnosis of oral infection cannot be confirmed, and then the pathology is considered neutropenia-related.



FIGURE 1 Oral candidiasis. Multiple white removable plaques presented on the dorsum of the tongue



FIGURE 3 An ulcer on the dorsum of the tongue in a patient with neutropenia



FIGURE 2 Reactivation of herpes simplex virus. Small vesicles and ulcers are present on the lower lip vermilion

2.1.3 | Pericoronitis

Gingival inflammation surrounding a partially erupted tooth in otherwise healthy patients is well known. However, in patients with a disease of white blood cells, this condition may be more severe and may become life-threatening. The inflammatory changes, edema and erythema may spread to the adjacent oral mucosa, which may necrose.

2.2 | Oral mucosal and other changes related to proliferation of white blood cells

2.2.1 | Gingival enlargement

Leukemic infiltrates may concentrate in the gingivae, causing enlargement. The gingivae usually bleed easily and show accumulation of plaque deposits secondary to the abnormal gingival anatomy and

challenges in oral hygiene. The gingivae may be painful. This may be due to secondary infection or cellular engorgement, particularly in the keratinized gingivae, and such changes are more common in monocytic leukemia, but can occur in other leukemia subtypes.^{6,7} Accumulation of leukemic infiltrate may also present as an isolated mass in the oral cavity.⁸

2.2.2 | Rapidly progressive periodontitis

Leukemic infiltrates involving the alveolar bone, combined with neutropenia, may lead to rapid destruction of periodontal tissues with necrotic papillae, loss of alveolar bone support, mobility of teeth and bone exposure.

2.2.3 | Neuropathy

Although this is not a mucosal disease per se, the patient may complain of abnormal mucosal sensations. Nerve damage may manifest as paresthesia, anesthesia or pain. It may be caused by microscopic leukemic infiltration adjacent to the nerve, resulting in compression of the nerve or due to central involvement. Anticancer treatment may also trigger neuropathy (see "Oral mucosal complications secondary to hematologic cancer treatment").

2.2.4 | Plasmacytoma

Typical in multiple myeloma, plasma cells accumulate in isolated areas. Often there is more than one plasma cell mass simultaneously. When this mass is in the skeleton it can be identified radiographically as a lytic lesion. When the plasma cell mass is superficial, it may present as a raised nonpainful mucosal mass covered by normal mucosa.

2.2.5 | Lymphoma

Lymphoma may also appear as a mass in the gingiva or the jaw bone at the time of diagnosis. Most oral lymphomas develop in the tonsils or at the parotid gland.⁹ The most frequently reported signs and symptoms are swelling, pain, paresthesia, anesthesia, ulceration and discoloration.¹⁰ Notably, in the endemic type of Burkitt lymphoma, also known as African type, maxillary involvement is common.¹¹ In the case of post-transplantation lymphoproliferative diseases, the appearance of the lesions is highly variable and mucosal mass, ulceration or irregular surface anatomy may occur.¹²

2.3 | White blood cell dysfunction-related oral mucosal changes

Gingivitis and oral ulcerations are common manifestations. The gingivitis related to granulocyte defect diseases is not correlated with plaque levels. The gingivae have a red color and the papillae may be edematous and tend to bleed readily. Several granulocyte defect diseases present with oral ulcers, specifically in cyclic neutropenia, Chediak-Higashi syndrome, Job's syndrome and lazy leukocyte syndrome.¹³ Some understanding about the etiopathogenesis of oral ulcers in granulocyte defect diseases may be extrapolated based on studies in recurrent aphthous lesions. Studies in recurrent aphthous stomatitis indicate that the innate immune system contributes to the lesion, involving changes in reactive oxygen intermediates and expression of CD11b, TNF-RI and TNF-RII.¹⁴ These diseases are relatively rare and therefore there is limited data on the frequency of the oral ulcers and their management. The prevention and treatment of infections is a fundamental element in the clinical approach for the management of oral ulcers. Management of the underlying disease is critical for the resolution of oral lesions.¹⁵⁻¹⁷

2.4 | Other oral mucosal changes in white blood cell disorders

Amyloidosis-related oral mucosal manifestations are typical to multiple myeloma; paraprotein may accumulate in the tissues (see "Amyloidosis"). The presence of leukemic cells in the bone marrow volume may cause a significant decrease in platelet production and decreased red blood cell production (pancytopenia); furthermore, some of the antimalignancy treatments cause bone marrow aplasia (see "Platelet disorders-related oral manifestations" and "Anemia-related oral mucosal changes").

3 | RED BLOOD CELL LINEAGE DISORDERS

Polycythemia vera is a nonaggressive myeloproliferative disorder, characterized by an increase in red blood cell mass, often with uncontrolled production of granulocytes and platelets. Anemia represents a decrease in red blood cells and/or hemoglobin concentration; this

may be a result of a decrease or impaired production or an increased destruction or loss of red blood cells. The most common causes of anemia include dietary deficiencies of iron, folic acid, and/or vitamin B12, malabsorption (eg of B12 as part of pernicious anemia), chronic infections, inflammatory (autoimmune) connective tissue disorders, renal and hepatic diseases, malignancies (owing to chronic bleeding or bone marrow failure), splenomegaly, antibodies against red blood cells, snake venom, sickle cell disease and thalassemia.

3.1 | Polycythemia vera-related oral mucosal changes

The main oral manifestations of this disorder include a red-purple color of the oral mucosa and gingiva, glossitis, gingival bleeding and oral ecchymoses.¹⁸

3.2 | Oral mucosal changes related to anemia

In patients with anemia, the oral mucosa may be pale (or yellowish in sickle cell disease, due to hemolytic jaundice; Figure 4). Anemia caused by iron, folate or B12 deficiency may cause glossitis, which presents as tongue soreness, sometimes even before hemoglobin levels fall, especially in folate- and B12-related anemia.¹⁹ Later, tongue inflammation and atrophy of the filiform papillae cause the typical appearance of glossitis (Figure 5). Individuals with anemia are prone to recurrent aphthous stomatitis involving the nonattached movable oral mucosae, especially in folate or B12 deficiency. Indeed, anemia is a main cause for aphthae that start late in life (in comparison with classic idiopathic aphthae, which tend to start in the first three decades of life). In individuals already suffering from recurrent aphthous stomatitis, anemia can worsen the aphthae (eg shorten the interval between attacks, increase the number of lesions in each attack).¹⁹ Anemia, especially iron deficiency-related, is a risk factor for *Candida*-related lesions such as oral candidiasis and angular cheilitis (Figure 6). Anemia is one of the causes of gustatory dysfunction.²⁰



FIGURE 4 Yellowish hue is prominent in the gingivae and oral mucosa indicating jaundice in a patient with liver disease

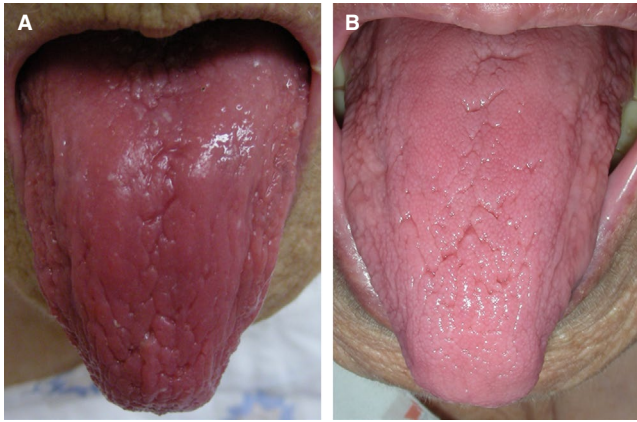


FIGURE 5 A, Glossitis; red depapillated, smooth, shiny tongue. The patient complained of a burning sensation in the tongue and a loss of taste. The patient's red blood cell count was of 3.67×10^6 cells/ μL (normal $3.80\text{--}5.20 \times 10^6$ cells/ μL), hemoglobin level of 10.3 g/dL (normal 12.0–16.0 g/dL for women), iron level of 46.9 $\mu\text{g/dL}$ (normal 37.0–170.0 $\mu\text{g/dL}$) and transferrin level of 176.8 mg/dL (normal 200.0–400.0 mg/dL). B, Normal appearance of the tongue of the same patient after resolving



FIGURE 6 Angular cheilitis can be seen in patients with anemia and other nutritional deficiencies

Anemia is common in several patient populations and with other comorbid conditions. Common comorbidities associated with anemia, which also may contribute to taste alterations and/or sensory disturbance, include cancer, gastrointestinal diseases and chronic kidney disease.^{21–25} These patients are often on poly-drug treatment, which may also contribute to an altered taste sensation.²⁰

