Hematologic disorders

Oral pathology lecture 13 and 14

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HEMOPHILIA:

Hemophilia (hemo ¼ blood; philia ¼ loving) represents a variety of bleeding disorders associated with a genetic deficiency of any one of the clotting factors of the blood. Because this is an X-linked hereditary condition, a significant proportion of the male members of these families had hemophilia. Because hemophilia A (factor VIII deficiency) is the most significant and widely recognized form of hemophilia and accounts for 80%–85% of the bleeding diatheses associated with a specific clotting factor deficiency, a deficiency of factor IX or hemophilia B (Christmas disease) also may be encountered.Hemophilia B is similar to hemophilia A in its presentation,being transmitted in an X-linked fashion.

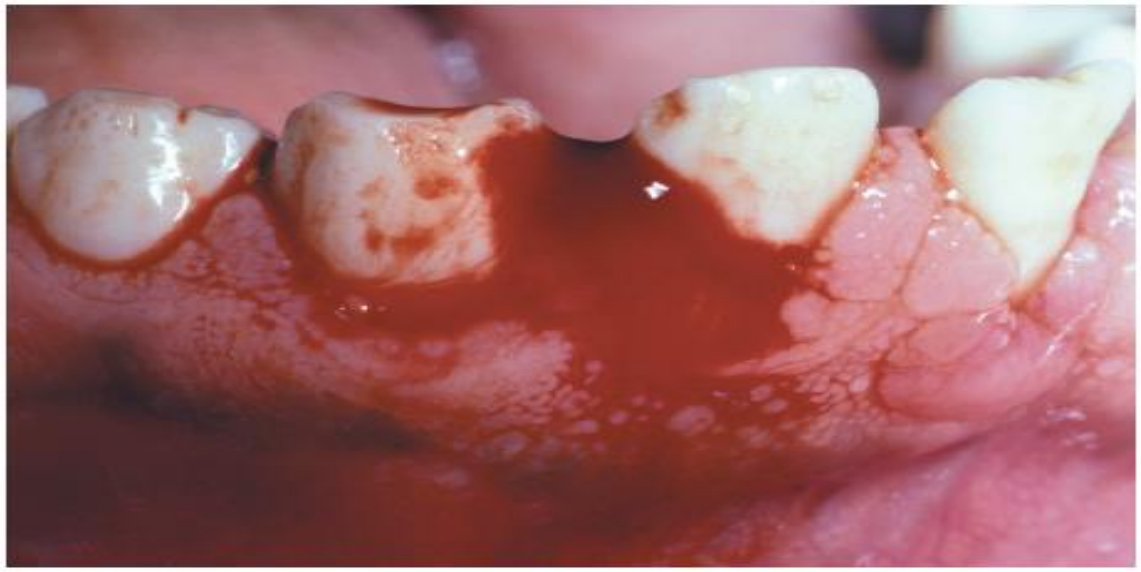
Hemophilia B is much less common than hemophilia A.

Another clotting disorder that is sometimes seen, von Willebrand disease,

is the result of a genetic deficiency of a plasma glycoprotein called von Willebrand factor.

This glycoprotein aids in the adhesion of platelets at a site of bleeding, and it also binds to factor VIII, acting as a transport molecule.

von Willebrand disease is a genetically heterogeneous condition, with several subtypes currently identified, and it may be transmitted in an autosomal dominant or recessive pattern. It is the most common of the inherited bleeding disorders.



• **Fig. 13.5 Hemophilia.** Hemorrhage in a patient with factor IX deficiency occurred after routine periodontal curettage.

TABLE 13.1 Comparison of the Most Commonly Encountered Inherited Bleeding Disorders

Type	Defect	Inheritance	Findings
Hemophilia A (classic hemophilia)	Factor VIII deficiency	X-linked recessive	Abnormal PTT
Hemophilia B (Christmas disease)	Factor IX deficiency	X-linked recessive	Abnormal PTT
von Willebrand disease	Abnormal von Willebrand factor, abnormal platelets	Autosomal dominant	Abnormal PFA, abnormal PTT

PFA, platelet function assay (replaces bleeding time test); *PTT*, partial thromboplastin time.

Clinical Features

Hemophilia A is an X-linked disorder. Females typically carry the trait, but it is expressed primarily in males. Failure of normal hemostasis after circumcision is typically one of the first signs that a bleeding disorder is present.

The severity of the bleeding disorder depends on the extent of the clotting factor deficiency. Hemophilia A is a heterogeneous disorder that is caused by any one of a variety of mutations associated with the gene for factor VIII.

In infants, oral lacerations and ecchymoses that involve the lips and tongue are a frequent occurrence as a result of the common falls and bumps experienced by this age group. If not treated appropriately, then such lacerations may result in significant blood loss in more severely affected patients.Sometimes deep hemorrhage occurs during normal activity and may involve the muscles, soft tissues, and weight-bearing joints (hemarthrosis), especially the knees. result of such uncontrolled bleeding is the formation of scar tissue as the body removes the extravasated blood.

This often causes a crippling deformity of the knee joints secondary to arthritis and ankylosis. Sometimes the tissue hemorrhage results in the formation of a tumorlike mass, which has been called pseudotumor of hemophilia. Such lesions have been reported in the oral regions.

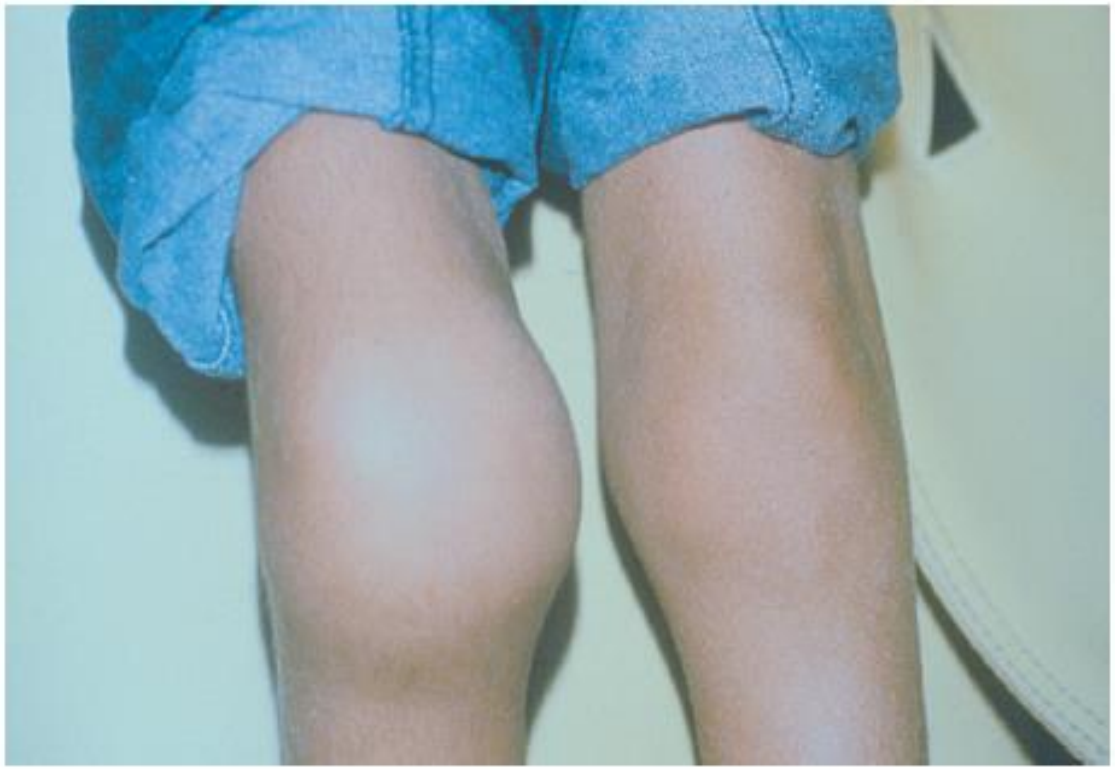
In most instances, pseudotumors of hemophilia occur in patients affected with hemophilia A, but these lesions also have been described rarely in hemophilia B and von Willebrand disease.

