THE UNIVERSITY OF WESTERN AUSTRALIA

Oral Health Centre of Western Australia

Haematological diseases and immunodeficiency

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2026

Learning Outcomes

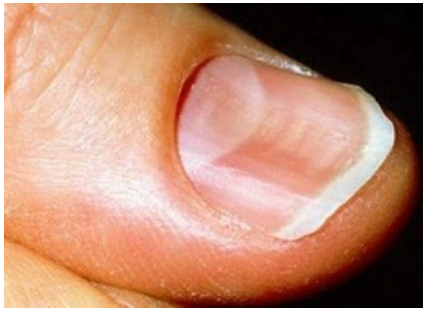
- Gain an understanding of an overview of haematogical diseases and immunodeficiency
- To recognise the oral manifestations and management of patients with these conditions
- To develop an awareness when medically compromised patients should be referred to secondary care

Anaemia

- Term used for either a decrease in the volume of RBC or in the concentration of haemoglobin
- Result from decreased production of RBCs or increased destruction or loss (trauma, menstruation, GI bleeding) of RBCs
- General symptoms are related to reduced oxygen-carrying capacity of blood
- Tiredness, shortness of breath, tachycardia and palpitations
- Pallor of mucous membrane

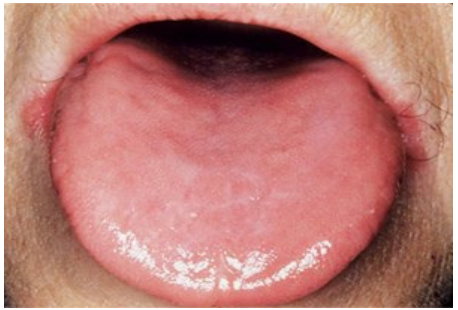
Iron-deficiency anaemia

- Most common cause of anaemia
- Classified a s hypochromic microcytic anaemia
- Causes
  - Decreased dietary intake of iron
  - Decreased absorption of iron (e.g. Coeliac disease
  - Excessive blood loss (e.g. menstrual or GI bleeding)
  - Increased demand for red blood cells (e.g. pregnancy)



Signs and symptoms
- Fatigue, dyspnoea
- Koilonychia (spoon-shaped) nails, pica (craving for specific foods/dirt), blue sclera

Oral findings
- Pale oral mucosa
- Depapillated atrophic tongue
- Glossodynia (burning sensation)
- Candidiasis/Angular cheilitis
- Aphthous-like ulcers



Plummer-Vinson(Patterson-Brown-Kelly) syndrome

- Severe and chronic form of iron deficiency
- Middle-aged female
- Atrophic glossitis (smooth, atrophic and red tongue)
- Pharyngeal and oesophageal webbing
- Dysphagia (due to webbing)
- Predisposition to post-cricoid and oral squamous cell carcinoma

Dental management considerations

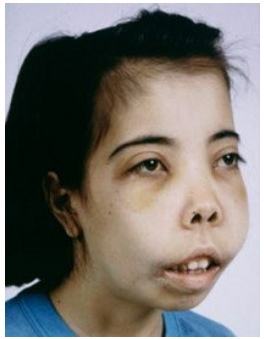
- Anaesthesia
  - In poorly controlled anaemia: use LA without epinephrine because it may aggravate cardiac symptoms
- Anxiety/sedation
  - Nitrous oxide can be used
  - GA avoided if the Hb level is 10g/dL
- Iron deficiency in men may indicate an occult GI cancer; refer for evaluation

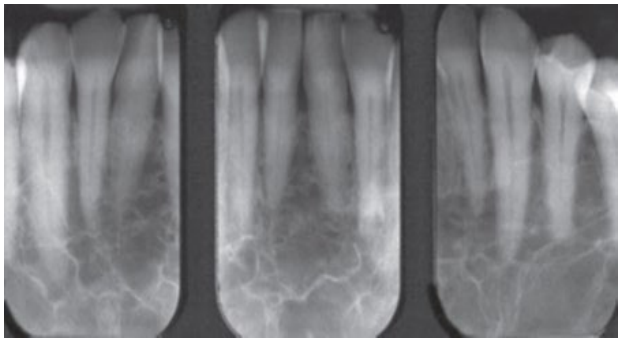
Thalassemia

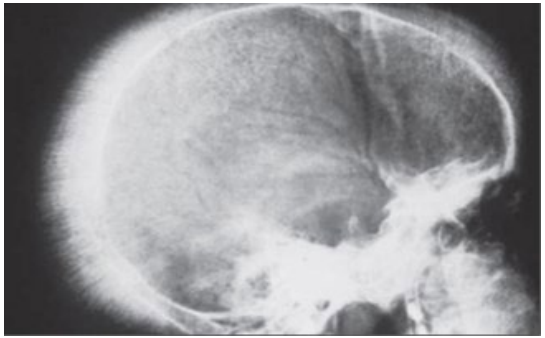
- A hereditary haemoglobinopathy characterised by reduction in production of globin chains in the haemoglobin molecule
- More prevalent in Mediterranean, African, Asian populations
- Types
  - Alpha-thalassemia
  - Beta-thalassemia
- Deletion or mutations in the alpha or beta globin genes
- Decreased haemoglobin production and the formation of malformed RBCs