Patients with thalassemia major who undergo treatment with regular blood transfusions may suffer from hyposalivation and xerostomia due to iron overload and deposition in, and damage to, the salivary glands. This indirectly may affect the oral mucosa, leading to irritation and erythema. Although bone pathology is not within the scope of this review, it is relevant to mention that thalassemia patients may be treated with bisphosphonates for the prevention of osteoporosis. Consequently, mucosal changes secondary to osteonecrosis of the jaws may be present, such as erythema and edema, granulation tissue surrounding the exposed bone and purulent discharge.²⁶

Plummer-Vinson syndrome is a rare condition (also known as Paterson-Kelly syndrome and sideropenic dysphagia) is associated with iron-deficiency anemia and manifests as painful glossitis and dysphagia caused by abnormal bands in the esophagus – termed esophageal webs. Other possible manifestations include angular cheilitis and spoon-shaped disfiguration of the nails (koilonychias). These patients are at risk of oral, hypopharyngeal and esophageal squamous cell carcinoma.²⁷

4 | BLEEDING DISORDERS

Bleeding disorders can be classified as platelet disorders, coagulopathies and disorders of the blood vessel wall. Disorders of platelets may be due to a reduced quantity or impaired platelet function. Thrombocytopenia is a significant decrease in the number of circulating platelets, resulting from reduced production (eg in bone marrow failure), increased destruction (eg in HIV disease, systemic lupus erythematosus and idiopathic immune thrombocytopenic purpura) and sequestration in the spleen (eg in hepatic disease and Gaucher disease). Altered platelet function may be due to a change in the adhesion, activation or aggregation of the platelets. The platelet dysfunction may be reversible (eg in the case of administration of nonsteroidal anti-inflammatory drugs) or irreversible (eg in the case of administration of aspirin and in inherited diseases such as Glanzmann's thrombasthenia).

Clotting disorders caused by coagulation defects may be hereditary (eg hemophilia A and B, von Willebrand disease) or acquired (eg vitamin K deficiency), or arise from advanced liver disease, anticoagulant therapy. In hemophilia A, factor VIII is deficient; in hemophilia B, factor IX is deficient; in von Willebrand disease, von Willebrand factor is deficient. As von Willebrand disease binds and stabilizes factor VIII, patients with von Willebrand disease suffer from factor VIII deficiency too.^{27–29} The acquired coagulopathies are related to a disease- or medication-induced lack of factors or cofactors needed for the coagulation cascade.^{30,31}

Bleeding tendency may be due to disorders of the blood vessel walls. The endothelium and the connective tissue surrounding the blood vessel are implicated in the pathogenesis of such bleeding.^{32,33} Disorders of the vessel walls may be due to vessel structural malformation or inherited or acquired connective tissue disorders. Examples are scurvy due to vitamin C deficiency resulting in impaired collagen synthesis (see “Scurvy”), Cushing syndrome due to excessive (endogenous or exogenous) corticosteroids resulting in general protein wasting and loss of the perivessel support of connective tissue, Ehler-Danlos syndrome, which is characterized by hyperelasticity of the skin, and Osler-Weber-Rendu syndrome with abnormal telangiectasia, which can profusely bleed spontaneously or with only minor injury.

4.1 | Bleeding disorders-related oral mucosal changes

4.1.1 | Bleeding

Bleeding is the main oral complication of platelet disorders, either thrombocytopenia (including autoimmune- and HIV-related

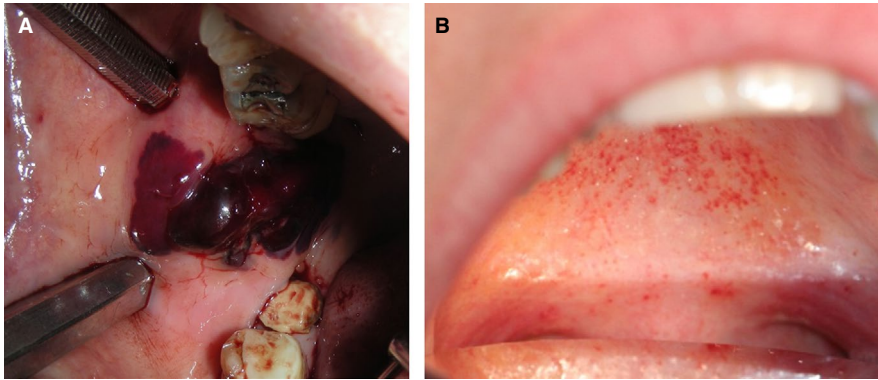


FIGURE 7 Oral manifestations of thrombocytopenia. A, Submucosal hemorrhage in a patient with a platelet count of 10×10^9 cells/L (normal $>140 \times 10^9$ cells/L). B, Palatal petechiae

thrombocytopenia) or qualitative platelet defects, and may present as petechiae, ecchymoses, excessive (gingival) bleeding and blood blisters anywhere on the lining oral mucosa. Excessive and prolonged bleeding may immediately follow a minor oral injury (even unnoticed injury), but usually eventually stops spontaneously in the presence of normal coagulation processes. Petechiae, purpura and ecchymoses result from platelet disorders and develop as a result of bleeding into the skin or mucosa. These three types of “easy bruising” differ by size, ie < 3 , 3 - 10 , > 10 mm, respectively (Figure 7).

4.2 | Coagulopathy-related oral mucosal changes

Delayed bleeding after an injury is typical of coagulopathies. Individuals with coagulopathy typically show bleeding after a short delay after the injury due to normal vascular and platelet responses at the initial stage of hemostasis. In contrast to bleeding related to platelet disorders, coagulopathy-related bleeding is persistent and, if untreated, can continue for days, weeks (or even until death) (Figure 8). Spontaneous gingival bleeding with swelling and ulceration are reported in plasminogen-related coagulopathies.³⁴ A thin film of fibrin (pseudomembrane) may be present along the gingivae as a result of dysfunctional fibrinolysis.³⁵

4.3 | Blood vessel wall disorder-related oral mucosal changes

Bleeding may arise from the gingiva or the oral mucosa, particularly from sites prone to trauma, such as the buccal and lingual mucosa adjacent to the occlusal line due to blood vessel wall defects. As a result, purpura and ecchymoses manifest as reddish point-size multifocal discoloration, visible through the mucosa, caused by hemorrhage into the tissues. It is typically observed in the soft palate. According to MeSH, when the size of the discoloration is > 2 - 3 cm it is generally called ecchymoses. This definition may be more appropriate to the skin than to the oral mucosa, although size is the most commonly used descriptor to distinguish purpura from an ecchymosis.

5 | PANCYTOPENIA

Pancytopenia may be a manifestation of a number of diseases. When the root of the disease is in bone marrow failure, the disease

is named aplastic anemia. Aplastic anemia is a hematologic disorder in which the hematopoietic precursor cells fail to produce an adequate quantity of red and white blood cells and platelets, resulting in pancytopenia. Aplastic anemia may be acquired or idiopathic. Possible causes for acquired aplastic anemia include immune disease or exposure to chemicals, drugs or radiation. In about half the cases it is idiopathic. Genetic predisposition plays a role in both types.^{36,37} Inherited causes of bone marrow failure include a small group of diseases.³⁷ Fanconi anemia is the most common inherited cause of bone marrow failure. Fanconi anemia patients are predisposed to myelodysplastic syndrome and acute myeloid leukemia during the first three decades of life and have increased risk of oral squamous cell carcinoma. In addition, these patients typically have short stature and other anomalies and café au lait spots on the skin.³⁸ Hematopoietic stem cell transplantation is the only curative modality for the hematologic manifestations of Fanconi anemia.