An increased coagulation time (delay in blood clotting), of course, is the hallmark feature of this group of conditions. Uncontrollable or delayed hemorrhage may result from any laceration; this includes surgical incisions, dental extractions, and periodontal curettage . Measurements of the platelet count, platelet function assay, prothrombin time (PT), and partial thromboplastin time (PTT) should be ordered as screening tests for any patient with a possible bleeding disorder.

Treatment and Prognosis

The treatment of clotting factor deficiencies essentially consists of replacement therapy with the appropriate clotting factor. treatment depends on the severity of the clotting factor deficiency. If surgery is to be performed, then clotting factor replacement therapy may be indicated.For patients with severe deficiencies (less than 1% of normal levels of factor VIII), injections with the clotting factor must be performed as soon as a hemorrhagic episode occurs to prevent such complications as the crippling joint deformities of the knees. The use of aspirin is strictly contraindicated because of its adverse effect on blood platelet function. Severe hemorrhage may result if these patients use aspirin-containing medications. Optimal dental care is strongly encouraged for these patients to prevent oral problems that might require surgery. If oral or periodontal surgery is necessary, then consultation with the patient's physician is mandatory. The patient is usually prepared for the procedure by the administration of clotting factor just before the surgery. With an extensive surgical procedure, additional doses of clotting factor may be needed subsequently. In addition, epsilon-aminocaproic acid (EACA), an antifibrinolytic agent that inhibits clot degradation, should be given 1 day before the surgery and continued for 7–10 days afterward.

clotting factor replacement therapy has resulted in complication for many of these patients. Cryoprecipitation, the traditional method of concentrating clotting factors from the plasma, resulted in the concentration of several viruses, including the hepatitis viruses and HIV.



• **Fig. 13.4 Hemophilia.** The enlargement of the knees of this patient with factor VIII deficiency is due to repeated episodes of bleeding into the joints (hemarthrosis). Inflammation and scarring have resulted.

ANEMIA:

Anemia is a general term for either a decrease in the volume of red blood cells (hematocrit) or in the concentration of hemoglobin. This problem can result from a number of factors, including a decreasedproductionof erythrocytes or anincreased destruction or loss of erythrocytes. Laboratory studies, such as the red blood cell (RBC)count, hematocrit ,hemoglobin concentration,mean corpuscular volume (MCV), mean corpuscular hemoglobin(MCH), and mean corpuscular hemoglobin concentration (MCHC), can help indicate the probable cause of the anemia.anemia is often a sign of an underlying disease, such as renal failure, liver disease,chronic inflammatory conditions, malignancies, or vitamin or mineral deficiencies.

Clinical Features

The symptoms of anemia are typically related to the reduced oxygen-carrying capacity of the blood, which is a result of the reduced numbers of erythrocytes. Symptoms such as tiredness, headache, shortness of breath, or lightheadedness are often present. Pallor of the mucous membranes may be observed in severe cases of anemia. The palpebral conjunctiva is often the site where this paleness is most easily appreciated, but the oral mucosa may show similar signs.

Treatment and Prognosis

The treatment of anemia depends on determining the underlying cause of the anemia and correcting that problem, if possible.

CAUSES OF ANEMIA

Anemias With Disturbed Iron Metabolism

- Iron deficiency anemia
- Sideroblastic anemias

Megaloblastic Anemias

- Cobalamin (B12) deficiency (pernicious anemia)
- Folic acid deficiency

Anemia Associated With Chronic Disorders

- **Anemia of chronic infection** (infective endocarditis, tuberculosis, osteomyelitis, lung abscess, and pyelonephritis)
- **Anemia of inflammatory connective tissue disorders**(rheumatoid arthritis, lupus erythematosus, sarcoidosis,temporal arteritis, and regional enteritis)
- **Anemia associated with malignancy**
- Secondary to chronic bleeding
- Myelophthisic anemia
- Anemia of uremia
- Anemia of endocrine failure
- Anemia of liver disease

Hemolytic Anemias

- **Extrinsic causes**
- **Splenomegaly**
- **Red cell antibodies**
- **Trauma in the circulation**
- **Direct toxic effects**

(various microorganisms, copper salts, and venom of certain snakes)

- **Membrane abnormalities**
- **Spur cell anemia**
- **Paroxysmal nocturnal hemoglobinuria**
- **Hereditary spherocytosis**
- **Hereditary elliptocytosis**
- **Disorders of the interior of the red cell**
- **Defects in the Embden-Meyerhof pathway**
- **Defects in the hexose monophosphate shunt**

Disorders of Hemoglobin

Sickle cell anemia and Thalassemias

THALASSEMIA

Thalassemia represents a group of disorders of hemoglobin synthesis that are characterized by reduced synthesis of either the α-globin or β-globin chains of the hemoglobin molecule. people who carry the trait for one of the forms of thalassemia seem to be more resistant to infection by the malarial organism. it is considered one of the most common inherited conditions that affect humans.

The hemoglobin molecule is a tetramer that is composed of two α chains and two β chains; if one of the chains is not being made in adequate quantities, then the normal amount of hemoglobin cannot be made. the excess globin chains accumulate within the erythrocyte,further compromising the structure and function of the cell. These abnormal erythrocytes are recognized by the spleen and selected for destruction (hemolysis). In addition, there is evidence of ineffective erythropoiesis caused by premature cell death of erythrocyte precursors in the bone marrow because of activation of apoptotic mechanisms. The net result is that the patient has hypochromic, microcytic anemia.

Because two genes code for the β chain and four genes code for the α chain, the degree of clinical severity in these conditions can vary considerably. The severity depends on which specific genetic alteration is present and whether it is heterozygous or homozygous. In the heterozygous state, an adequate amount of normal hemoglobin can be made and the affected patient experiences few signs or symptoms. In the homozygous state, however, the problems are often severe or even fatal.

Clinical and Radiographic Features :

β-Thalassemia :

If only one defective gene for the β-globin molecule is inherited (thalassemia minor), no significant clinical manifestations are usually present.When two defective genes for the β-globin molecule are inherited, the patient typically is affected with thalassemia major, also called Cooley anemia or Mediterranean anemia. The disease is usually detected during the first year of life because a severe microcytic, hypochromic anemia develops when fetal hemoglobin synthesis ceases after 3–4 months of age. The red blood cells (RBCs) that are produced are extremely fragile and survive for only a few days in the peripheral circulation.to maintain adequate oxygenation, the rateof hematopoiesis (despite being ineffective) is greatly increased (up to 30 times normal), resulting in massive bone marrow hyperplasia, as well as hepatosplenomegaly and lymphadenopathy because of extramedullary hematopoiesis.The bone marrow hyperplasia may affect the jaws especially, producing an altered trabecular pattern and marked, painless enlargement of the mandible and maxilla . This results in a characteristic “chipmunk” facies and causes reduced size or obliteration of the paranasal sinuses. Frontal bossing is also present, and a skull radiograph may show a prominent “hair-on-end” appearance of the calvaria. Generalized maturational delay of the patient is typically seen. Delayed development of the dentition also has been described, with the teeth showing a mean delay of approximately 1 year compared with a matched population.Without therapy, tissue hypoxia worsens and serious bacterial infections with pneumococcal organisms often develop.

α-Thalassemia

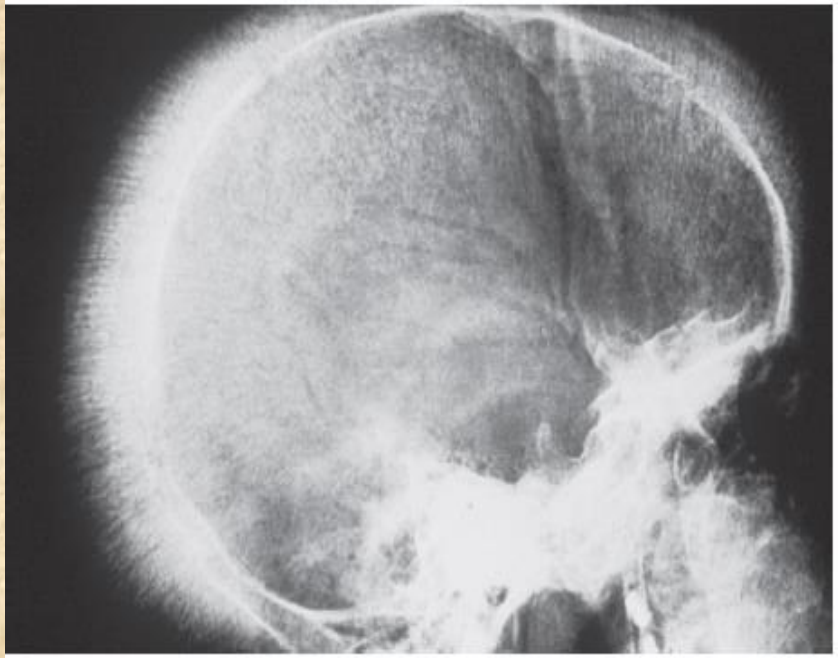
Because four α-globin genes may be affected, α-thalassemia has a broader spectrum of involvement than does β-thalassemia. The condition is caused by deletion at the α-globin gene locus.