Clinical features

- Severe jaundice, pallor, growth retardation, splenomegaly in the 1st year of life
- Typical symptoms of anaemia
- Bone expansion (result of intramedullary haematopoiesis)
  - Maxillary protrusion with spacing of teeth
  - Thin cortical plates and spongy marrow
  - Thin, widely spaced trabeculae
  - Hair-on-end appearance on a lateral skull radiograph





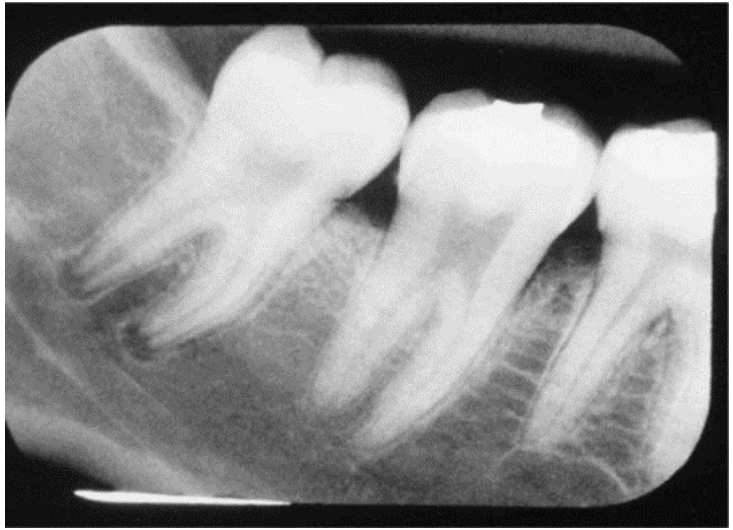


Sickle cell anaemia

- A hereditary haemoglobinopathy in which red cells contain an abnormal haemoglobin, HbS
- Autosomal recessive disorder
- More common in Mediterranean, African and Far East countries
- A point mutation of beta-globin gene
- Red cells become rigid and curved (sickle-shaped)
- Deformed sickle cells are vulnerable to haemolysis
- Newborn babies are screened for sickle cell status

Oral findings

- Pallor or jaundice of oral mucosa
- Widely spaced trabeculae
- Step-ladder appearance of bone trabeculation in PA x-rays
- Mandibular bone pain, osteomyelitis
- Asymptomatic pulpal necrosis
- Maxillary protrusion
- Delayed eruption, dental hypoplasia



Causes of excessive bleeding and bruising

- **Vascular disorders**
  - Capillary fragility
  - Hereditary haemorrhagic telangiectasia
- **Platelet disorders**
- Abnormal platelet number or function
- Inability to develop a temporary clot

- **Coagulation disorders**
- Defects in coagulation
  - Inherited (e.g. von Willebrand's disease, haemophilia)
  - Acquired (e.g. liver, anticoagulants)
- Inability to form definitive clot
- **Fibrolytic disorders**
- Inability to destroy free plasmin

Assessing risk for bleeding

- Bleeding problems in relatives (e.g. von Willebrand's disease, haemophilia)
- Bleeding after surgery, tooth extractions
- Bleeding after trauma (cuts)
- Medications may cause bleeding
  - Antiplatelets
  - Long term antibiotic therapy
  - Some herbal preparations
- Disease associated bleeding tendencies
  - Leukaemia, thrombocytopenia
  - Chemotherapy
  - Advanced liver disease
- Spontaneous bleeding from nose, mouth, GI

Platelet disorders

- Thrombocytopenia
  - Low platelet levels in blood
- Cause
- Decreased platelet production (e.g. bone marrow dysfunction)
  - Bone marrow infiltration by malignant cells (leukemia, myeloma, bone metastasis)
  - Toxic effects of chemotherapeutic drugs
  - Liver disease
- Increased platelet consumption or destruction
  - Drug induced immunologic responses (heparin, quinidine, methyldopa)
  - Systemic disease: SLE and HIV infection
  - Vaccinations and viral infections
  - Immune (idiopathic) thrombocytopenic purpura (ITP)
- Increased splenic sequestration (portal hypertension due to liver disease, tumour infiltration)
- Clinical evidence of thrombocytopenia not visible until platelet level falls below 100,00/µl (normal 150,000 to 450,000 µl)

Oral manifestations

- Petechiae, ecchymosis
- Spontaneous gingival bleeding
- Postoperative bleeding
- **Dental management considerations**
- History, clinical exam and tests (platelet count)
- If needed, refer and consult a haematologist
- Use local measures to control bleeding
- Do not prescribe aspirin
- **Risk of infection in patients with bone marrow suppression (e.g. leukemia**

Topical Hemostatic and Local Antifibrinolytic Agents used to Control Bleeding	
Product	**Description**
Gauze	2″×2″ sterile gauze pads; place over the wound and have the patient put pressure on it by closing or finger pressure
Surgicel®	A cellulose-based product (oxidized regenerated cellulose); exerts physical effect rather than physiologic; swells on contact with blood with resulting pressure adding to hemostasis; after 24-48 hours, it becomes gelatinous; can be left in place or removed
Avitene®	A collagen-based products (microfibrillar collagen hemostat); attracts platelets and triggers aggregation in fibrous mass
Gelfoam®	A gelatin-based products; absorbable gelatin sponge
Tranexamic acid	Tranexamic acid is an antifibrinolytic agent; works as a competitive inhibitor of plasminogen activation; (available only in Europe as 4.8% oral mouthwash; as Cyklokapron® or Lysteda® tablet and Cyklokapron® injection in the USA)
ε-Aminocaproic acid (EACA)	EACA (Amicar®) is an antifibrinolytic agent; works as a competitive inhibitor of plasminogen activation; used as a rinse (25% Amicar® syrup)
Thrombostat®	Topical thrombin; converts fibrinogen to fibrin
Other local measures include atraumatic/minimally traumatic surgery, and precise suturing technique	