5.1 | Aplastic anemia-related oral mucosal changes

The oral manifestations of aplastic anemia include those found in anemia, thrombocytopenia and neutropenia; mainly mucosal pallor, petechiae, purpura and ecchymoses, neutropenic ulcers, bleeding due to thrombocytopenia. Gingival swelling is also a manifestation. However, the exact reason is not yet known.³⁹



FIGURE 8 Gingival bleeding in coagulopathy

5.2 | Fanconi anemia-related oral mucosal changes

Fanconi anemia manifestations are similar to pancytopenia. However, Fanconi anemia patients have a high risk of head and neck cancer, most commonly found in the oral cavity.⁴⁰ The prognosis of these patients is poor.⁴¹ Considering that solid tumors are rare in Fanconi anemia during childhood, except in patients with BRCA2/FANCD1 mutations, genetic testing is important to guide clinical management.⁴² In addition to the genetic predisposition of Fanconi anemia patients for oral cancer, as hematopoietic stem cell transplantation and graft vs host disease are associated with an increased risk for oral squamous cell carcinoma, patients with Fanconi anemia who undergo hematopoietic stem cell transplantation are considered to be at a higher risk for oral malignant transformation. Furthermore, the oral chronic graft vs host disease mucosal changes make it difficult to detect sites of transformation at an early phase. Specifically, the incidence of squamous cell carcinoma is 8% and 14% at 10 and 15 years after transplantation, respectively. Additionally, squamous cell carcinoma is the predominant cause of late mortality in Fanconi anemia posthematopoietic stem cell transplantation.⁴³ Other mucosal and gingival complications posthematopoietic stem cell transplantation may develop in Fanconi anemia patients (see "Oral mucosal complications secondary to hematological cancer treatment").

6 | COMPLICATIONS SECONDARY TO HEMATOLOGIC CANCER TREATMENT

The treatment of hemato-oncologic diseases often includes high-dose cytotoxic therapies, with or without total body irradiation that may cause oral mucosal complications. The adverse effect may be due to a direct stomatotoxic effect and/or an indirect effect on the three blood lineages.⁴⁴ In the last decades, targeted therapy and immunotherapies have become increasingly used in the treatment of numerous hemato-oncologic diseases; as these regimens are used more frequently, the oral mucosal lesions related to them become apparent.^{45,46} Additionally, unique to hematopoietic stem cell transplantation, an iatrogenic autoimmune disease, namely chronic graft vs host disease, may affect the oral tissues.

Chemotherapy is the primary treatment for numerous types of cancer, particularly when there is systemic or metastatic spread. The cytotoxic agent circulates in the blood stream, reaching all cells, aiming to eliminate the rapidly replicating cancer cells. Specific chemotherapy protocols and portals are used for cancer in the central nervous system or in other protected anatomical sites.

Hematopoietic stem cell transplantation has two main indications: (a) high-dose cytotoxic treatment to eliminate host malignant cells followed by a rescue infusion of hematopoietic stem cells; (b) nonmyeloablative reduction of the host cells, leaving residual host bone marrow to trigger an alloimmune response. In autologous hematopoietic stem cell transplantation, the graft is the patient's own hematopoietic stem cells, whereas in allogeneic hematopoietic stem

cell transplantation, the graft originates from an unrelated donor. In general, the better the human leucocyte antigen match between the host and the donor the better the chances of success.

When considering oral mucosal complications of targeted therapy, the most relevant categories of targeted therapy are the mammalian target of rapamycin inhibitors, epidermal growth factor receptor inhibitors, vascular endothelial growth factor, monoclonal antibodies, tyrosine kinase inhibitors and multikinase inhibitors. Most of these agents interfere with pathways involved in carcinogenesis. The common oral mucosal toxicities include ulcers, also known as mucositis/stomatitis, lichenoid changes and taste alterations. Generally, when the chemotherapy or the hematopoietic stem cell transplantation results in neutropenia, the complications described above (see "Neutropenia-related oral manifestations") may occur. In other words, the treatment for cancer may result in some of the oral mucosal complications that are caused by hematologic malignancies.

6.1 | Cytotoxic treatment-related oral mucosal changes (mucositis)

According to the MeSH definition, mucositis is an inflammation of the mucosa accompanied by a burning or tingling sensation. It is characterized by atrophy of the squamous epithelium, vascular damage, inflammatory infiltration and ulceration. It occurs in the mucosal lining of the mouth, the gastrointestinal tract or the airway due to chemical irritation, chemotherapy or radiation therapy. Although this definition covers the mucosal damage induced by chemotherapy, radiotherapy and targeted therapy, the dynamics of mucositis over time, its presentation, the pathogenesis and its response to various interventions are different. Clinical practice guidelines for the management of oral mucositis were developed by the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) based on a systematic review and are updated periodically.⁴⁷

6.2 | Hematopoietic stem cell transplantation-related oral mucosal complications

Graft vs host disease is a systemic complication of allogeneic hematopoietic stem cell transplantation. It is the result of the donor immune cells attacking the recipient's tissues. Blood transfusion and other solid organ transplantations (eg kidney and gut) rarely cause graft vs host disease. It has an acute form, a chronic form and a combination form.⁴⁸ The oral manifestations of acute graft vs host disease are nonspecific and their prevalence is not well-reported. It may manifest as erythema or ulcerations, which are difficult to differentiate from oral mucositis. The oral tissues are involved in 25%-80% of chronic graft vs host disease patients.⁴⁹ The oral manifestations of chronic graft vs host disease typically present as lichenoid lesions, erythema, ulcerations, salivary gland dysfunction, multiple mucocoeles, desquamative gingivitis or tissue sclerosis. The first three oral manifestations are used in the National Institute

of Health scale to score the activity level of chronic oral graft vs host disease.^{50,51} The treatments for oral chronic graft vs host disease were reviewed in the National Institute of Health Consensus Development Project on Criteria for Clinical Trials in chronic graft vs host disease by the Ancillary Therapy and Supportive Care group.⁵² Of clinical significance is the late oral complication of increased risk of oral cancer.^{53,54}

6.3 | Targeted therapy-related mucosal changes

Although this entity falls within the definition of oral mucositis, its unique characteristics warrant description. The most commonly reported oral presentation is aphthous-like ulcers (major, minor or herpetiform) and severity is dose-related. As many of the targeted therapies are administered continuously, the oral manifestations may be chronic or recurrent in nature. Most importantly, unlike chemotherapy-induced oral mucositis, these lesions appear to respond well to topical steroids.^{55,56} Another form of targeted therapy-related oral mucositis has the appearance of oral lichen planus.⁵⁷ The reports of this type of oral "lichenoid" mucositis are sparse, yet considering its distinctive oral presentation it may be labeled as a separate entity in the future.

7 | LIVER DISEASES

Viral hepatitis, alcohol-induced liver disease and drug toxicity are the main causes of liver disease.⁵⁸⁻⁶⁰ Autoimmune hepatitis and primary biliary cirrhosis may also result in oral manifestations. It is important to note that many patients with liver disease are asymptomatic and the disease may remain subclinical for years. Oral manifestations primarily arise late in the disease process. The causes of the oral mucosal manifestations described will be divided into three groups: direct damage to the liver, diseases associated with hepatitis and complications of liver transplantation.

7.1 | Primary liver disease-related oral mucosal changes

Bleeding tendency is one of the alarming manifestations of liver disease. The oral mucosal manifestations are usually related to deficient production of liver proteins, specifically the coagulation factors. Additionally, with insufficient bile the absorption of fat-soluble vitamin K is limited, vitamin K storage in the liver is reduced and its availability as a cofactor for the coagulation system is compromised. Lastly, portal hypertension usually develops secondarily to liver insufficiency. The hypertension leads to hypersplenism, which may increase platelet destruction. The bleeding tendency may manifest as gingival bleeding, mucosal ecchymosis or petechiae.

Jaundice is another common manifestation and it is due to impaired bilirubin conjugation in the liver that leaves nonwater-soluble unconjugated bilirubin to be reabsorbed from the intestine into the blood. The unconjugated bilirubin accumulates in the blood and

is deposited in the oral mucosa, causing a yellowish appearance (Figure 4).

Patients with alcoholic cirrhosis are commonly malnourished (folic acid, vitamin B and iron). Anemia may also be caused by chronic bleeding from dilated esophageal varices. Both the vitamin deficiencies and the anemia may cause glossitis and angular cheilitis. In addition to the vitamin deficiencies and anemia, low albumin levels may impair wound healing.⁶¹

7.2 | Secondary disease-related oral mucosal changes

7.2.1 | Sjögren syndrome

Numerous reports describe the coexistence of hepatitis C and Sjögren syndrome, and this association was confirmed in a recent meta-analysis, potentially related to hepatitis C virus subtype.⁶² These patients present with a dry, atrophic oral mucosa due to the lack of saliva.

7.2.2 | Lichen planus

There is evidence that hepatitis C virus is associated with oral lichen planus. Meta-analyses indicated that the odds ratio of lichen planus patients having the hepatitis C virus vs healthy controls ranged from 2.5 to 5.4.⁶³ The positive association was more prevalent in East and Southeast Asia, South America and in Mediterranean countries.⁶⁴

7.2.3 | Oral cancer

Alcohol abuse, especially when combined with tobacco use, is a risk factor for oral cancer. This is relevant for patients with alcoholic liver disease. Hepatitis C infection in late stages may result in hepatocellular carcinoma. Metastasis to the oral cavity has been reported and its manifestations include intra-oral masses with irregular mucosal surfaces.⁶⁵

7.2.4 | Adverse effects of medications used to treat liver diseases

Of interest is Wilson disease, a rare inherited metabolic disease in which copper accumulates in various organs, including the liver. Penicillamine is used to treat Wilson disease. It is highly stomatotoxic and may result in oral ulcerations and erythema.