When only one deleted gene is inherited, no disease can be detected. With the inheritance of two deleted genes, the condition is known as α-thalassemia trait. These patients have a mild degree of anemia and microcytosis that is not clinically significant. With three deleted genes, the term hemoglobinH(HbH)disease is applied. Patients have problems with hemolytic anemia and splenomegaly. For patients with severe hemolysis, splenectomy may be indicated.

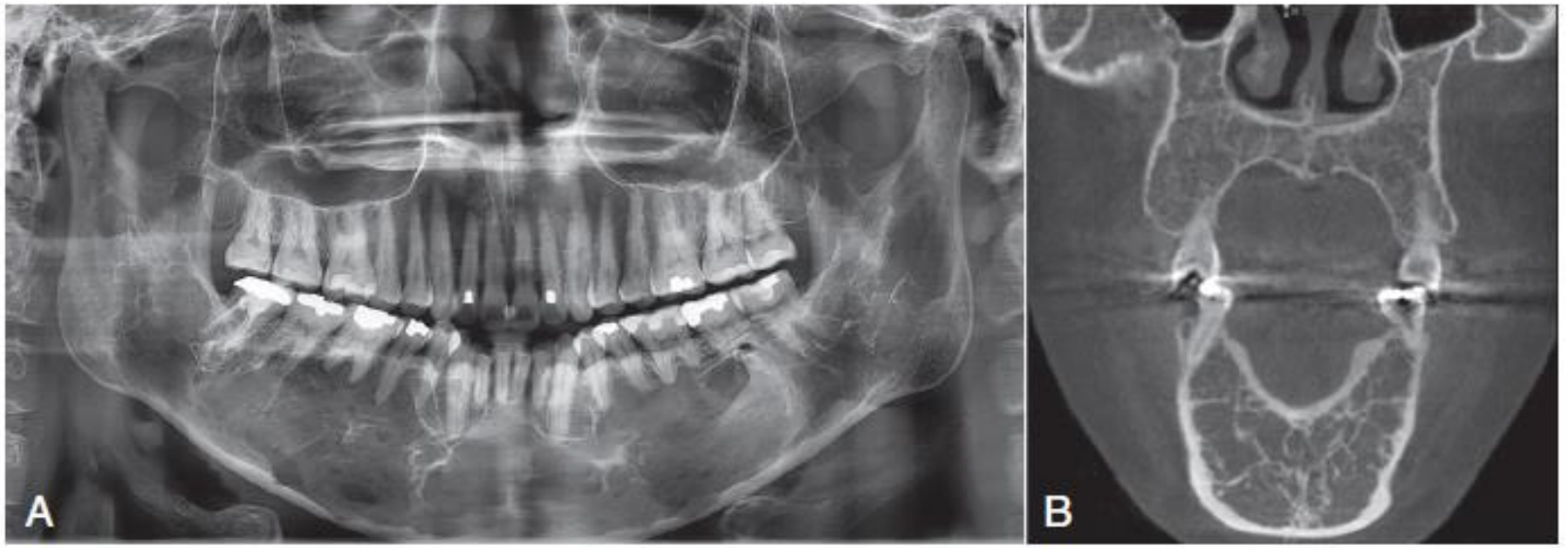
The homozygous state, in which all four genes are deleted, causes severe generalized fetal edema, a condition that has been termed hydrops fetalis. Hydrops fetalis is not specific for α-thalassemia and can be seen as a manifestation of other diseases, such as severe Rh incompatibility. Infants with α-thalassemia who are affected by this problem typically die within a few hours of birth.

Treatment and Prognosis

Thalassemia major is treated by means of blood transfusions. These should be administered every 2–3 weeks to simulate the normal hematologic state.with repeated blood transfusions, iron overload inevitably develops because of the constant infusion of exogenous RBCs. This is a serious problem, and often death is due to hemochromatosis, an abnormal deposition of iron throughout the tissues of the body. The heart, liver, and endocrine glands are particularly affected by the toxic accumulation of iron. To combat this problem, an iron-chelating agent, deferoxamine (also known as desferrioxamine), must be given. If adequate control of iron levels is not obtained, the addition of an orally administered iron chelator, either deferiprone or deferasirox, is often considered. Hematopoietic stem cell transplantation has also been used with considerable success for individuals who are relatively young, have little organ damage, and have an HLA-matched donor. For patients who have developed an abnormal facial appearance caused by thalassemia, surgical correction can be performed in many cases.



• **Fig. 13.10 Thalassemia.** Lateral skull radiograph depicting the characteristic "hair-on-end" appearance in a patient with thalassemia.



• **Fig. 13.9 Thalassemia. A,** Panoramic radiograph of a 42-year-old male with β-thalassemia shows mandibular enlargement, marked radiolucent change, and wispy trabeculae. **B,** Coronal CT image shows similar changes in the jaws. (Panel A: Courtesy of Dr. Nicole S. Pheifer. Panel B: Courtesy of Dr. Andrew P. Wightman.)

APLASTIC ANEMIA

Aplastic anemia is a rare, life-threatening hematologic disorder that is characterized by failure of the hematopoietic precursor cells in the bone marrow to produce adequate numbers of all types of blood cells (pancytopenia). A significant amount of evidence supports the concept that most cases of aplastic anemia represent an immune-mediated disease caused by cytotoxic T lymphocytes that target differentiating hematopoietic cells in the marrow. As a result, the hematopoietic stem cells do not seem to undergo normal maturation despite normal or increased levels of cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), which normally induce the production and maturation of several types of white blood cells. some cases of aplastic anemia are associated with exposure to certain environmental toxins (e.g., benzene), treatment with certain drugs (especially the antibiotic chloramphenicol), or infection with certain viruses (particularly non-A, non-B, non-C, or non-G hepatitis). A few genetic disorders, such as Fanconi anemia and dyskeratosis congenita are associated with an increased frequency of aplastic anemia.

Clinical Features

Because all of the formed elements of the blood are decreased in patients with aplastic anemia, the initial symptoms may be related to any one or several of the deficiencies. The erythrocyte deficiency produces signs and symptoms related to a decreased oxygen-carrying capacity of the blood; therefore, patients may experience fatigue, lightheadedness, tachycardia, or weakness. The platelet deficiency (thrombocytopenia) is seen as a marked tendency for bruising and bleeding, which affects a variety of sites. Retinal and cerebral hemorrhages are some of the more devastating manifestations of this bleeding tendency. Deficiency of white blood cells (neutropenia, leukopenia, or granulocytopenia) is the most significant complication of this disease, predisposing the patient to bacterial and fungal infections that often are the cause of death.

The oral findings related to thrombocytopenia include gingival hemorrhage , oral mucosal petechiae, purpura, and ecchymoses. The oral mucosa may appear pale because of the decreased numbers of red blood cells (RBCs).

Oral ulcerations associated with infection due to neutropenia, particularly those that involve the gingival tissues, may be present. Minimal erythema is usually associated with the periphery of the ulcers. Gingival hyperplasia has also been reported in association with aplastic anemia

Histopathologic Features

A bone marrow biopsy specimen usually demonstrates a relatively acellular marrow with extensive fatty infiltration. The histopathologic features of an oral ulceration in a patient with aplastic anemia show numerous microorganisms in addition to a remarkable lack of inflammatory cells in the ulcer bed.