Platelet function disorders

- **Inherited disorders**
  - Von Willebrand's disease (may have secondary factor VIII deficiency)
- **Acquired platelet dysfunction**
- Drug induced
  - e.g. aspirin, clopidogrel
  - NSAIDs, beta-lactum antibiotics (penicillin), calcium channel blocking drugs, phenytoin
- End-stage renal disease
  - Uraemia (high level of waste products (urea) in the blood due to kidney failure
    - Circulating toxins can impair platelet function
- Alcohol ingestion

Von Willebrand Disease

- Von Willebrand disease is the most common inherited bleeding disorder
  - Characterised by deficient or defective von Willebrand factor (vWF)
  - Caused by an inherited gene mutation on chromosome 12
  - Both males and females are affected
- vWF
  - serves as a carrier protein for Factor VIII
  - Affected patients experience platelet dysfunction and deficiency of Factor VIII
- Clinical features
  - Ecchymoses and nose bleeds common findings
  - Prolonged bleeding after tooth extraction
  - Severe forms: haemarthroses

Coagulation disorders

- **Hereditary**
  - Von Willebrand's disease
  - Haemophilia
    - Haemophilia A
      - Factor VIII deficiency
    - Haemophilia B
      - Factor IX deficiency

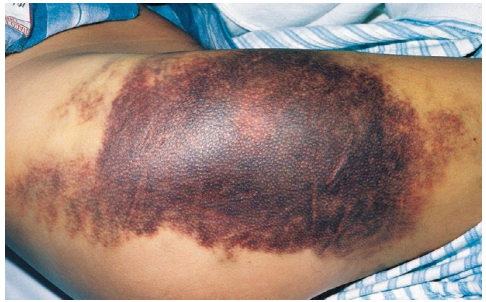
- **Acquired**
  - Anticoagulants
    - Oral anticoagulants
      - Warfarin
  - Heparin therapy
  - Viral hepatitis
  - Alcoholism
  - Vitamin K deficiency
    - Long term use of broad-spectrum antibiotics
    - Malabsorption

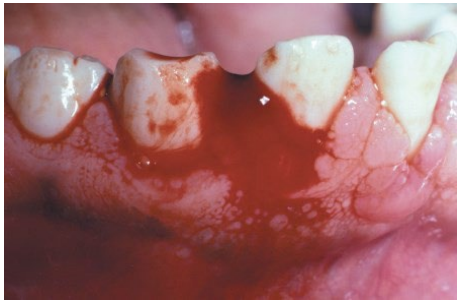
Haemophilia A

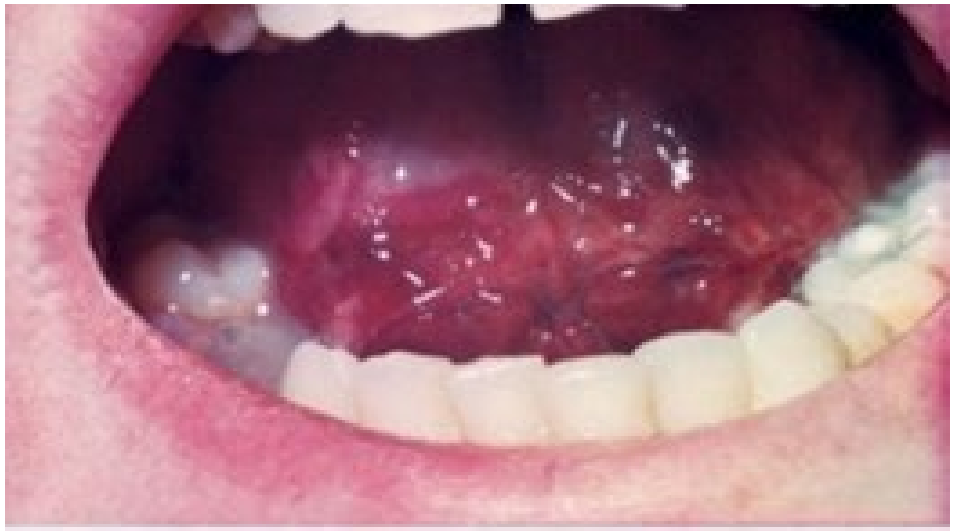
- X-linked recessive disorder characterized by factor VIII deficiency
- Primarily affects males, females are usually carriers
- Normal haemostasis requires 30% factor VIII activity
- Mild haemophilia
  - Factor VIII level between 5-30%
  - Patients asymptomatic
- Moderate haemophilia
  - Factor VIII level between 1-5%
- Severe haemophilia
  - Factor VIII level less than 1%

Clinical features

- Ecchymoses, hemarthrosis, dissecting haematomas are common findings
- Oral findings
  - Persistent bleeding after dental surgery
  - Bleeding after tooth extraction may be first evidence of mild haemophilia
- Liver clots and haematomas
- Spontaneous mucosal or gingival bleeding
- Hemarthrosis of TMJ is a rare finding

