

Blood Disorders

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Neutropenia or Agranulocytosis

Introduction

- Like the other cellular components of blood, white blood cells or leukocytes are formed within the bone marrow from the same pluripotential stem cells that form erythrocytes.
- Differentiation results in the formation of a lymphoid stem cell that develops into lymphocytes and a myeloid stem cell that develops into monocytes, granulocytes, platelets, and erythrocytes.

Neutropenia I

Etiology:

- Neutropenia is defined as a low neutrophil count, less than 1500 cells per microliter (μL) of blood.
- Agranulocytosis usually refers to severe neutropenia with neutrophil counts less than 200 cells/ (μL) of blood.

Neutropenia - Etiology I

The most common cause of neutropenia is:

- Idiosyncratic or adverse reaction to a drug.
- Inherited syndromes
- Overwhelming viral or bacterial infections
- Autoimmune destruction of the neutrophils
- Bone marrow neoplasms
- Transient neutropenia is an expected side effect of almost all of the chemotherapeutic agents used to treat cancer.

Neutropenia - Epidemiology I

Epidemiology:

It occurs more frequently in women than in men, and it occurs in all age groups.

Neutropenia - Pathogenesis I

Pathogenesis:

- The decreased results from:
 - decreased production
 - production of defective cells
 - increased destruction
- The major effect of this condition is an increased susceptibility to infections.
- Individuals are usually asymptomatic until the neutrophil count approaches about 500 cells/ μ L).

Neutropenia - Pathogenesis II

- One specific form of inherited neutropenia is associated with drops in neutrophil numbers that occur on a regular basis of every 21 to 30 days and last for about 3 to 6 days. This type of disorder is appropriately called **cyclic neutropenia**. Cyclic neutropenia is inherited as an autosomal dominant disorder.

Neutropenia I

Clinical Features:

- Fatigue, fever, malaise, and extreme weakness.
- Vital signs may show a rapid pulse, increased respirations, and hypotension due to septic shock (a condition that causes dilation of the peripheral blood vessels).
- Obvious signs of skin infections, but without the purulent exudate and erythema that would accompany a cellular immune response.
- Upper respiratory and genitourinary tract infections are very common and are usually caused by microorganisms that inhabit the body and are not normally pathogenic.

Neutropenia I

Oral Manifestations:

- Oral infections are common and very severe.
- Periodontal disease in these individuals is very aggressive and painful.
- Chronic neutropenia and the cyclic form of neutropenia invariably lead to premature loss of the dentition.
- Oral ulcers are common with this condition and can impair the individuals ability to maintain adequate nutrition and hydration.

Neutropenia I

Dental Implications:

- Dental care for individuals with neutropenia focuses on preventing infections and preserving the dentition.
- Strict oral hygiene is critical. Preventing oral infections is not only crucial in preserving the dentition, but it plays a key role in decreasing the chance of a systemic infection as well.
- Appropriate medical consultation and laboratory tests should be obtained, since dental treatment should not be performed when neutrophil levels are below **1000** cells/ μ L.

Neutropenia I

Differential Diagnosis:

Any disorder that presents with severe periodontal infections needs to be ruled out, including the following:

- 1 Papillon-Lefevre syndrome
- 2 Leukemia
- 3 Diabetes associated periodontal disease

Papillon-Lefèvre Syndrome



Neutropenia I

Treatment and Prognosis:

- Treatment focuses on using antibiotics to prevent infections and boosting the production of neutrophils by administering drugs that contain **colony-stimulating factor**.
- This factor stimulates the precursor cells in the bone marrow to produce more neutrophils, thereby accelerating their maturation and releasing them into the circulation.
- The prognosis for neutropenia depends on the type, cause, and severity of the disorder. Untreated neutropenia usually results in death from infection.

Leukemias I

Definition

- Leukemias are neoplasms of the white blood cells. The disease occurs in all races and may develop at any age. Leukemias exhibit a slight predilection for males.
- In many instances, **oral lesions may be the first indication** of the underlying leukemia. Furthermore, these patients can develop a high risk for systemic infection of oral origin secondary to their underlying disease or cancer therapies, which produce profound, prolonged immunosuppression.

Leukemias I

Pathogenesis

- Most cases are of unknown etiology
- Leukemia can be caused by exposure to **chemical carcinogens** or **high-dose ionizing radiation**.
- **Chemicals** and drugs associated with development of leukemia include benzene, phenylbutazone, arsenic, and chloramphenicol.
- **Genetic** susceptibility also appears to increase risk of disease.