Diagnosis

The diagnosis of aplastic anemia is usually established by laboratory studies. A pancytopenia is characterized by at least two of the following findings:

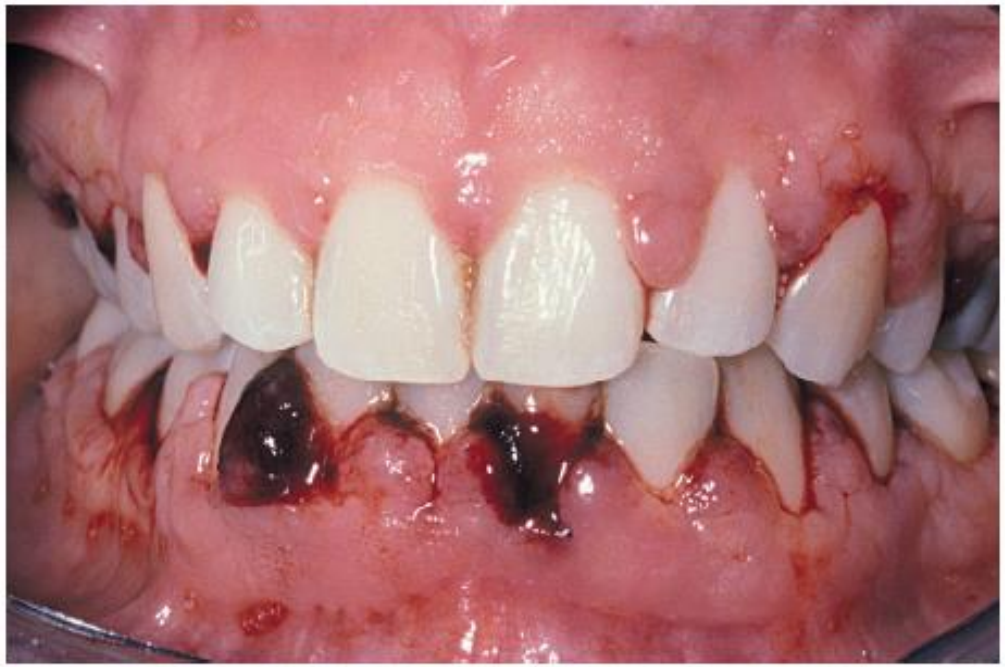
- Fewer than 500 granulocytes/µL
- Fewer than 20,000 platelets/µL
- Fewer than 20,000 reticulocytes/µL

Treatment and Prognosis

The course for patients with aplastic anemia is unpredictable.For the milder forms of the disease, spontaneous recovery of the marrow may occur ; progression to severe aplastic anemia may be seen in others. In severe cases, the chances of spontaneous recovery are slim. If a particular environmental toxin or drug is associated with the process, then withdrawal of the offending agent may sometimes result in recovery.

The treatment is initially supportive. Appropriate antibiotics are given for the infections that develop, and transfusions of packed RBCs or platelets are administered for symptomatic treatment of anemia and bleeding problems, respectively.

Definitive therapy for aplastic anemia is to replace the defective marrow with normal marrow, either by bone marrow transplantation or peripheral blood stem cell transplantation from a matched donor.



• **Fig. 13.11 Aplastic Anemia.** Diffuse gingival hyperplasia with sulcular hemorrhage.

NEUTROPENIA

Neutropenia refers to a decrease in the number of the circulating neutrophils below 1.5x109/L in an adult. It is often associated with an increased susceptibility of the patient to bacterial infections. Clinicians must be aware of this disorder because infection of the oral mucosa may be the initial sign of the disease. A decrease in neutrophils may be precipitated by several mechanisms, most of which involve decreased production or increased destruction of these important inflammatory cells. A decreased production of neutrophils and the other formed elements of the blood may result from the destruction of the bone marrow by malignancies, such as leukemia or by metabolic diseases, such as osteopetrosis . Several different types of malignancy, including Hodgkin and non-Hodgkin lymphoma ,melanoma and renal cell carcinoma, a have been reported to trigger destruction of neutrophils by various autoimmune mechanisms.

Many drugs may affect neutrophil production, either through direct toxic effects on the bone marrow progenitor cells or by triggering autoimmune mechanisms that destroy neutrophils. These drugs include the following:

- Anticancer chemotherapeutic agents (e.g., nitrogen mustard, busulfan, chlorambucil, and cyclophosphamide)
- Antibiotics (e.g., penicillins and sulfonamides)
- Phenothiazines • Tranquilizers • Diuretics

Nutritional deficiencies of vitamin B12 or folate, which may be a consequence of malabsorption syndromes, can inhibit neutrophil production as well.

A variety of viral and bacterial infections not only may reduce production of neutrophils but also seem to increase their destruction, typically at the sites of infection. Autoimmune mechanisms of neutrophil destruction may also be induced by viral or bacterial infections. Viral infections that have been implicated include the following:

- Hepatitis A and B
- Rubella
- Measles
- Respiratory syncytial virus
- Varicella
- HIV

Numerous bacterial infections, such as typhoid, tuberculosis, brucellosis, and tularemia, may also cause neutropenia.

Clinical Features

Most patients with neutropenia have some form of bacterial infection rather than a viral or fungal infection, particularly if the other elements of the immune system (lymphocytes, plasma cells, and monocytes) are still intact. Staphylococcus aureus and gram-negative organisms seem to cause the most problems for patients with neutropenia.

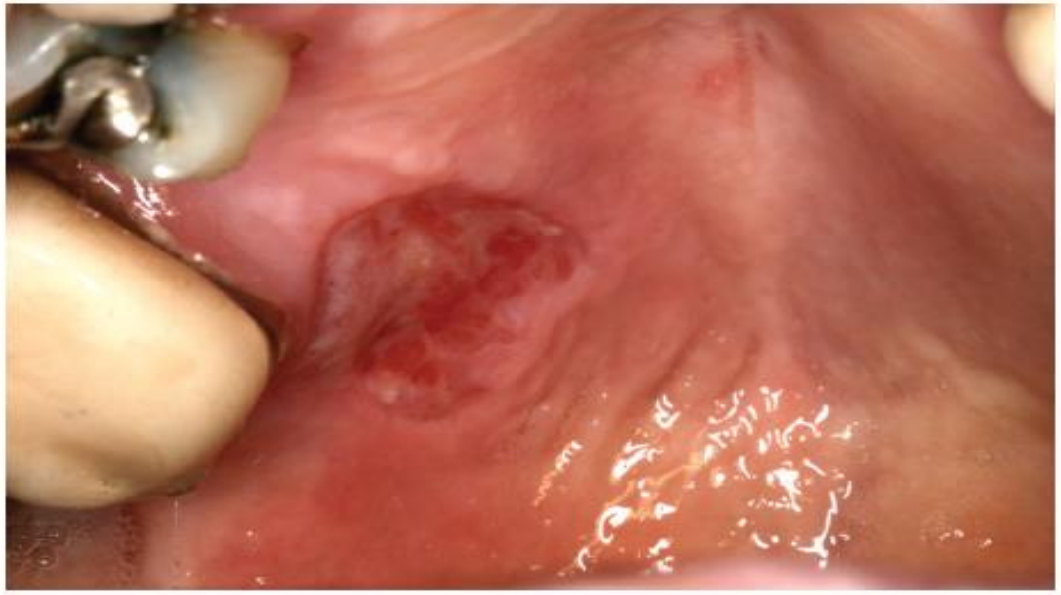
The most common sites of infection include the middle ear, the oral cavity, and the perirectal area. The oral lesions of neutropenia consist of ulcerations that usually involve the gingival mucosa, probably because of theheavy bacterial colonization of this area and the chronic trauma that it receives. These ulcers characteristically lack an erythematous periphery . Premature periodontal bone loss with exfoliation of the deciduous dentition has been described.

Histopathologic Features

A biopsy specimen of neutropenic ulceration usually shows a reduced number or the absence of neutrophils. Bacterial invasion of the host tissue may be apparent in some instances.

Treatment and Prognosis

Infections related to neutropenia are managed with appropriate antibiotic therapy. The patient should be encouraged to maintain optimal oral hygiene to decrease the bacterial load in the oral cavity. Studies using recombinant human granulocyte colony-stimulating factor (G-CSF; filgrastim; pegfilgrastim),a cytokine that promotes the growth and differentiation of neutrophils, have shown remarkable Patients with severe neutropenia have a significant increase in neutrophil counts and resolution of infections after treatment with this agent.