7.3 | Liver transplantation-related oral mucosal changes

Post-transplant immuno-suppression increases the risk of infection (see "Hematologic diseases"). Therefore, the patients may present with oral mucosal manifestations of fungal, viral and bacterial infections. Hairy leukoplakia, which is caused by Epstein-Barr virus present as a white nonremovable bilateral lingual change, has been reported infrequently in liver transplant patients (see "Kidney transplant").⁶⁶ Moreover, drug-induced

mucosal changes are also seen in this group of patients. Sirolimus, also known as rapamycin, is used to prevent liver transplant rejection. This medication causes aphthous-like oral lesions. Cyclosporine may induce gingival overgrowth; tacrolimus may do so too, although oral lesions are not as frequent.

8 | KIDNEY DISEASES

End-stage kidney disease is the ultimate result of chronic kidney disease-related nephron destruction and can be caused by diabetes mellitus, hypertension and glomerulonephritis.⁶⁷ These patients suffer from various organ disturbances, including increased susceptibility to infection, cardiovascular disease (hypertension, congestive heart failure, cardiomyopathy, arrhythmia), anemia, lymphocytopenia, coagulopathy, renal osteodystrophy, secondary hyperparathyroidism, nausea, vomiting, headache, neuropathy and impaired growth (in pediatric patients). These secondary complications explain the diverse oral mucosal manifestations that may develop.

8.1 | Kidney failure-related oral mucosal changes

Renal failure and end-stage disease present a multitude of oral manifestations. The mucosa may appear pale secondary to reduced secretion of erythropoietin from the kidney and the resultant anemia.

An increased tendency for gingival bleeding is also an important presentation that may be secondary to the coagulopathy and the anticoagulation during dialysis. Gingival bleeding, petechiae, purpura and ecchymosis are the most common manifestations.

Patients with renal failure may also suffer from hyposalivation and xerostomia. This may be caused by reduced salivary flow secondary to atrophy and fibrosis of the salivary glands, use of certain medications and restriction of fluid intake.⁶⁸ Oral candidiasis and mucosal atrophy may develop secondary to hyposalivation. Moreover, taste changes (dysgeusia) occur with chronic kidney disease, independent of age and gender differences, with specific impairment in sour, umami and salty tastes.⁶⁹ It is unclear how the increased levels of urea, sodium, potassium and phosphate in their saliva compared with those without renal disease and genetics contribute to these symptoms.⁷⁰

Uremic stomatitis appears infrequently in patients with long-standing renal failure as painful white epithelial plaques with a crenated surface. These lesions resolve following effective dialysis or renal transplantation.⁷¹ Renal patients, especially those on dialysis, may produce more calculus⁷² and develop increased gingival inflammation, although studies do not show this to be more prevalent in these patients compared with the general population.⁷³ Halitosis (oral malodor) may also develop due to the urea (ammonia) odor.

8.2 | Kidney transplantation-related oral mucosal changes

Following renal transplantation, cyclosporine may be administered to prevent rejection. This medication may cause persistent gingival

enlargement with deep pseudopockets, which may eventually progress to periodontal destruction. Many such patients also suffer from hypertension and when a calcium channel blocker such as nifedipine is also given the gingival overgrowth may worsen. Some patients develop Epstein-Barr virus-related hairy leukoplakia along the lateral borders of the tongue post-transplant due to the chronic immuno-suppressive treatment. High-dose steroids that are administered immediately after the transplantation and anemia may cause delayed wound healing.

Post-transplantation patients are at risk for post-transplant lymphoproliferative disease. The oral involvement in this is rare but can present as gingival or mucosal masses with/without surface ulceration (see "White blood cell proliferation-related oral manifestations"). As these patients are immuno-suppressed they are at risk for various oral infections. The most common oral infection is candidiasis. Bacterial and viral infections may also occur. Targeted therapy-related oral mucosal ulcers are also seen, especially related to treatment with sirolimus (see "Liver transplantation").

9 | CONNECTIVE TISSUE DISEASES

Lupus erythematosus is a connective tissue autoimmune disease. When lupus is limited to the skin and mucous membranes it is termed discoid or it may be systemic, affecting the kidneys, bones, joints and muscles, nervous system, cardio- and cerebrovascular systems. A combination of genomic aberrations and environmental factors lead to immune dysregulation, resulting in autoantibody production, immune complex formation, complement activation, neutrophil dysfunction and augmentation of proinflammatory cytokines, resulting in organ damage.⁷⁴

Scleroderma is a rare autoimmune disease characterized by the thickening of the skin and mucosa due to fibrosis that results in impaired function and esthetics. In the generalized form, termed systemic sclerosis, the patients also have a visceral fibrosis causing a multisystem connective tissue disease affecting various internal organs, such as the heart, lung, kidney and gastrointestinal tract, causing impaired function of these organs. The organ damage is a result of vasculopathy, fibrosis and inflammation. Arterial hyperactivity, oxidative stress and immune-mediated disorders contribute to the pathogenesis. Environmental factors may contribute to the disease occurrence (exposure to silica, chlorinated solvents, trichloroethylene, welding fumes, aromatic solvents and ketones, and white spirit). The disease also has a genetic component.⁷⁵

Sjögren syndrome is an autoimmune disease with characteristic lymphocytic infiltration to exocrine glands, causing dysfunction and destruction of the glands. As the salivary and lacrimal glands are the primarily affected glands, the syndrome primarily manifests as oral and ocular dryness. In primary Sjögren syndrome, also called sicca syndrome, the dry mouth and dry eyes are not associated with any other connective tissue disease. Secondary Sjögren syndrome has the same oral and ophthalmic signs and symptoms and is associated

with other connective tissue diseases, often rheumatoid arthritis. The European League Against Rheumatism developed a disease activity index score to assess the severity of involvement in all organs and systems.⁷⁶

9.1 | Lupus erythematosus oral mucosal changes

Lupus erythematosus may manifest as painful white or red mucosal lesions. Lichen planus-like lesions affect about 20% of patients and include white lesions with radiating striae or sometimes white dots/plaque-like changes, irregular atrophic areas presenting as irregular erythema and shallow erosions. Unlike lichen planus, lupus lesions are typically less sharply defined (Figure 9). In addition, oral atrophy, erythema and telangiectasia may be commonly seen. The most common oral sites are buccal mucosae, gingiva and labial mucosae. Isolated red lesions may occur on the palate. There may be a small elevation in the risk of lower lip malignancy in discoid lupus patients.^{77,78} About one-third of systemic lupus patients develop Sjögren syndrome.

9.2 | Scleroderma-related oral mucosal changes

The typical oral manifestations of scleroderma are stiffening of the perioral skin, constricted lips (called fish mouth), limitation of tongue movement and restricted mouth opening. Firm whitish/yellowish fibrotic mucosal plaques and bands may be seen, particularly in the buccal mucosa or vestibular sulci. The loss of elasticity may also manifest in the tongue, resulting in a stiff and narrowed tongue (called chicken tongue). As a result of this and fibrosis of the esophagus, dysphagia may develop in scleroderma patients. There is some evidence of an increased risk for oral cancer in patients with systemic sclerosis.⁷⁹



FIGURE 9 Erosive erythematous lesions in a systemic lupus erythematosus patient involving the tongue bilaterally. Similar signs on the buccal mucosa and palate

9.3 | Sjögren syndrome-related oral mucosal changes

The hallmark of Sjögren syndrome is hyposalivation. In the early stages of the disease the oral mucosa may appear moist despite the measured hyposalivation. However, as the severity of hyposalivation increases the mucosa appears dry and may have a shiny red appearance. The tongue may appear atrophic and red, with a cobblestoned dorsum. The oral microbiome may be altered by hyposalivation, which may facilitate oral infections by relatively nonvirulent organisms such as candida. This may also be associated with taste changes and mucosal sensitivity (Figure 6).

Sjögren patients may develop noninfectious nonpainful swellings of the parotid glands (about one-third of patients) and some experience infectious suppurative parotitis secondary to hyposalivation. Moreover, Sjögren patients are also at risk of mucosa-associated lymphoid tissue lymphoma. There is an increased risk for lymphoma in the salivary gland, which may relate to the lymphocytic infiltrate.