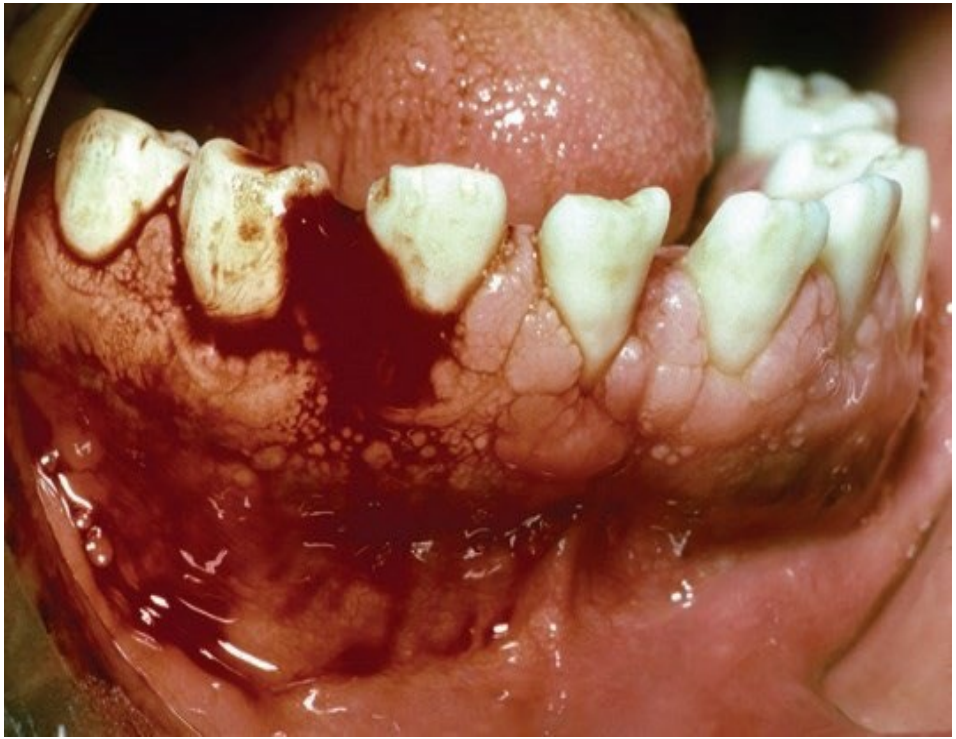






Haemophilia B (Christmas disease)

- Sex-linked recessive disorder characterised by Factor IX deficiency
- Clinical features are identical to Haemophilia A
- Classified as mild, moderate, or severe
- 20-45% of haemophilia cases are severe
- Lab tests: prolonged PTT (partial thromboplastin time) and Factor IX deficiency
- Medical management: Factor IX replacement



Dental management for patients on Warfarin

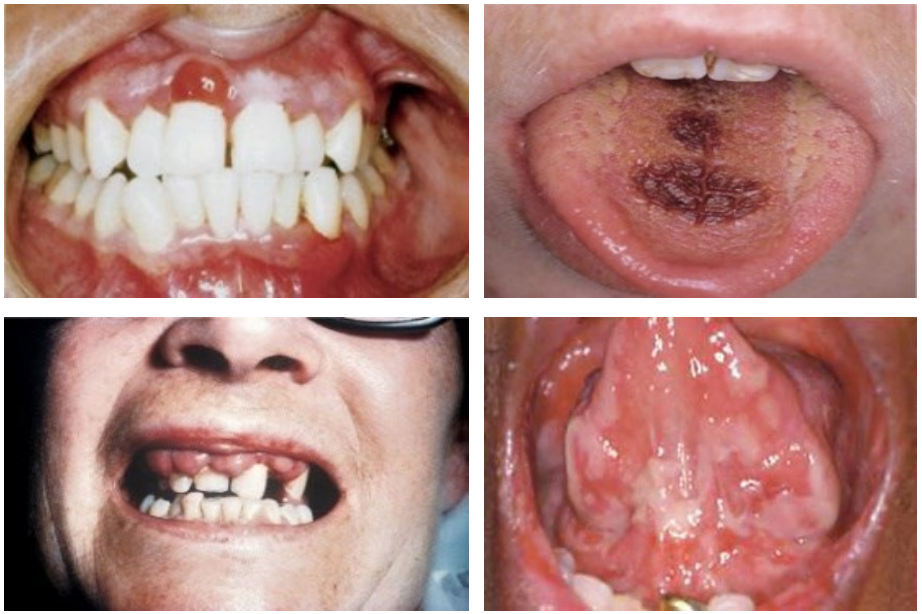
- Determine the reason for anticoagulant therapy
- Bleeding
  - Confirm INR level
  - INR ideally taken within 72 hours of the scheduled dental procedure
  - Consult with the patient's physician if needed
- If INR is 3.5 or less
  - Minor procedures can be performed with local haemostatic measures
- If the INR is greater than 3.5
  - Consult the physician
  - Delay the dental procedure by 3-5 days, confirm INR level
- INR should be less than 3.0 for major oral surgery
- If post-operative bleeding is uncontrollable, Vitamin K or fresh frozen plasma may be used