• **Fig. 13.12 Neutropenia.** Palatal neutropenic ulceration that was seen in a patient with large granular lymphocyte leukemia, a rare form of leukemia that induces a severe decrease in neutrophils.

THROMBOCYTOPENIA

Thrombocytopenia is a hematologic disorder that is characterized by a markedly decreased number of circulating blood platelets (formed elements derived from megakaryocyte precursors in the bone marrow). Platelets are necessary for hemostasis and clot formation. A platelet count of 200,000–400,000/mm3 is considered normal. The decrease in platelets may be the result of the following:

- Reduced production
- Increased destruction
- Sequestration in the spleen

REDUCED PLATELET PRODUCTION

Reduced production of platelets may be the result of various causes, such as infiltration of the bone marrow by malignant cells or the toxic effects of cancer chemotherapeutic drugs. In such instances, decreases in the other formed elements of the blood are also seen.

INCREASED PLATELET DESTRUCTION

Increased destruction of platelets may be caused by an immunologic reaction,which is often precipitated by any one of more than 100 different drugs; heparin is one of the most common offending agents. autoantibodies directed against platelets, specifically certain surface glycoproteins,may on rare occasions be induced by viral infection or vaccination. certain systemic diseases may have thrombocytopenia as a component, such as systemic lupus erythematosus (SLE) and HIV infection. Increased destruction may also occur because of increased consumption of platelets associated with abnormal blood clot formation. This occurs in patients with conditions, such as thrombotic thrombocytopenic purpura (TTP). This serious disorder of coagulation is caused by a deficiency of a von Willebrand factor-cleaving metalloprotease (ADAMTS13), which triggers the formation of numerous thrombi within the small blood vessels of the body.

SEQUESTRATION IN THE SPLEEN

in normal conditions, one-third of the platelet population is sequestered in the spleen. Conditions that cause splenomegaly (e.g., portal hypertension secondary to liver disease and splenic enlargement secondary to tumor infiltration cause larger numbers of platelets to be taken out of circulation.

the result for the patient is a bleeding problem because normal numbers of platelets are not available for proper hemostasis.

Clinical Features

Clinical evidence of thrombocytopenia is not usually seen until the platelet levels drop below 100,000/mm3. The severity of involvement is directly related to the extent of platelet reduction.

The condition often is initially detected because of the presence of oral lesions. Minor traumatic events are continuously inflicted on the oral mucosa during chewing and swallowing of food. In a patient with thrombocytopenia, the thrombi do not form properly.This results in a leakage of blood from the small vessels. Clinically, this usually produces pinpoint hemorrhagic lesions known as petechiae. If a larger quantity of blood is extravasated, then an ecchymosis or bruise results. With even larger amounts of extravasated blood, a hematoma (hemat ¼ blood; oma ¼ tumor) will develop.

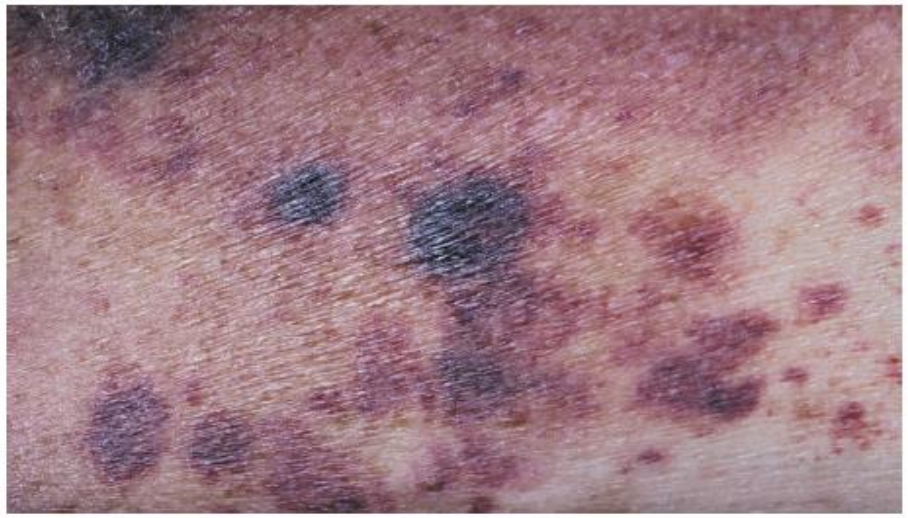
Spontaneous gingival hemorrhage often occurs in these patients, as does bleeding from sites of minor trauma. With severe thrombocytopenia (<10,000 platelets/mm3), massive bleeding from the gastrointestinal or urinary tract may be fatal. Epistaxis is often present in these patients, and hemoptysis indicates significant pulmonary hemorrhage. Intracranial hemorrhage is also a potentially fatal complication of severe thrombocytopenia.

Immune thrombocytopenic purpura (ITP) or immune thrombocytopenia, which used to be known as idiopathic thrombocytopenic purpura or idiopathic thrombocytopenia, can present as either an acute or chronic process. Acute ITP usually occurs during childhood, classically after a nonspecific viral infection. The symptoms of thrombocytopenia appear quickly and may be severe. Most cases, however, resolve spontaneously within 4–6 weeks, and90%of patients recover by 3–6 months. Chronic ITP most frequently affects women between 20 and 40 years.

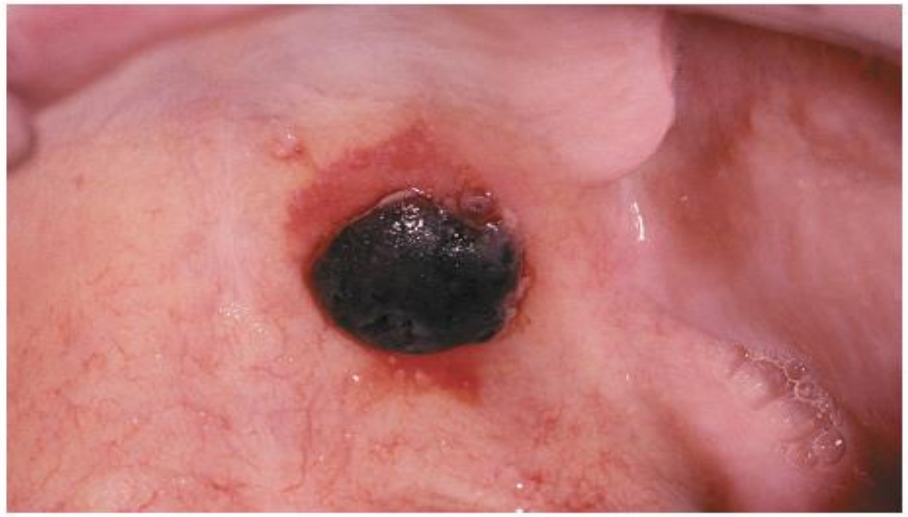
Treatment and Prognosis

If the clinician believes the thrombocytopenia to be drug related,the drug should be discontinued immediately. In most instances, the platelet count returns to normal afterseveral days. Platelet transfusions and corticosteroid therapy may be necessary if life-threatening hemorrhage occurs.

ITP often resolves spontaneously, but those cases that are more severe may require corticosteroid therapy or intravenous immunoglobulin (IVIG) therapy.



• **Fig. 13.15 Thrombocytopenia.** The bruising (purpura) seen on this patient's forearm is a result of reduced platelet count secondary to myelodysplasia, a preleukemic bone marrow disorder.



• **Fig. 13.16 Thrombocytopenia.** This dark palatal lesion represents a hematoma caused by a lack of normal coagulation, characteristic of thrombocytopenia.

LEUKEMIA

Leukemia represents several types of malignancies of hematopoietic stem cell derivation. The disease begins with the malignant transformation of one of the stem cells, which initially proliferates in the bone marrow and eventually overflows into the peripheral blood of the affected patient.

Leukemias are classified according to their histogenesis and clinical behavior. the broad categories would be acute or chronic (referring to the clinical course) and myeloid or lymphocytic /lymphoblastic (referring to the histogenetic origin). Myeloid leukemias can differentiate along several different pathways; thus they produce malignant cells that usually show features of granulocytes or monocytes, and less frequently, erythrocytes or megakaryocytes.