10 | ENDOCRINE DISEASES

The most common endocrine disease is diabetes, which can present with numerous manifestations in the oral mucosa. Although diabetes represents a group of endocrine diseases with variable pathogenesis, the oral mucosal manifestations are similar; therefore, we will consider them as one entity. The diabetes epidemic is largely secondary to the epidemic of excess weight and obesity contributing to the development of type 2 diabetes. The target organs affected by this degenerative metabolic disease are the eyes, kidneys and peripheral and autonomic nervous system. Diabetics may have delayed healing and suffer from complications such as end-stage kidney disease and amputations. In addition, both type 1 and type 2 diabetes increase the risk of cardiovascular disease two- to five-fold.⁸⁰ This chapter will also review adrenal insufficiency and other rare endocrine diseases with unique oral mucosal involvement.

10.1 | Diabetes-related oral mucosal changes

Diabetic patients are at high risk of progressive and severe periodontitis compared with healthy controls. Furthermore, severe periodontitis may have a negative impact on glycemic control.⁸¹⁻⁸³ Reduced salivary flow in diabetics may contribute to oral infection risk, which may also be affected by increased glucose concentration in saliva. Their oral mucosa may be dry and patients seem to suffer from increased physiologic frictional irritation. As a result, the oral mucosa is often erythematous, atrophic and thin and secondary candidiasis is common. The tongue may be depapillated and sensitive to spicy foods.

Oral fungal infections are common among uncontrolled diabetics. The most common oral infection is candidiasis, which presents as white removable plaques, erythema of the palate, middle and dorsal surfaces of the tongue and/or angles of the mouth, or rarely as hyperplastic or nodular candida leukoplakia. The combination of a dry mouth, qualitative changes in the saliva and immune changes may contribute to the

increased risk. Deep fungal infections, such as aspergillosis and mucormycosis, have been reported in patients with uncontrolled diabetes.

Impaired wound healing in diabetics is also a prominent clinical problem, caused by hyperglycemia, chronic inflammation, white blood cell dysfunction, micro- and macrocirculatory dysfunction, hypoxia, autonomic and sensory neuropathy, and impaired neuropeptide signaling.⁸⁴ Neuropathies secondary to longstanding diabetes are also common. In the mouth, patients may complain of a burning sensation in lingual and labial mucosa that appears healthy. In the past an association between oral lichen planus, diabetes mellitus and hypertension was suggested, termed "Grinspan syndrome". This correlation appears to be the result of the high prevalence of both diseases and because medications for hypertension, and probably also for diabetes, are capable of provoking oral lichenoid lesions.⁸⁵

10.2 | Rare endocrine diseases-related oral mucosal changes

Primary hypo-adrenocorticism (Addison's disease) is a rare autoimmune condition. The atrophic adrenal cortex does not secrete appropriate amounts of cortisol, thereby stimulating the hypothalamus. The hypothalamus secretes higher levels of the precursor to melanocyte-stimulating hormone. Patients may present with diffuse focal hyperpigmentation of several mucosal surfaces.

Multiple endocrine neoplasia syndrome is a group of rare diseases affecting several endocrine glands. In multiple endocrine neoplasia type 2B, multiple neuromas may arise in the oral mucosa. Clinically they appear as soft, small raised masses. The characteristic intra-oral site is the mucosa adjacent to the angles of the mouth and the anterior surface of the tongue.

Syndrome of inappropriate antidiuretic hormone secretion (Schwartz-Bartter syndrome) causes elevation of antidiuretic hormone and as a result hyponatremia, excessive natriuresis, a high urinary osmolarity, as well as changes in the concentration of urea and uric acid in the plasma and in the urine. This syndrome has a number of causes, including being paraneoplastic; 3% of cases are reportedly associated with oral cancer.^{86,87}

11 | PULMONARY DISEASES

The most common noninfectious pulmonary diseases are asthma and chronic obstructive pulmonary disease. In asthma, bronchial hyper-reactivity causes smooth muscle constriction and reversible airway obstruction.²⁸ Chronic obstructive pulmonary disease is a slowly progressing, chronic, irreversible disease occurring in smokers and individuals exposed to other environmental pollutants.⁸⁸

11.1 | Asthma and chronic obstructive pulmonary disease-related oral mucosal changes

Long-term use of steroids, either systemic or inhalers, is common among asthma and chronic obstructive pulmonary disease patients.

Oral candidiasis may develop in these patients because of chronic steroid use. Recently some inhalers have been designed to minimize this effect. As chronic obstructive pulmonary disease is a result of cigarette smoking, smokers' palate (nicotine stomatitis) is a common finding among these patients as well. The characteristic clinical presentation is a whitish palatal mucosa with numerous reddish papules, which represent inflamed openings of ducts of minor salivary glands. It is obvious that heavy tobacco smoking contributes to severe periodontal disease and, therefore, it may be present in patients with chronic obstructive pulmonary disease. Cigarette smoking among these patients may increase the risk of oral cancer.⁸⁹

12 | IMMUNOLOGIC DISEASES

This section addresses three multiorgan immunologic diseases with oral involvement: angioedema, Behçet disease and inflammatory syndromes. Angioedema is a diffuse swelling of the soft tissues, including subcutaneous and submucosal connective tissues, but may also affect internal organs. The most common form is allergic angioedema caused by mast cell degranulation and histamine release. Medication-associated angioedema may be caused by various agents, most commonly angiotensin-converting enzyme inhibitors, which activate bradykinin.⁸⁵

Hereditary angioedema is an autosomal dominant disease caused by a deficiency in functional C1 esterase inhibitor and presents as recurrent episodes of nonpruritic, nonpitting, subcutaneous/mucosal edema that may be local or extensively spread. Perioral (lips) and particularly intra-oral (tongue and floor of the mouth) swelling are uncommon in hereditary angioedema but quite common in allergic and medication-associated angioedema. Usually, the swelling is preceded by a prodromal tingling sensation and worsens slowly but relentlessly over the first 24 hours, then gradually subsides over the subsequent 48-72 hours. Approximately one-third of cases are accompanied by a nonpruritic serpiginous rash (erythema marginatum).⁹⁰ The diagnosis of Behçet disease (also known as Adamantiades syndrome) is based on the coexistence of aphthous-like ulcers, genital ulceration and uveitis. It may involve the cardiovascular system, lungs, gastrointestinal track, nervous system and musculoskeletal system. A list of diagnostic criteria has been defined, including clinical findings and a pathergy test.⁹¹ The pathogenesis is immune-mediated vasculitis.

The inflammatory syndromes are rare periodic syndromes characterized by recurrent episodes of fever and inflammation. The following inflammatory syndromes are relevant to the topic of oral mucosal manifestations in systemic diseases: aphthous-like oral ulceration has been reported as one manifestation in several of the syndromes, including periodic fever, aphthous stomatitis, pharyngitis and adenitis, familial Mediterranean fever, hyperimmunoglobulinemia D and periodic fever syndrome, tumor necrosis factor receptor-associated periodic syndrome and pyogenic sterile arthritis, pyoderma gangrenosum and acne.^{92,93} An underlying genetic defect has been identified in some of these syndromes.

12.1 | Behçet disease and autoinflammatory syndromes-related oral mucosal changes

Aphthae are rounded/elliptical ulcers of variable size (Figure 10). They may appear repeatedly and concomitantly. Aphthous stomatitis is common to Behçet disease, periodic fever, aphthous stomatitis, pharyngitis and adenitis, and some of the periodic fever syndromes.⁹² Aphthae are not specific to these diseases and may manifest in other systemic diseases (inflammatory bowel disease, nutritional deficiencies, celiac disease and HIV infection). They may also appear as an isolated oral disease; however, as this review is focused on oral mucosal manifestations of systemic diseases, it is beyond the scope of this review.