Leukemias II

- **Viral** causation of human leukemia is not fully substantiated. Human T-lymphotrophic virus (HTLV-1) is linked to human adult T-cell leukemia/lymphoma. Despite widespread distribution of this virus worldwide, it accounts for a remarkably low percentage of leukemia in humans. Fulminant infection and hemorrhage are primary causes of death.

Leukemias I

Classification

Two basic classifications denote whether the disorder involves cells that are derived from a lymphoid stem cell, B and T lymphocytes, or cells that are derived from a myeloid progenitor cell, granulocytes and monocytes. Further classification identifies whether the disease is acute or chronic. There are four main types of acute and chronic leukemia, listed below, see also table (1):

Leukemias - Classification I

- ① Acute lymphoblastic leukemia (ALL)
- ② Chronic lymphocytic leukemia (CLL)
- ③ Acute myelogenous leukemia (AML)
- ④ Chronic myelogenous leukemia (CML)

Leukemias I

Table: Four major kinds of leukemia

Cell type	Acute	Chronic
Lymphocytic leukemia	Acute lymphoblastic leukemia	Chronic lymphocytic leukemia
lymphoblastic	(ALL)	(CLL)
Myelogenous leukemia	Acute myelogenous leukemia	Chronic myelogenous leukemia
myeloid	(AML)	(CML)

Leukemias - Clinical I

Clinical features:

- The initial symptoms of ALL and AML are similar. Patients normally exhibit symptoms associated with anemia (fatigue, pallor, etc.), infection (fever, night sweats), thrombocytopenia (epistaxis, petechiae, bruising), increased metabolism of the cancer cells (weight loss), bone marrow expansion (bone pain), and the infiltration of the liver, spleen, and lymph nodes by leukemic cells, causing enlargement of these organs.

Leukemias - Clinical II

- Leukemic infiltration of the skin can cause pruritus. Infiltration of the central nervous system is more common in ALL than in AML and can cause headache, nerve dysfunction, nausea, vomiting, and sometimes seizures.
- Hyperviscosity of the blood caused by leukocytosis (leukocyte levels of 100,000 cells/mm³), can effectively plug up the microvasculature, causing infarcts and vessel rupture in the lungs, brain, and other organs.

Leukemias - Clinical III

- Chronic leukemia may be present for years without being noticed and may only be discovered while performing routine blood work. Symptoms of CLL are usually not apparent at diagnosis but appear slowly as the bone marrow is gradually overtaken by the production of lymphocytes.
- Symptoms include those associated with anemia, neutropenia, and thrombocytopenia. Repeated infections, increasing fatigue, enlargement of the lymph nodes, increased bleeding tendencies, and bone pain signal progression of the disease.

Leukemias I

Oral Manifestations:

- Increased gingival or periodontal infections
- Increased gingival bleeding
- Unexplained petechiae or purpura in the oral soft tissues
- Gingival enlargement due to leukemic infiltrate. Gingival enlargement is seen most often in AML and CML.
- Many patients seek dental care prior to medical care because of the rapid decline in oral health and appearance of the tissues.

Leukemic Gingiva



Leukemias I

Microscopic Features:

- Biopsy from the enlarged gingiva will reveal the presence of a leukemic infiltrate.
- Differential diagnosis from inflammatory gingival hyperplasia is made by presence of mononuclear blast cells that show cytological atypia.
- Immunohistochemistry may be needed to ascertain whether the cells are of the lymphoid or myeloid type.
- Some forms of myeloid leukemia can produce a quite large swelling known as *granulocytic sarcoma*.

Leukemias I

Dental Implications:

- The clinician must investigate any case of gingival or periodontal inflammation or infection that does not respond to normal interventions, especially if other systemic manifestations, such as fever, weight loss, or night sweats are present.
- Patients should be referred to their physician for further evaluation.
- Elective dental care would not be appropriate during periods when bleeding is excessive or white cell counts are low.

Leukemias I

Differential Diagnosis:

Should be differentiated from gingival enlargement associated with hormonal influences in puberty or pregnancy or that induced by drugs as calcium channel blockers (antihypertensives), phenytoin (antiseizure), and cyclosporine (immunosuppressive).

Bleeding Disorders I

- The normal vascular system maintains a delicate balance between clotting mechanisms and clot lysis (fibrinolysis), with the result that internal or external bleeding is controlled and pathologic thrombosis prevented.

Bleeding Disorders I

- Several factors acting in concert maintain this equilibrium:
 - ① **Vasoconstriction of the Blood vessels** maintain anatomic integrity and a smooth endothelium.
 - ② **Platelets** form the initial plug that seals a site of vascular injury. Platelets also play a major role in forming the permanent thrombus that seals the injury.
 - ③ **Blood coagulation** is the formation of fibrin from plasma precursors. Fibrin and platelets constitute the permanent plug.
 - ④ **Fibrinolysis** is the production of factors such as plasmin from plasma precursors that lyse and remove fibrin thrombi which may be formed in the circulation.