Acute leukemias, if untreated, run an aggressive course and often result in the death of the patient within a few months. Chronic leukemias tend to follow a more indolent course, although the end result is the same. One of the greatest successes in cancer treatment has been achieved in acute lymphoblastic leukemia of childhood, a condition that used to be uniformly fatal but now is often capable of being controlled.Leukemias are probably the result of a combination of environmental and genetic factors.

certain types of leukemia show specific chromosomal abnormalities. The first chromosomal abnormality to be detected was found in patients with chronic myeloid leukemia, and this malignancy was characterized by a genetic alteration called the Philadelphia chromosome.This abnormality represents a translocation of the chromosomal material between the long arms of chromosomes22 and 9.

environmental agents are associated with an increased risk of leukemia, Exposure to pesticides, benzene, and benzene-like chemicals. Ionizing radiation has also been implicated; this was documented by the increased frequency of chronic myeloid leukemia in the survivors of the atomic bomb blasts at Hiroshima and Nagasaki during World War II. Viruses have been shown to produce leukemia,The most studied is the retrovirus known as human T-cell leukemia/lymphoma virus type 1 (HTLV-1), which is transmitted by contaminated blood from infected to uninfected individuals.

Clinical Features

If all types of leukemia are considered ,more males than females are affected. The myeloid leukemias generally affect an adult population; acute myeloid leukemia affects a broader age range, which includes children. The median age of patients diagnosed with chronic myeloid leukemia is approximately 59 years. Acute lymphoblastic leukemia, in contrast, occurs predominantly in children and represents one of the more common childhood malignancies. Chronic lymphocytic leukemia, the most common type of leukemia, primarily affects older adults. Many of the clinical signs and symptoms of leukemia are related to the marked reduction in the numbers of normal white and red blood cells, a phenomenon that results from the crowding out of the normal hematopoietic stem cells by the malignant proliferation (myelophthisic anemia).

Because of the reduced red blood cell (RBC) count and reduction in oxygen-carrying capacity of the blood, patients complain of fatigue, easy tiring, and dyspnea on mild exertion. The malignant cells may also infiltrate other organs and often cause splenomegaly, hepatomegaly, and lymphadenopathy. Leukemic patients may also complain of easy bruising and bleeding, problems that are caused by a lack of blood platelets (thrombocytopenia), the result of megakaryocytes being crowded out of the marrow.

Petechial hemorrhages of the posterior hard palate and the soft palate may be observed, and these may be accompanied by spontaneous gingival hemorrhage, especially with platelet counts less than 10,000–20,000/mm3. A fever associated with infection may be the initial sign of the leukemic process. Perirectal infections, pneumonia, urinary tract infections, and septicemia are common infectious complications. The microorganisms that are typically involved include gram-negative bacteria, gram-positive cocci, and certain Candida species.

Ulceration of the oral mucosa is often present as a result of the impaired ability of the host to combat the normal microbial flora. Usually, the gingival mucosa is the most severely affected because of the abundant bacteria normally present around the teeth. The neutropenic ulcers that are produced are typically deep, punched-out lesions with a gray-white necrotic base. Oral candidiasis is often a complication of leukemia, involving the oral mucosa diffusely. Herpetic infections are the most common viral lesions, and these may involve any area of the oral mucosa rather than being confined to the keratinized mucosa, as in immunocompetent patients.

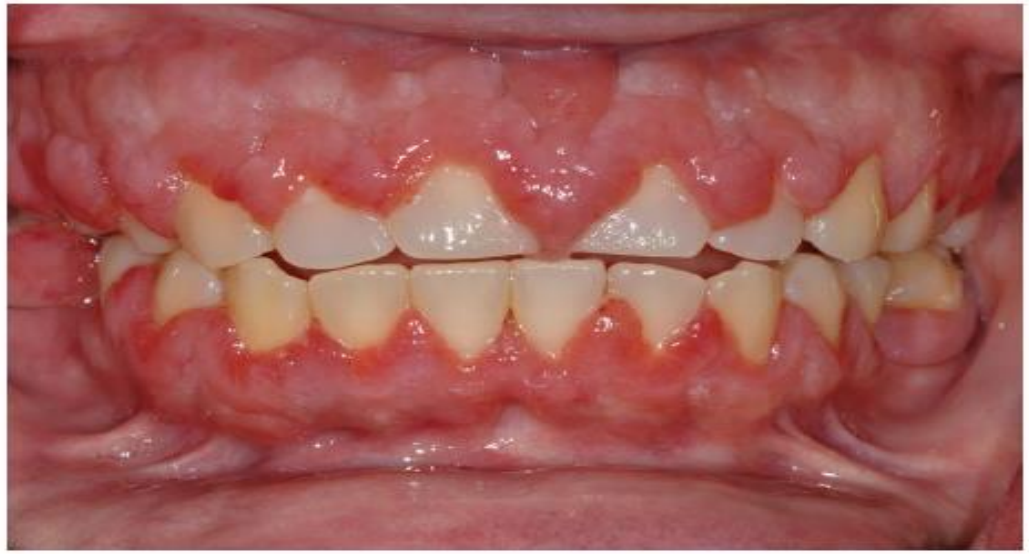
the leukemic cells infiltrate the oral soft tissues and produce a diffuse, boggy, nontender swelling that may or may not be ulcerated. This occurs most frequently with the myelomonocytic types of leukemia, and it may result in diffuse gingival enlargement or a prominent tumorlike growth . The tumorlike collection of leukemic cells is known as myeloid sarcoma, a designation that has replaced the older terms, granulocytic sarcoma and extramedullary myeloid tumor the proliferation of leukemic cells was called chloroma because it is often greenish (chlor ¼ green; oma ¼ tumor) on fresh-cut sections.

Histopathologic Features

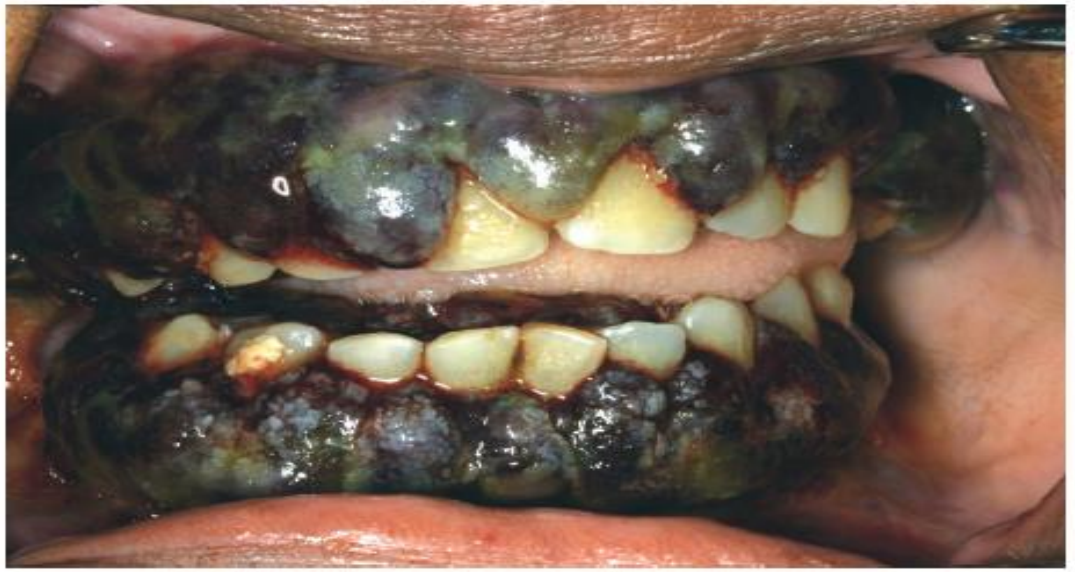
Microscopic examination of leukemia-affected tissue shows diffuse infiltration and destruction of the normal host tissue by sheets of poorly differentiated cells with either myelomonocytic characteristics or lymphoid features