13 | NUTRITIONAL DEFICIENCIES

Severe vitamin deficiency may be due to reduced intake, impaired absorption or increased demand and may occur in patients with alcohol dependence syndrome, individuals on restriction diets and those with eating disorders or malabsorption conditions. Among their many functions, some vitamins have a role in the maintenance of epithelial tissues (ie the skin and mucous membranes). Due to the rapid turnover rate of epithelial cells of the oral mucosa (3-7 days) compared with cutaneous epithelium turnover (up to 28 days) and because of the unique oral microenvironment, including the microbiologic environment in the oral cavity, and the constant exposure of the oral mucosa to local trauma, signs (and/or symptoms) of nutritional deficiencies are often seen in the mouth earlier than on the skin.⁹⁴ The oral manifestations of iron, vitamin B2, B3, B6, B9 (folic acid) and B12 deficiencies are quite similar and include a smooth atrophic tongue ("glossitis") with or without a burning sensation or

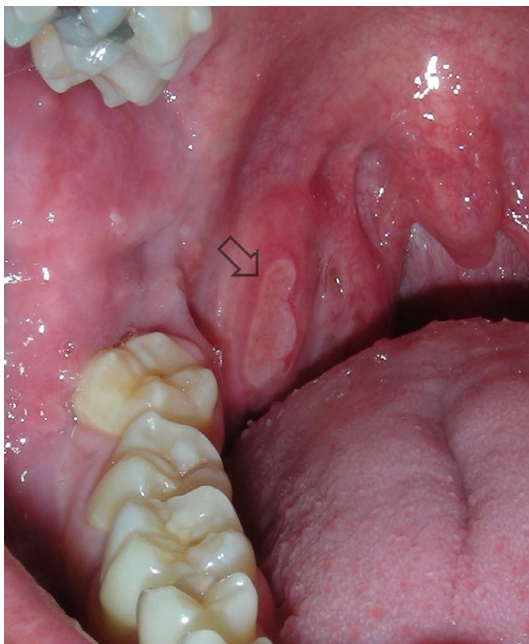


FIGURE 10 Major aphthous-like ulcer seen in Behçet disease

pain, and cracking and fissuring of the lips ("cheilitis"), especially at the corners of the mouth ("angular cheilitis"). The smooth appearance of the tongue is caused by the atrophy of the filiform papillae; over time, the larger fungiform papillae may also undergo atrophy; therefore, skilled clinicians could evaluate nutritional deficiency by tongue appearance. In some studies, up to one-quarter of angular cheilitis cases are associated with deficiencies of iron or B group vitamins.^{95,96}

13.1 | Vitamin A (retinol) deficiency

Vitamin A deficiency may cause hyposalivation and increased rates of infection, including periodontal disease. In infants/children with vitamin A deficiency, impaired tooth development may be noted.⁹⁴ Vitamin A deficiency may play a role in the development of oral carcinoma and supplementation of vitamin A may cause regression of potentially malignant leukoplakia.⁸⁹

13.2 | Vitamin B2 (riboflavin) deficiency

Chronic deficiency of B2 may cause normocytic, normochromic anemia, which manifests orally as (magenta-colored) glossitis and glosso-dynia, angular cheilitis and erythema, with or without swelling of the mucosae. These changes may appear separately or be part of the riboflavin deficiency-related oculo-oro-genital syndrome, which includes interstitial keratitis and corneal vascularization, magenta-colored glossitis, (angular) cheilitis and genital lesions.⁹⁵ The gingivae are not affected.¹⁹

13.3 | Vitamin B3 (niacin) deficiency

Chronic deficiency of B3, termed pellagra, may develop in people whose diet is mainly corn-based. Pellagra may manifest orally as a high prevalence of dental caries in these patients.⁹⁴

13.4 | Vitamin B6 (pyridoxine) deficiency

Although B6 is quite common in foods, deficiency of this vitamin may occur in individuals taking certain medications (eg isoniazid) that act as pyridoxine antagonists. This deficiency may manifest orally as stomatitis, glossitis, (angular) cheilitis; in addition, seborrhea-like changes around the lips, nose and eyes may appear.^{95,97}

13.5 | Vitamin B7 (biotin) deficiency

B7 deficiency may cause peri-orificial dermatitis with erythema and fine scaling around the mouth, eyes, nose, genitalia and anus, but does not manifest in the oral mucosa.⁹⁴

13.6 | Vitamin C (ascorbic acid) deficiency

Vitamin C is a cofactor for the collagen-forming enzymes prolyl hydroxylase and lysyl hydroxylase and therefore has an essential role

in collagen formation. Vitamin C deficiency occurs in individuals who do not consume enough fresh fruit and vegetables. This condition, termed scurvy, may manifest orally as blue/red swollen gingivae (hemorrhagic gingivitis), spontaneous bleeding and mucosal ulceration.⁹⁸ Capillary fragility causes petechiae or more extensive ecchymosis. A low intake of vitamin C increases the risk of periodontal attachment loss by 20%.⁹⁹ It is unclear if the teeth mobility and loss of teeth are exclusively related to the deteriorated attachment loss. Impaired wound healing is also reported.⁹⁴

13.7 | Vitamin K (phylloquinone) deficiency

Vitamin K is an essential cofactor in the synthesis of the procoagulant factors II (prothrombin), VII, IX and X, and the anticoagulant protein C and protein S. Deficiency or inhibition of vitamin K may be seen in individuals who suffer from malabsorption conditions. Vitamin K deficiency mainly clinically manifests as bleeding. The bleeding can affect any site, including the oral cavity, and may appear as submucosal hemorrhage and gingival bleeding. Oral manifestations of iron, B9 (folate) and B12 deficiencies are discussed above in the red blood cell diseases section.

14 | DERMATOLOGIC DISEASES

Dermatologic diseases with relatively common or significant oral involvement will be reviewed. A detailed description of dermatologic diseases can be found in other chapters in this volume. Lichen planus is a common skin and mucosal disease. The diagnostic histopathologic findings include a subepithelial band of lymphocytes. There are several forms with variable clinical presentations that can occur concomitantly. Among the side-effects of certain medications is a mucosal reaction with a similar appearance to lichen planus, termed "lichenoid reaction". Lichen planus is a potentially malignant disorder and 1%-4% of the patients may develop oral cancer.

Pemphigus is a mucocutaneous disease with several forms: vulgaris, vegetans, erythematous, foliaceus, drug-induced and IgA pemphigus. Oral involvement is common in pemphigus vulgaris and may be the first site of involvement. Circulating autoantibodies against the desmosome are found in the blood. When the only autoantibodies are against desmoglein 3, only the oral cavity is affected. When circulating autoantibodies are against desmoglein 3 and 1, skin involvement is likely. Oral mucosal lesions may be the first site of lesions and may linger for up to 1 year after cutaneous lesions resolve.

Paraneoplastic pemphigus, also known as paraneoplastic autoimmune multiorgan syndrome, is a distinct mucocutaneous disease associated with a neoplasm, usually lymphoma or chronic lymphocytic leukemia, but other malignant diseases have been reported.¹⁰⁰ The diagnosis may be very challenging.¹⁰¹ A number of circulating autoantibodies against the desmosomes are found and the most specific are antidesmoplakin 1 and 2. Autoantibodies against desmoglein 1 and 3 may also be present.

Pemphigoid is a rare mucocutaneous disease with several forms: mucous membrane, bullous, lichenoid. Mucous membrane pemphigoid, also known as cicatricial pemphigoid, is the form that affects the oral mucosa most commonly; therefore, we will focus on this entity.

Erythema multiforme is an acute mucocutaneous condition that may be triggered by an infection (herpes simplex), exposure to medications or due to unidentified factors. Severe cases with more than 10% body surface involvement are termed Steven Johnson syndrome. Extremely severe cases with skin detachment in over 30% of the body surface are termed toxic epidermal necrolysis. Concentric erythematous rings, or "target lesions" when present on the skin, are typical in erythema multiforme. There is controversy if these diseases represent various degrees along the spectrum of the same pathogenetic process.

14.1 | Lichen planus-related oral mucosal changes

Lichen planus is a relative common muco-cutaneous disorder where oral manifestations are quite frequent. Several forms of oral lichen planus have been described based on their appearance. In the reticular form of lichen planus, a white interlacing pattern (Wickham striae) is seen on the mucosa, with or without erythema. White papules or plaques may also be seen. The dorsum of the tongue may be depapillated if involved. Superficial mucocelles are occasionally observed in involved mucosal sites.

In the erosive form of lichen planus, the oral mucosa will show atrophy, erythema and/or ulceration. White striae may also be present. This form is usually symptomatic. In severe cases, bullous lesions may develop. This clinical presentation is not unique, therefore a biopsy may be needed to differentiate it from other mucocutaneous diseases. Desquamative gingivitis is a clinical presentation of a number of conditions, with changes limited to gingivae. The gingivae may be fragile and painful, resulting in limited plaque control that further aggravates the lesions.