Leukaemia

- Cancer of WBCs that affects the bone marrow and circulating blood
- Involves exponential proliferation of clonal or lymphoid cell
- Acute leukaemia
  - Sudden onset and rapid course
  - Immature, undifferentiated WBCs
- Chronic Leukaemia
  - Slower onset
  - More mature, functional cells
- Types: ALL, AML, CLL, CML

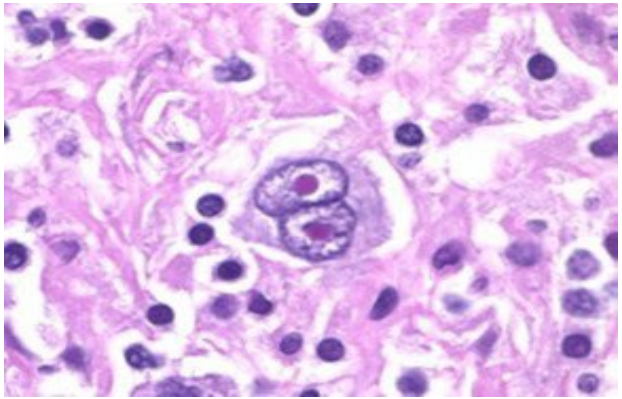
Oral manifestations of leukaemia

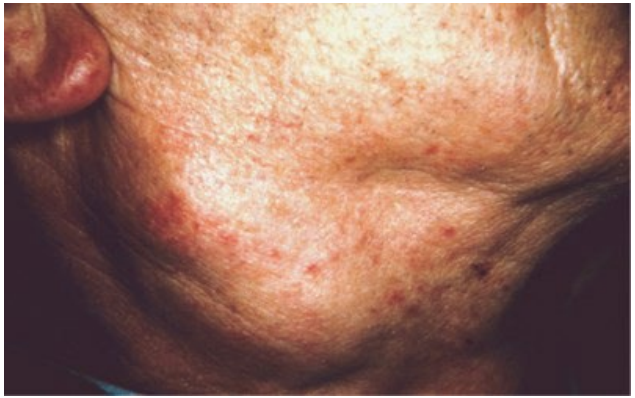
- Mucosal pallor (an important sign in children)
- Gingival bleeding, petechiae or purpura
- Oral ulcers (herpetic, neutropenic or drug-induced
- Oral infections (e.g. candidiasis, CMV)
- Localised or generalised gingival enlargement
  - Caused by leukemic infiltrates
  - Gingiva is boggy, bleeds easily
- Myeloid sarcoma
  - Localised mass of leukemic cells
  - Involve maxilla, palate, gingiva, tongue, oral mucosa
- Cervical lymphadenopathy



Lymphoma

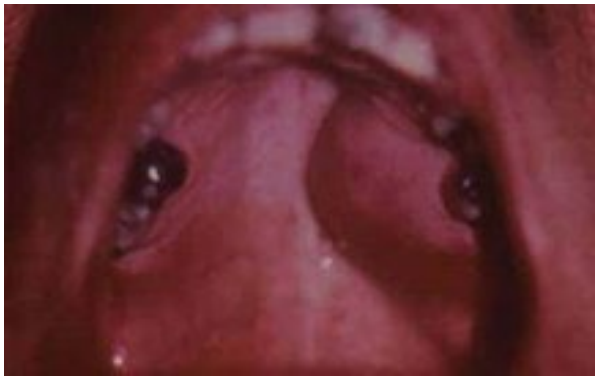
- Cancer of the lymphoid organs and tissues that present as discrete masses
- Main types: Hodgkin and Non-Hodgkin lymphomas
- **Hodgkin Lymphoma (HL)**
- HL is a B lymphocyte neoplasm
- Contains a characteristic tumour cell
  - Reed-Sternberg cell (large, bi-nucleated tumour cell)
- Most common in adolescents and young adults
- Has a bimodal incidence pattern: 20-30 and 50-70 years
- EBV linked to 40% of cases
- Typically manifest as painless firm enlarged lymph nodes (rubbery consistency)
  - Mediastinal and cervical lymph nodes affected
  - Oral involvement is rare
- Pruritus, fatigue, fever, weight loss, night sweats are common

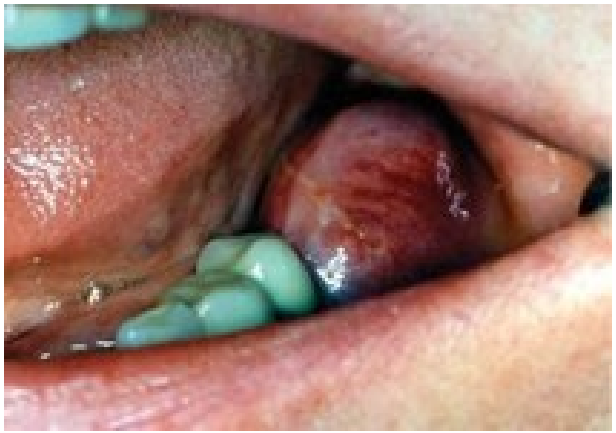




Non-Hodgkin lymphoma (NHL)