Treatment and Prognosis

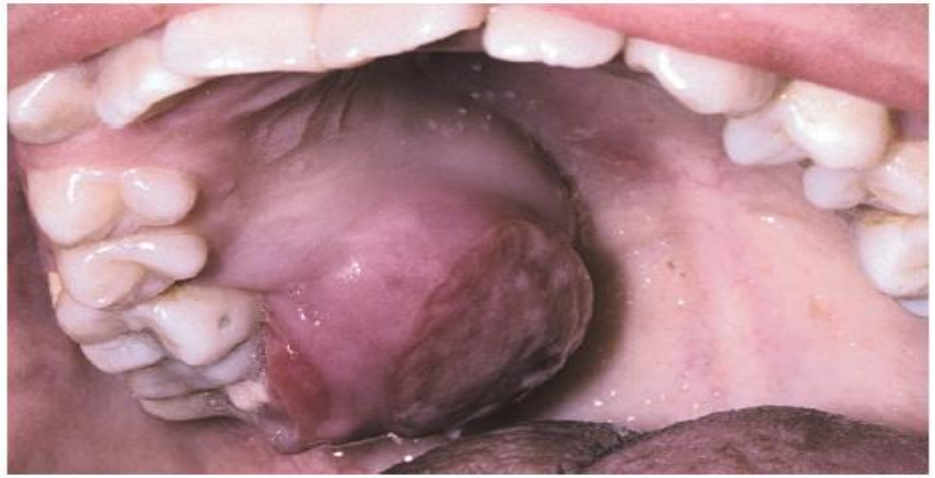
the treatment of a patient with leukemia typically consistsof various forms of chemotherapy; the type of leukemia dictates the chemotherapeutic regimen. In most cases the purpose of chemotherapy is to destroy as many of the atypical cells as possible in a short time, thus inducing a remission .For this reason, this technique has been termed induction chemotherapy. this phase of chemotherapy requires high doses of toxic chemotherapeutic agents; often, the patient experiences a number of unpleasant side effects during treatment. Once remission has been induced, this state must be maintained. This is the purpose of maintenance chemotherapy, which typically requires lower doses of chemotherapeutic drugs given over a longer period.



• **Fig. 13.17 Leukemia.** Diffuse gingival enlargement, as depicted in this photograph, may occur in leukemic patients, particularly in those with monocytic leukemia. (Courtesy of Dr. Spencer Shoff.)



• **Fig. 13.18 Leukemia.** Extensive hemorrhagic enlargement of the maxillary and mandibular gingivae. (Courtesy of Dr. Michael Tabor.)



• **Fig. 13.19 Leukemia.** The ulcerated soft tissue nodule of the hard palate represents leukemic cells that have proliferated in this area.

HODGKIN LYMPHOMA (HODGKIN DISEASE)

Hodgkin lymphoma represents a malignant lympho-proliferative disorder, unlike most malignancies, the neoplastic cells (Reed-Sternberg cells) make up only about 0.1%–2% of the cells in the enlarged lymph nodes that characterize this condition. Current evidence regarding the histogenesis of the Reed-Sternberg cell points to a B-lymphocyte origin. the disease can cause death if appropriate therapy is not instituted, although the treatment of this malignancy is one of the few major success stories in cancer therapy during the past 30 years. the cause of this disease is unknown, molecular studies have linked Epstein-Barr virus (EBV) infection to a significant percentage of these lesions.

Clinical Features

Hodgkin lymphoma always begins in the lymph nodes, and any lymph node group is susceptible. The most common sites of initial presentation are the cervical and supraclavicular nodes (70%–75%) or the axillary and mediastinal nodes (5%–10% each). The disease initially appears less than 5% of the time in the abdominal and inguinal lymph nodes.a male predilection is observed, and a bimodal pattern is noted with respect to the patient's age at diagnosis.One peak is observed between 15 and 35 years of age; another peak is seen after the age of 50.

The usual presenting sign is the identification by the patient of a persistently enlarging, nontender, discrete mass or masses in one lymph node region. In the early stages, the involved lymph nodes are often movable; as the condition progresses, the nodes become more matted and fixed to the surrounding tissues. If it is untreated, then thecondition spreads to other lymph node groups and eventually involves the spleen and other extralymphatic tissues, such as bone, liver, and lung. Oral involvement is rare.

other systemic signs and symptoms include weight loss, fever, night sweats, and generalized pruritus (itching). The absence of these systemic signs and symptoms is considered to be better in terms of the patient's prognosis, and this information is used in staging the disease. Patients who have no systemic signs are assigned to category A and those with systemic signs to category B. The staging of Hodgkin lymphoma is important for planning treatment and estimating the prognosis for a givenpatient. The staging procedure typically includes confirmation of the pathologic diagnosis, careful history and physical examination, abdominal and thoracic computed tomography (CT) scans or magnetic resonance imaging (MRI) studies, chest radiographs, and routine hematologic studies (e.g., complete blood count, serum chemistries, and erythrocyte

sedimentation rate). Evaluation of the extent of disease involvement using (18F)-fluorodeoxyglucose positron emission tomography (FDG PET/CT) scans is now part of the standard protocol, particularly at large institutions. The radiolabeled glucose is given intravenously, and the Hodgkin lymphoma cells metabolize this compound to a much greater extent than the normal tissues, thus identifying sites where tumor is present.

TABLE 13.2 Ann Arbor System for Classification of Hodgkin Lymphoma

Stage	Defining Features
I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or one or more lymph node regions with an extralymphatic site (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), possibly with an extralymphatic organ or site (III_E), the spleen (III_S), or both (III_{SE})
IV	Diffuse or disseminated involvement of one or more extralymphatic organs (identified by symbols), with or without associated lymph node involvement
	A: Absence of systemic signs B: Presence of fever, night sweats, and/or unexplained loss of 10% or more of body weight during the 6-month period before diagnosis

Adapted from Gobbi PG, Ferreri AJM, Ponzoni M, et al: Hodgkin lymphoma, *Crit Rev Oncol Hematol* 85:216–237, 2013.

Histopathologic Features

Hodgkin lymphoma is recognized to comprise two main forms, (1) nodular lymphocyte–predominant Hodgkin lymphoma and (2) classical Hodgkin lymphoma, the latter of which is divided into five subtypes. this group of diseases has certain features in common, These features include effacement of the normal nodal architecture by a diffuse, often mixed, infiltrate of inflammatory cells that is interspersed with large, atypical neoplastic lymphoid cells. In the case of classical Hodgkin lymphoma,this atypical cell is known as a Reed-Sternberg cell which is typically binucleated("owl-eye" nuclei), although it may be multinucleated ("pennies on a plate"), with prominent nucleoli. The malignant cell in nodular lymphocyte–predominant Hodgkin lymphoma is the "popcorn cell," which is so-named because of the resemblance of the nucleus to a kernel of popped corn. The pathologist must see one of these types of distinctive atypical cells to make a diagnosis of Hodgkin lymphoma, although their presence does not automatically imply that diagnosis, because similar cells may be seen in certain viral infections, especially infectious mononucleosis. Hodgkin lymphoma is currently classified in the following manner:

1) Nodular lymphocyte–predominant Hodgkin lymphoma,

2) Classical Hodgkin lymphoma (comprising five histopathologic subtypes):

1. Lymphocyte rich
2. Nodular sclerosis
3. Mixed cellularity
4. Lymphocyte depletion
5. Unclassifiable

1)Nodular lymphocyte–predominant Hodgkin lymphoma :

constitutes 4%–5% of all cases of Hodgkin lymphoma in the United States. In the past, this form was probably combined with the lymphocyte-rich subtype, but the presence of the characteristic popcorn cells is a significant clue to the diagnosis.

Lymphocyte-rich classical Hodgkin lymphoma represents about 6% of all cases. Sheets of small lymphocytes withfew Reed-Sternberg cells characterize this form.

The nodular sclerosis subtype makes up 60%–80% of cases and occurs more frequently in females during the second decade of life. This type gets its name from the broad fibrotic bands that extend from the lymph node capsule into the lesional tissue. Reed-Sternberg cells in the nodular sclerosis form appear to reside in clear spaces and, therefore, **are referred to as lacunar cells.**

The mixed cellularity form accounts for about 15%–30% of the cases and is characterized by a mixture of small lymphocytes, plasma cells, eosinophils, and histiocytes with abundant Reed-Sternberg cells.

The lymphocyte depletion subtype, the most aggressive type, makes up less than 1% of the cases in recent reports.In thisform of Hodgkin lymphoma, numerous bizarre giant Reed-Sternberg cells are present, with few lymphocytes.