14.2 | Pemphigus-related oral mucosal changes

Pemphigus is a classic autoimmune disorder that affects the skin and mucosal surfaces, particularly the oral mucosa. The condition presents as vesicles, bullae and ulcerations. Depending on the phase of blister development/rupture and the size of the lesion, the oral mucosa may show superficial vesicles, bullae or ulcerations. Nikolsky sign is a finding observed when gentle lateral pressure on healthy-looking oral mucosa results in sloughing of the mucosa with little or no bleeding due to intra-epithelial separation. This sign is not specific for pemphigus vulgaris and has low sensitivity in the early stages of the disease. When bullae or vesicles rupture, mucosal bleeding could result, leading to blood-tinged saliva from an oral or oro-pharyngeal source. When esophageal mucosal involvement is extensive, the injured mucosa may bleed, and the blood will be expectorated into the oral cavity.

14.3 | Paraneoplastic pemphigus-related oral mucosal changes

Paraneoplastic pemphigus has been described recently that is secondary to a malignant neoplasm, particularly lymphomas. The clinical presentation is similar to pemphigus vulgaris but presents as a very aggressive form and generally poorly responds to steroid treatment.

14.4 | Pemphigoid-related oral mucosal changes

Pemphigoid is an autoimmune blistering disorder that primarily affects the basement membrane of the epithelium. Hence, the roof of the vesicles is thicker than in pemphigus vulgaris and although differentiation may be difficult clinically, the lesions are less likely to rupture. Therefore, vesicles may be observed more commonly. Eventually the vesicle ruptures, creating an ulcer. The blisters may be blood filled. Oral lesions may appear as vesicles, bullae, ulceration or as desquamative gingivitis.

14.5 | Erythema multiforme-related oral mucosal changes

The oral mucosal lesions may appear as vesicles, bullae and ulcerations. The erosions and ulcerations are diffuse and irregular, which gives the disease its name "multiforme". Lip lesions appear as hemorrhagic and crusted. Although this presentation is nonspecific, when present it is suggestive of erythema multiforme. Other mucocutaneous diseases, such as linear IgA, dermatitis herpetiformis and epidermolysis bullosa acquisita, are rare and their clinical presentation is nonspecific. Generally, the oral lesions include vesicles, erosions and ulcers.¹⁰²

14.6 | Oral mucosal changes in other paraneoplastic diseases with dermatologic manifestations

14.6.1 | Papillary oral mucosal lesions in malignant acanthosis nigricans

Acanthosis nigricans is an acquired benign dermatologic disease. Its malignant variant may be associated with an internal malignancy, particularly gastric adenocarcinoma.¹⁰⁰ Oral mucosal lesions occur in 25%-50% of patients with acanthosis nigricans. The papillary texture is subtle, involving the tongue or the lips and, to a lesser extent, the buccal mucosa.

14.6.2 | Oral ulcerations in Sweet syndrome

Sweet syndrome is an acute neutrophilic dermatosis that may be associated with an underlying malignant disease. It is characterized by tender asymmetrical erythematous lesions, fever and neutrophilia. In about 20% of the patients, hematologic malignancy may be present. The oral mucosal presentation is nonspecific ulcerations.¹⁰⁰

14.6.3 | Perioral hyperpigmented lesions in Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is a rare inherited syndrome with skin involvement. The lesions appear as blue-black macules localized around the mouth, nose, eyes, anus and genitals.¹⁰⁰ The vermillion border is affected in almost all patients. The patients typically develop small intestine polyposis and approximately 2% of these transform into adenocarcinoma. Other malignancies, including breast and pancreatic cancer, are reportedly associated with this syndrome.

14.6.4 | Red macules in hereditary hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia is also known as "Osler-Weber-Rendu syndrome". It is an uncommon inherited mucocutaneous disorder. The proteins produced by the mutated genes induce vascular hamartomas in the skin and the mucosa. The oral mucosal lesions are small red papules, which blanch upon pressure. The number of telangiectasia increase with age. A rare variant of hereditary hemorrhagic telangiectasia presents with intestinal polyps and these patients have an increased risk of developing colorectal carcinoma.

15 | VASCULAR DISEASES

The clinical presentation of vascular diseases is highly variable. Diseases of chronic vasculitis with possible oral manifestations and congenital malformations of the large blood vessels will be addressed here. Other types of vasculopathy are mentioned under the sections "Bleeding disorders" and "Amyloidosis", which both describe increased blood vessel fragility.

15.1 | Oral mucosal changes in various vascular diseases

In certain congenital heart diseases, particularly right to left shunts (eg tetralogy of Fallot), oxygenation is impaired and hypoxic blood loses its red color. As a result, the oral mucosa has a bluish-purple hue (cyanosis of the oral mucosa). Polyarteritis nodosa is an immune complex disease characterized by necrotizing vasculitis and ulcers rarely develop in the oral mucosa. Giant cell arteritis, also known as temporal arteritis, is an immune-mediated cranial vasculitis. It affects medium-sized arteries, creating microscopic granulomas. Although the typical maxillofacial manifestation is pain, it is reviewed here in the context of the oral mucosal manifestation. Giant cell arteritis patients rarely present with oral ulcers and ischemic tongue necrosis.¹⁰³

16 | GASTROINTESTINAL DISEASES

Oral mucosal manifestations may arise in several gastrointestinal diseases, with similar lesions found in several disorders. Each disease

will be described separately. Celiac disease (gluten-sensitive enteropathy) is a common genetic disease caused by a hypersensitivity of the small intestinal mucosa to the gliadin component of gluten. The hypersensitivity reaction leads to local inflammation, atrophy of the jejunal villi and malabsorption.¹⁰⁴

Crohn's disease is an inflammatory bowel disease. It causes transmural granulomatous inflammation in segments of the distal ileum, proximal colon and rectum.¹⁰⁵ Ulcerative colitis is an inflammatory bowel disease with lesions that start in the colon/rectum and spread to include the entire large intestine and ileum. The continuous inflammatory process results in epithelial erosions and hemorrhage, pseudopolyps, crypt abscess and submucosal fibrosis. There is an elevated risk of colon cancer.¹⁰⁶ Gastroesophageal reflux disease is a relatively common condition caused by regurgitation of stomach acid on to the esophageal and pharyngeal mucosa. Less frequently, gastroesophageal reflux disease involves the oral mucosa.¹⁰⁷

16.1 | Celiac disease-related oral mucosal changes

Recurrent aphthous-like lesions have been reported in celiac disease. A gluten-free diet may improve healing and reduce the number of episodes.¹⁰⁸ Anemia and nutritional deficiency are commonly seen in celiac disease and, hence, atrophy of the oral mucosa, depapillation of the tongue, burning symptoms and angular cheilitis are possible lesions in patients with anemia or nutritional deficiency.

16.2 | Crohn's disease-related oral mucosal changes

Crohn's disease may manifest as oral ulcers and often have a deep linear appearance, often located in the vestibule. Aphthous-like lesions may also be present. Secondary fibrosis may result in mucosal tags and cobblestoning of the mucosa.¹⁰⁹ These patients are also vulnerable to developing anemia and nutritional deficiency-related oral lesions (see "Celiac disease"). Pyostomatitis vegetans is an uncommon manifestation of Crohn's disease, presenting as serpentine pustules that coalesce in a "snail track" pattern.¹⁰⁹ Patients with Crohn's disease have a higher prevalence of dry mouth, which indirectly may cause oral mucosa atrophy and impact mucosal integrity and mucosal healing (see "Sjögren syndrome").¹¹⁰ Some of the newer biologics used in Crohn's disease are reported to cause oral mucosal lichenoid reaction.^{111,112}

16.3 | Ulcerative colitis-related oral mucosal changes

Oral mucosal lesions are generally rare. Pyostomatitis vegetans, mucosal lesions related to anemia and nutritional deficiencies, and discrete hemorrhagic ulcers may occur (see "Crohn's disease").

16.4 | Gastric regurgitation-related oral mucosal changes

The direct effect of the gastric acid on the mucosa may result in altered taste. It may result in lower oral intake, which in turn will result

in elongation of the filiform papillae. The elongated filiform papillae may provide a ground for subclinical oral candidiasis. Therefore, it may be difficult at first look to clearly point at the gastric regurgitation as the sole etiology of the altered taste. Persistent mucosal irritation by gastric acid may result in oral mucosal atrophy, erythema of the palatal mucosa and uvula, with an associated burning sensation. Patients with pernicious anemia may have oral mucosal features of anemia as well (see "Anemia-related oral mucosal changes").