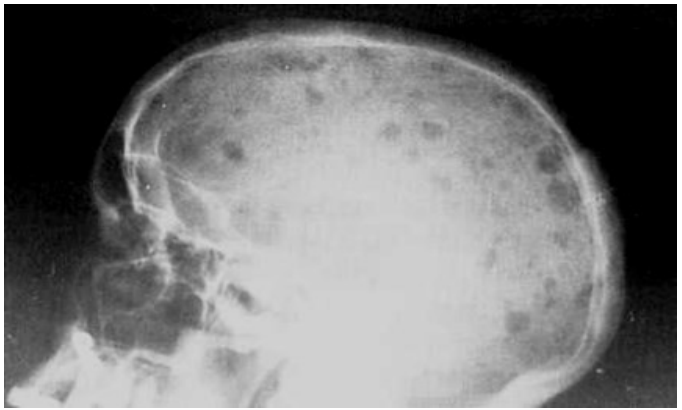
- Large group of lymphoproliferative disorders derived from B, T and natural killer cells
  - B-cell proliferation accounts for 85-90% of cases
- Can occur at any age (median age at the time of diagnosis is 67 years)
- Causative agents include genetic factors, infectious agents, autoimmune diseases (Sjögren syndrome,) and immunodeficiency states (AIDS)
- Involvement can be nodal or extra nodal
  - Painless, firm enlarged cervical lymph nodes
- Oral submucosal mass may or may not be ulcerated
- Salivary glands, those affected by Sjögren syndrome
- Jaw bones in African children with Burkitt's Lymphoma





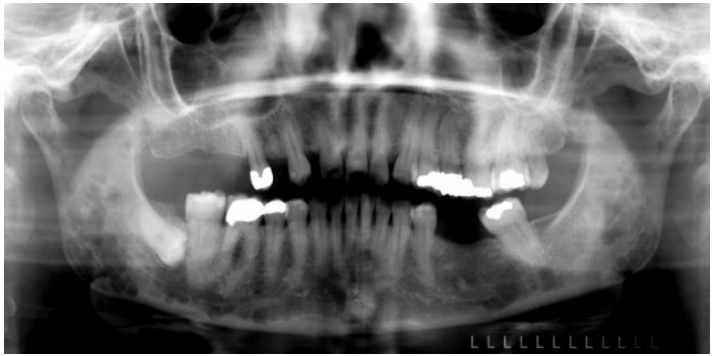
Multiple myeloma

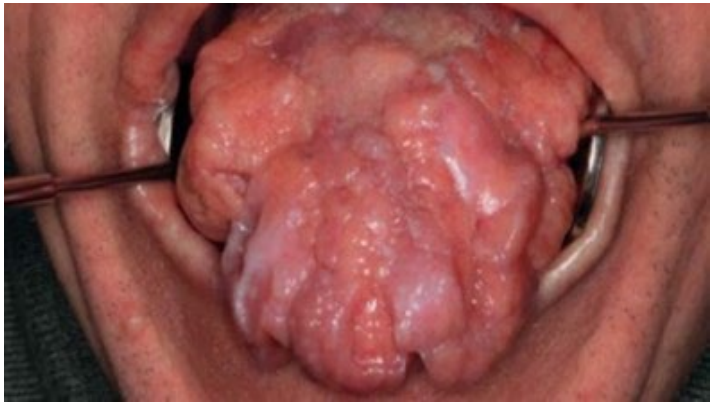
- Malignant neoplasm composed of plasma cells which occurs as disseminates disease involving many bones
- Clinical features
- Men over 50 years, persistent bone pain
- Multiple osteolytic bone lesions
  - Multiple punched-out lesions or mottled areas on the radiograph
  - Vertebrae, sternum, ribs and pelvic bones commonly affected
  - Osteolytic lesions of the jaws in 30% of patients
  - Lead to serum hypercalcaemia
  - May cause pathological fracture
- Fever and recurrent infections(result of neutropenia)
- Proteinuria and renal failure
- Amyloid deposition in various tissues (e.g. heart liver, liver, nervous tissue)



Oral manifestations

- Radiographs of jaws may show “punched-out” lesions
  - Can cause bone pain, paraesthesia and cortical enlargement
  - This could be the initial manifestation of the disease
- Amyloid deposition in the tongue cause macroglossia and pain
- Medication-related osteonecrosis of the jaw (MRONJ)
  - Potential serious complication of long-term bisphosphonates
  - Commonly observed in the mandible
- Petechiae, pallor, susceptibility to bleeding and infections





IMMUNODEFICIENCY

Primary immunodeficiency

- Genetically based
- Predominantly B or T-cell defects or a combination or due to a selective immunodeficiency (IgA deficiency)
- Result in life-threatening conditions
- Affected individuals tend to die young as result of recurrent infection
- Candida infections are often predominant in these patients
- More susceptible to periodontal infections

Secondary immunodeficiency

- Malignancies
  - Leukaemia, lymphoma, multiple myeloma
- Medications
  - Corticosteroids and immunosuppressants; chemotherapy
- Malnutrition
- Autoimmune disorders
- Radiation
- Diabetes mellitus
- Chronic renal failure
- Infections (**HIV**, TB)

Human immunodeficiency virus infection

- RNA retrovirus infection

Spread through:

- sexual contact
- parenteral exposure to blood
- mother to foetus

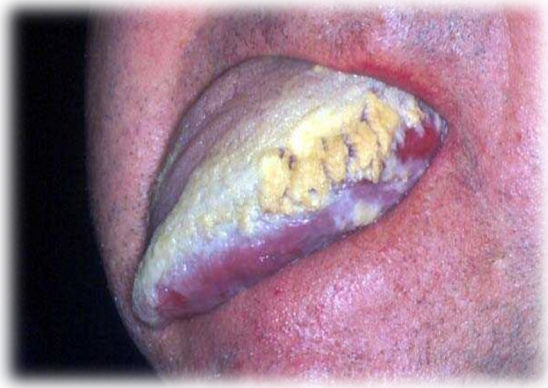
- Immune deficiency due to damage to CD4