Bleeding Disorders I

- Disturbance of any one of these mechanisms may produce abnormal bleeding on one hand or abnormal thrombosis on the other hand.
- In general, bleeding tendencies occur when there are pathologic conditions that affect
 - 1 Platelet adhesion to damaged vascular walls and aggregation of platelets to one another. Disease in which there is reduction in blood platelets is known as thrombocytopenia.
 - 2 Coagulation factor cascade and its fibrinolytic counterpart pathways.
 - 3 Fragility of small vessel walls. The latter is rare and will be discussed briefly.

Bleeding Disorders I

- The clinical findings include purpura; spontaneous gingival, nasal, or genital tract bleeds; and hemarthrosis. These signs typically occur in the absence of any causative traumatic event.

Bleeding Disorders I

- Two major types of purpura are encountered:
 - ① *petechiae*, which are punctate 1 to 2mm red spots of skin or mucosa and are more common in platelet disorders.
 - ② *ecchymoses*, which appear as diffuse macular blue, red, or brown bruises and are more often encountered among patients with clotting factor deficiencies.

Bleeding Disorders - Causes I

① Vascular defects

- Senile purpura (increased capillary fragility especially in the elderly)
- Hypersensitivity vasculitis; many autoimmune disorders
- Vitamin C deficiency (scurvy, defective collagen)
- Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
- Ehlers-Danlos disease (defective collagen)
- Marfan's syndrome (defective elastin)

② Disorders of platelets

- Decrease (thrombocytopenia)
- Abnormal platelet function

Bleeding Disorders - Causes II

③ Disorders of coagulation

- Deficiency of coagulation factors
- Presence of anticoagulant factors

④ Excessive fibrinolysis

- Disseminated intravascular coagulation
- Dry socket

Bleeding Disorders I

Clinical considerations for dental care

- Uncontrolled bleeding from tooth extraction, or other oral and maxillofacial surgery procedures can occur in patients with either platelet disorders or coagulation defects.
- Two dilemmas can occur in dental patients:
 - ① Unknowingly performing a surgical procedure on a hemorrhagic subject
 - ② Performing necessary extractions or surgeries in a patient with a known coagulation disorder.

Bleeding Disorders II

- The first scenario can often be avoided by taking a thorough medical history. Any sign indicative of a bleeding disorder warrants the acquiring of appropriate blood tests, such as platelet count, platelet aggregation, PT. If leukemia is suspected, a complete blood count should be ordered as well.
- If a surgical procedure is undertaken and bleeding becomes problematic, the patient should be admitted to the emergency department. Thrombin packs with direct pressure should be placed over the wound until the patient can be admitted.

Bleeding Disorders III

- For patients with thrombocyte deficiency who need tooth extraction or other oral surgical interventions, the patient should be treated in the hospital or surgical center with hematologic consultation. A platelet transfusion can then be administered prior to oral surgery. Aspirin or indomethacin toxicity may be encountered in patients with arthritis or chronic headache. The drug should be withdrawn, using a substitute analgesic without aspirin (acetometaphine with codeine or hydrocodone), and surgery postponed for 5 to 7 days.
- Patients with factor deficiencies should be hospitalized in consultation with a hematologist. Missing factor can be administered intravenously just prior to dental surgery.

Bleeding Disorders IV

- For patients on antithrombotic drugs requiring immediate surgery for severe odontalgia, vitamin K can be given intravenously under direction of the patient's physician, and coagulation status can be monitored by obtaining a prothrombin time.
- For elective surgery, the dentist should consult with the physician about withdrawing the antithrombotic drugs for 3 to 4 days prior to surgery.
- In general, anyone with a platelet count below 50,000 should not have dental or periodontal surgery in the general office setting.

Bleeding Disorders V

- Extraction sites are sutured and occluded with fibrin sealant. Antifibrinolytic preparations, such as tranexamic acid, may also be used in patients with coagulopathic disorders.
- Patients who are heparinized while undergoing hemodialysis for end-stage renal disease should be treated the day prior or 1 day subsequent to dialysis. Heparin is rapidly metabolized, and its anticoagulant effects last only 4 to 6 hours.
- Capillary fragility is generally not a problem in dental practice. Although hereditary hemorrhagic telangiectasia involves the oral mucosa, fragile vessels are not present in the periodontal tissues.