17 | OTHER DISEASES

Amyloidosis occurs in several diseases when an extracellular protein is produced and deposited in a single or multiple organs. It is classified as primary, secondary (eg secondary to chronic inflammation), associated with multiple myeloma, hereditary or other (ie senile amyloidosis, hemodialysis-associated amyloidosis). The deposition of amyloid can occur in the presence of an abnormal protein, in association with prolonged excess abundance of a normal protein and, for reasons unknown, accompanying the ageing process.¹¹³ The most common form is the acquired systemic immunoglobulin light chain amyloidosis, which is considered a plasma cell dyscrasia and is treated with chemotherapy and hematopoietic stem cell transplantation.¹¹³

17.1 | Amyloidosis-related oral mucosal changes

Oral mucosal changes related to submucosal accumulation of paraprotein are macroglossia, loss of elasticity, tongue induration and yellowish/orange discolored mucosal lesions; submucosal masses have been reported.¹¹⁴ Oral mucosal ulcerations rarely occur.¹¹⁵ The oral ulcerations may be the cause of the burning-like pain.¹¹⁶ The deposition of paraprotein in the blood vessel walls increases vessel fragility and increases bleeding tendency. These oral mucosal changes may present as submucosal purpura or hematoma, or as frank intra-oral bleeding.¹¹⁴ Amyloidosis may concur concomitantly with Sjögren syndrome. Pulmonary amyloidosis is more common than oral mucosal amyloidosis; however, a case of salivary gland amyloidosis has been reported (see "Sjögren syndrome").

18 | ORAL MUCOSAL MANIFESTATIONS OF NEOPLASMS

Head and neck cancer is estimated to be 2.8% of all new cancers in the body.¹¹⁷ Head and neck cancer includes a broad spectrum of neoplasms; this review will focus on the oral mucosal manifestations of the most common oral cancer and pharyngeal cancer. Historically, complications from treatment for head and neck cancer were mainly due to surgery and radiotherapy. Recently, these malignancies have been treated with combined surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy, and the oral mucosal complications in head and neck cancer patients have

changed accordingly. The most common type of cancer in the head and neck region is squamous cell carcinoma and will be the focus of this review. Squamous cell carcinoma is easier to identify in the oral cavity than in the nasopharynx due to access for visualization. Symptoms may be present late in the cancer progression, which may delay the diagnosis. The treatment modalities for head and neck cancer include surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy. The oral mucosal changes related to the latter treatment modalities were described elsewhere in this review (see "Oral mucosal complications secondary to hematologic cancer treatment"). This section will expand on oral mucosal complications related to surgery and radiotherapy. Ionizing radiation is focused on the tumor site and has several uses: curative (to completely destroy the cancer), adjunctive (to kill residual cancer cells after surgical resection of the tumor) or palliative (to reduce the cancer locally in order to relieve the symptoms). In hemato-oncologic diseases, radiotherapy is used in relatively lower doses compared with head and neck cancer, and often the field of irradiation is directed at the lymph nodes (total body or total lymphoid irradiation and regional lymph node irradiation), although it may be delivered locally at the site of oral involvement in some cases (eg lymphoma, palliation for multiple myeloma-related lesions).

18.1 | Oral mucosal manifestations of head and neck cancer

Patients with head and neck cancer may present with discomfort, which may be present in 85% of patients at diagnosis.⁸⁹ Dysphagia, odynophagia, otalgia, limited movement, neck masses and weight loss may occur with advanced disease. Unilateral sensory or motor loss should raise a high level of suspicion of the presence of a neoplasm.¹¹⁸ Clinical signs that may appear in the mucosal surfaces include a red, white or mixed red-and-white lesion. An irregular, granular, rough or crusted texture of the mucosa is suggestive of a possible dysplastic or malignant lesion, although squamous cell carcinoma has been described as the "great imitator" and distinguishing squamous cell carcinoma/dysplasia from more common inflammatory disease is necessary. All lesions with a white or red mucosal change, regardless of the texture, should be explored. The presence of a persistent ulcer, with no identifiable causative factors, is an indication for biopsy. The literature describes malignant mucosal ulcerations as having irregular indurated borders. This is not a diagnostic criterion and the absence of these characteristics should not prevent further investigation. Head and neck cancer in the deeper tissues may cause asymmetric expansion of the face or intra-oral surfaces.

18.2 | Oral mucosal complications of treatment for head and neck cancer

Surgery disrupts anatomical structures and postsurgery fibrosis. This may change the appearance of the oral tissues and the relationship between structures. Skin grafts may be lighter in color than the

surrounding mucosa and occasionally feel firmer due to the thickness of the epidermis with skin appendages.

Surgery may result in neuropathy, anesthesia, paresthesia, hyperesthesia and taste change. These changes are usually localized to the surgical site and high-dose radiation volumes and may be permanent. Pain may be present intra- or extra-orally. When neck dissection is performed, musculoskeletal pain originating from the cervical structures may be present. Although this complication does not affect the oral mucosa directly, it has a strong impact on oral functions, such as eating, swallowing and speaking. Mouth opening may be limited postsurgery. This may be due to postsurgical scarring or as a result of radiotherapy-induced fibrosis and consequent trismus. Tongue mobility may be limited or disturbed after soft-tissue resection. Tongue function may compensate following a small partial glossectomy and regain much of the pretreatment function. However, when the glossectomy is extensive, and fibrosis limits movement, tongue function may be impaired.

Radiotherapy can have a multitude of complications in the oral cavity. The dry mouth after radiotherapy to the head and neck area can be profound. The use of intensity-modulated radiation therapy minimizes the damage to the salivary glands, particularly in lateralized cancers. Oral mucosal changes secondary to the dry mouth have been described elsewhere in this review (see "Sjögren syndrome"). Oral candidiasis is a common immediate and late complication in patients treated with head and neck radiotherapy. The changes in saliva quantity and quality alter the oral flora, predisposing the patient to yeast infections.

Radiotherapy-induced oral mucositis is almost an inevitable complication. Although the dynamics of oral mucositis over time are different for radiotherapy-induced mucositis and chemotherapy-induced mucositis, the clinical presentation is relatively similar other than localization to the radiation fields. This is modified in patients receiving targeted therapies such as epidermal growth factor inhibitor, where increased pain and erythema may extend beyond the radiation field and immunotherapy may cause lesions with a lichenoid appearance. When the radiotherapy exceeds 6000 cGy, the mucosa in the field of radiation is usually damaged and the jaw bones in the field are also affected. Although osteoradionecrosis is a bony complication, it may cause a loss of mucosal coverage over necrotic bone and secondary inflammation and, therefore, has been included in this review. The necrotic bone becomes exposed to the oral cavity and the break in the mucosal barrier, the lack of vascular supply and the lack of circulating inflammatory/immune cells facilitate secondary infection. In addition, the loss of osteocytes disturbs bone repair. Pain associated with osteoradionecrosis may make plaque control more difficult, further increasing the risk of infection. This may present with bone exposure, suppuration and erythematous swollen mucosal margins and fistula formation that may lead to pathologic fracture. In persistent lesions, granulation tissue may develop in the marginal oral mucosa. Since the invention of intensity-modulated radiation therapy, osteonecrosis is becoming less common. Radiotherapy may also induce periodontal damage. The literature

suggests that the periodontal attachment loss is greater in teeth that were in the field of radiation.¹¹⁹

19 | SUMMARY AND FUTURE DIRECTIONS

Oral mucosal and gingival manifestations may be identified, leading to the diagnosis of a systemic condition, or develop during the course of a previously diagnosed disease. Oral complications may arise due to side-effects/toxicity of the required medical management. Identification of abnormality is the initial step, allowing steps to be taken to achieve diagnosis. Development of new adjuncts for detection, including imaging, salivary diagnostics, cytology with molecular measures, biopsy with molecular evaluation and liquid biopsy (molecular measures in blood/plasma) will continue to be developed and improved detection, diagnosis, staging and potential tools to assess effective management or progression of the condition will become increasingly available. Application of these technologies to facilitate diagnosis will be applied to screen at-risk people; however, application in a screening setting is challenging with rare diseases. These molecular measures will not only enhance diagnosis and staging but are expected to be used to direct molecularly directed therapy and improve the precision of diagnosis and the effectiveness of treatment ("precision medicine"). Management of oral manifestations of systemic disease will continue to advance, paralleling systemic management, and, in some cases, applied locally to oral conditions. In addition, new therapies will be increasingly based upon the molecular pathogenesis of the condition. These principles are expected to continue, with benefits anticipated throughout the continuum of diagnosis and management. We are entering a new era of diagnosis and management for oral disease and oral manifestations of systemic disease. Recognition of oral tissue involvement may lead to diagnosis, appropriate management and that contraindicated procedures are avoided. Following recognition, referral for diagnosis and management may be indicated and consultation with dental or medical specialists may be needed. In complex cases, involvement by dental experts may be important within the medical team.

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