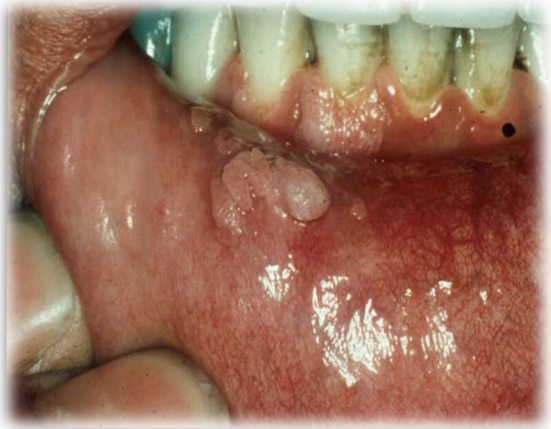
T-lymphocytes

Predisposition to infections with:

- Viruses and virally induced malignancies
- Fungi
- Mycobacteria

- Autoimmune disease
- Neurological damage

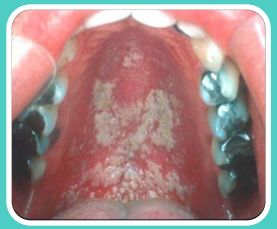




Classification of stages of HIV infection (Centre for Disease Control, USA)

Stages	Description
Stage I	Seroconversion illness (2-3 weeks) Fever, malaise, lymphadenopathy, pharyngitis, mouth ulcers Antibodies develop within 3-6 months
Stage II	Asymptomatic stage: (chronic phase ~10 years)
Stage III	Persistent generalized lymphadenopathy: (~ 10 years)
Stage 1V (A-E)	Symptomatic stage (diseases involving entire body, neurological disease, secondary infectious disease, secondary cancers, other conditions

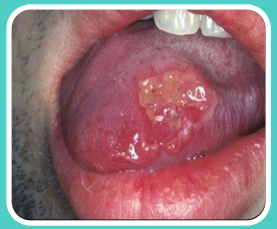
Classification of oral lesions in HIV



Group I

Lesions strongly associated with HIV infections

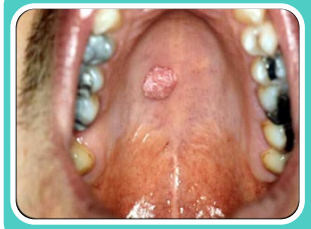
HIV associated candidosis



Group II

Lesions less commonly associated with HIV infection

HIV associated CMV ulcer



Group III

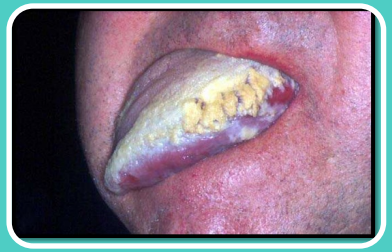
Lesions possibly associated with HIV infection

HIV associated wart

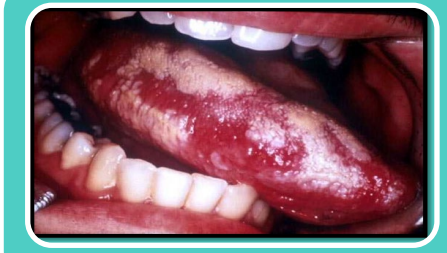
Oral Lesions in HIV disease

Candidiasis
Hairy leukoplakia
Kaposi’s sarcoma
Gingival and periodontal disease
Ulcers
Other orofacial conditions

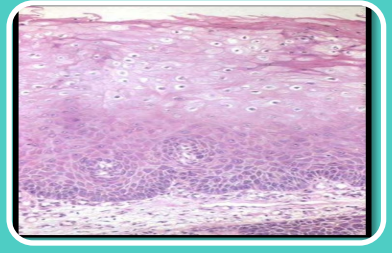
Hairy leukoplakia



White patch which cannot be removed
Vertical white folds on the lateral aspects of tongue
Associated with EBV

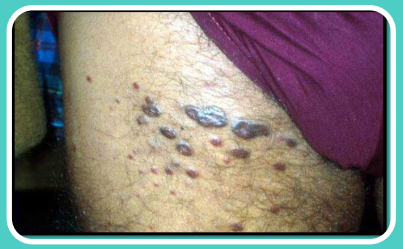


Lesion not premalignant
Usually superimposed by candida
Common in patients with late-stage HIV infection
Development may herald onset of AIDS

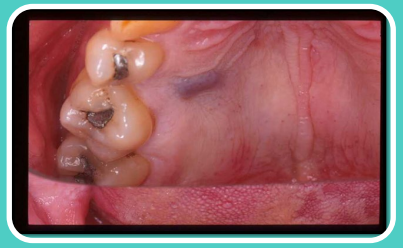


Development may herald onset of AIDS
Diagnosis: Clinical
Biopsy: balooned cells with perinuclear vacuoles, swollen cells contain EBV

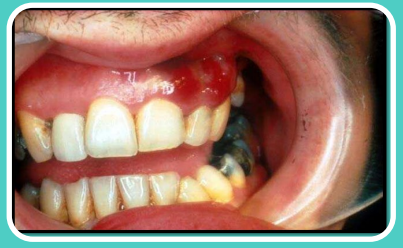
Kaposi's Sarcoma



Most common malignancy in HIV patients
Involves skin and mucosal surfaces
Tip of the nose frequent facial site
Caused by human herpes type 8

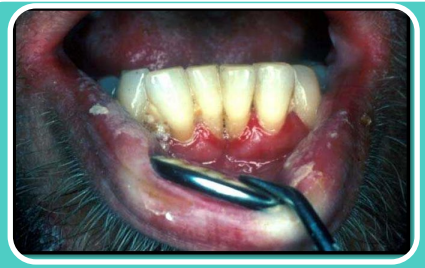


Common in homosexuals, can occur in all risk groups
Arises from vascular endothelial cells
Hard palate and gingiva are common sites



Presents as a reddish-purple patches
Becomes nodular and ulcerate
Diagnosis must be supported by biopsy

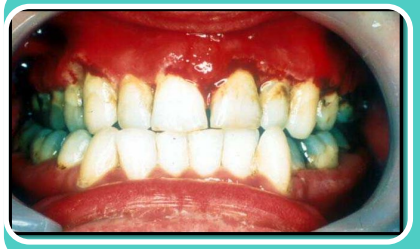
HIV-associated periodontal diseases



Linear gingival erythema

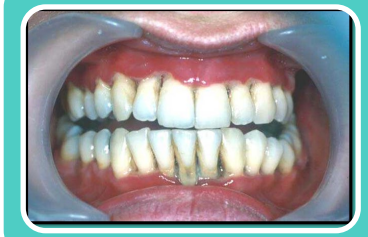
Red band involving free gingival margins

Not related to accumulation of dental plaque



Punched-out ulceration of the interdental papillae

Necrotizing ulcerative gingivitis

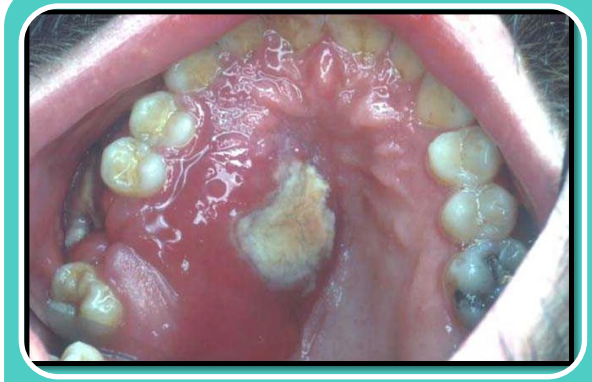


Necrosis of gingival and periodontal tissues

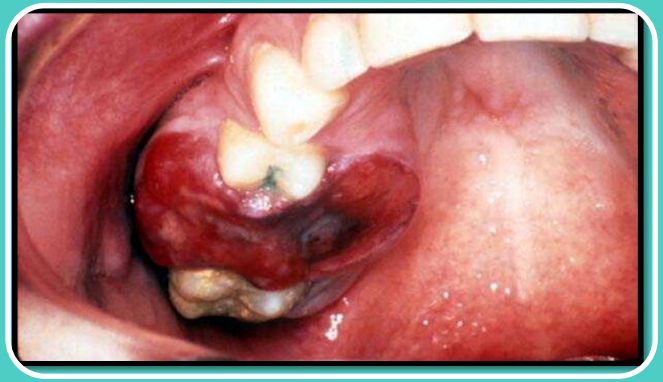
Sometimes exposure and sequestration of alveolar bone

Destructive periodontitis

Lymphoma



Oral lesions: soft tissue enlargement or ulcerative lesion of gingiva



Increased incidence of NHL

Some associated with EBV

Acquired immunodeficiency syndrome (AIDS)

- AIDS is the final stage of HIV disease
- CD4 cell count: <200 cells/mm^3
- CD4 cell %: <14%
- Highly active antiretroviral therapy (HAART) has improved the quality and length of survival for many

HIV Diagnosis

- Diagnosis is clear: patient with obvious lesions for e.g., HL, candidiasis, Kaposi's sarcoma
- Serological confirmation is necessary (enzyme linked immunosorbent assay)
- HIV P24 antibody confirmed by Western Blot
- Polymerase chain reaction (PCR) to detect HIV RNA

Key points: HIV infection

- Caused by retrovirus
- Transmitted sexually, IV drug abuse, blood & blood products
- Progressive deterioration of cell-mediated immunity
- Oral signs and symptoms may be the initial manifestation
- Oral candidiasis most prevalent oral lesion
- Hairy leukoplakia may indicate progression to AIDS
- Kaposi’s sarcoma and lymphomas often in the oral regions
- Neurological and psychological disorders
- Death mainly due to opportunistic infections

Dentist's role: management of patients with HIV infection

Refer to a specialist if diagnosis has not been made
Understand the disease and management
Oral health care; in particular to avoid causes of infection or pain
Avoid needle stick accidents, avoid surgery where possible, treat xerostomia
Oral health education of the patient
Treat diagnosis with confidentiality
Avoid drug interactions with antiretroviral agents
Strict adherence to infection control measures