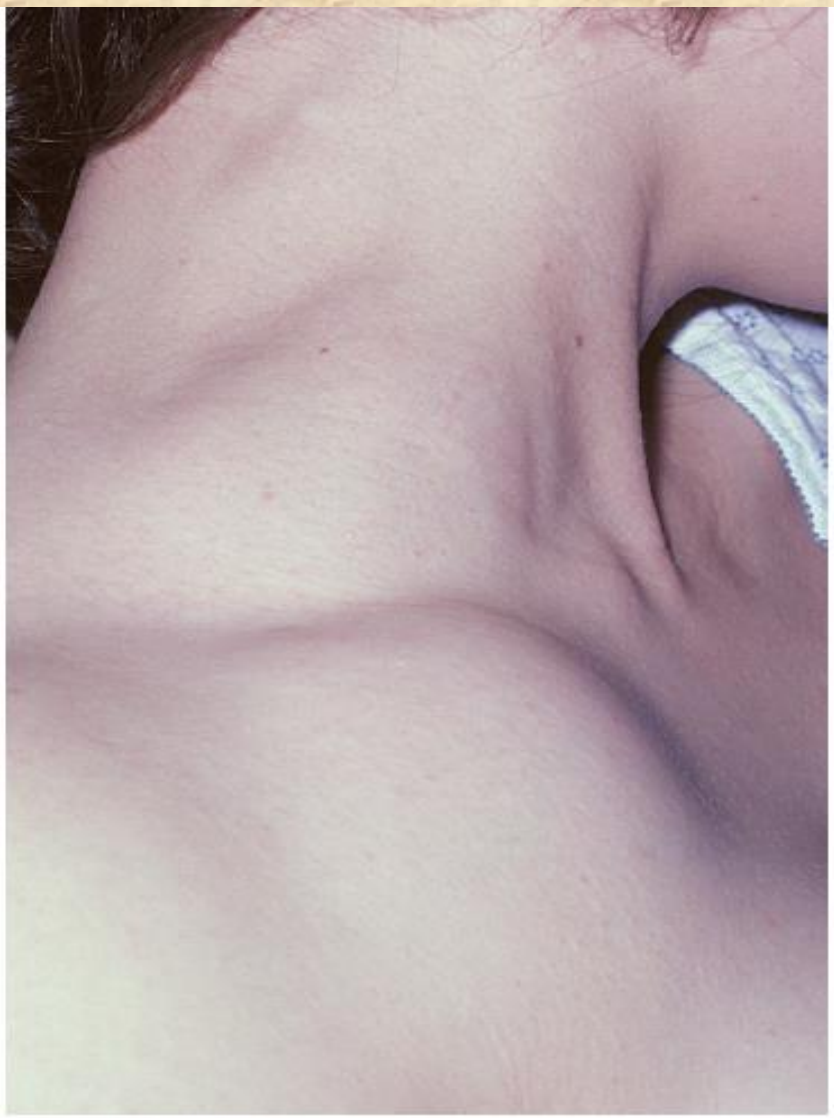
examples of Hodgkin lymphoma are encountered that really do not fit the criteria for any of the known subtypes, and these are designated as **unclassifiable.**

Treatment and Prognosis

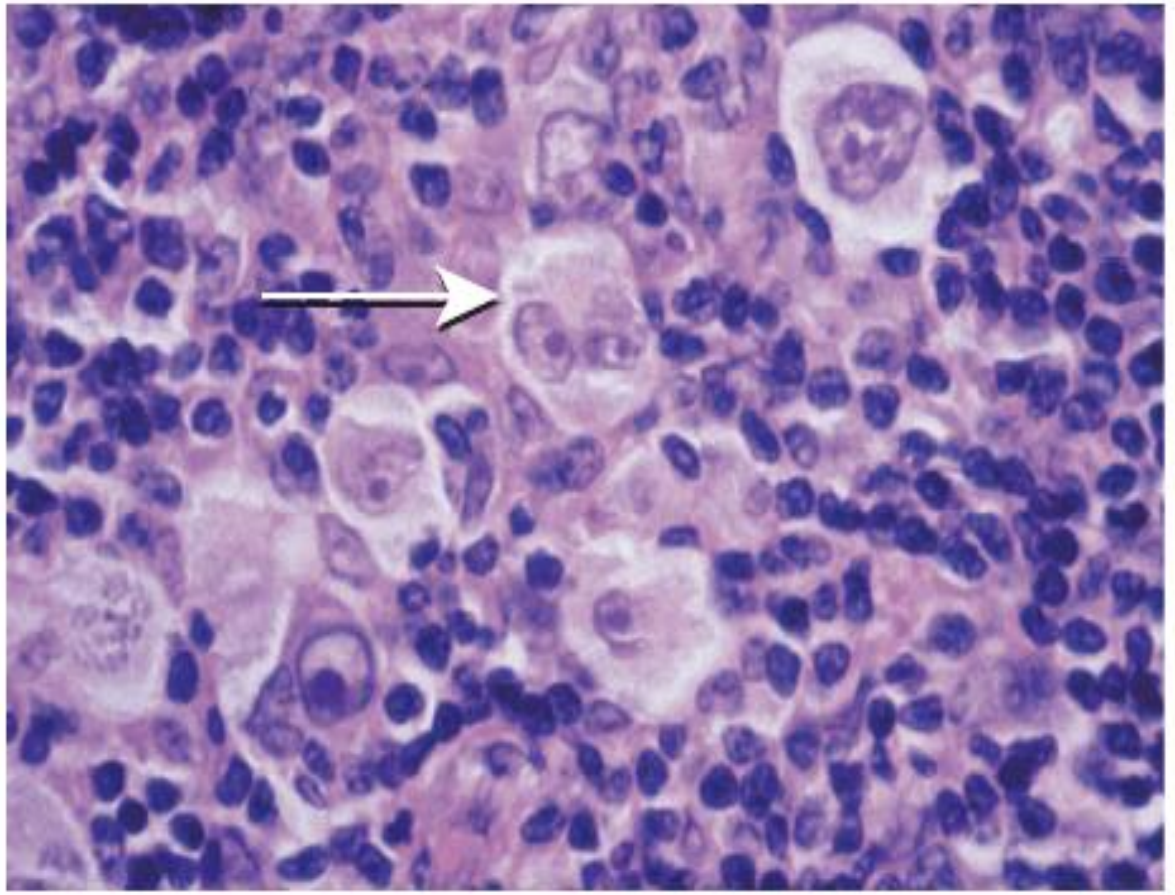
The treatment of Hodgkin lymphoma depends on the stage of involvement. combine less extensive radiotherapy fields with milder multiagent chemotherapy regimens to maximize disease control and minimize long-term complications of therapy.

Patients with stage III or IV disease require chemotherapy; radiation therapy is used conjointly if significant mediastinal involvement or residual disease is detected.

The histopathologic subtype of Hodgkin lymphoma appears to have minimal impact on the response to therapy. the stage of disease now plays a more important role in determining the patient's prognosis than does the histopathologic subtype. After 15 years posttreatment, patient mortality is due to the complications of therapy: either secondary malignancy or cardiovascular disease. research is focused on the development of treatment regimens that decreasing the risk of treatment-related complications.



• **Fig. 13.25 Hodgkin Lymphoma.** The prominent supraclavicular and cervical masses represent Hodgkin lymphoma.



• **Fig. 13.26 Hodgkin Lymphoma.** This high-power photomicrograph shows the characteristic Reed-Sternberg cell *(arrow)* of Hodgkin lymphoma, identified by its "owl-eye" nucleus.

NON-HODGKIN LYMPHOMA

The non-Hodgkin lymphomas include a diverse and complex group of malignancies of lympho-reticular histogenesis and differentiation. they initially arise within lymph nodes and tend to grow as solid masses. This is in contrast to lymphocytic leukemias which begin in the bone marrow and are characterized by a large proportion of malignant cells that circulate in the peripheral blood. The non Hodgkin lymphomas most commonly originate from cells of the B-lymphocyte series. Tumors with a T-lymphocyte derivation are less common. many of the lesions that had been classified as histiocytic were in fact neoplasms composed of transformed B lymphocytes. In the early 1980s, a group of American pathologists devised a classification scheme, known as the Working Formulation for Clinical Use, which may still be referred to in the United States. Based on this classification, lymphomas were broadly grouped into three categories:

1. Low grade
2. Intermediate grade
3. High grade

the Working Formulation has been shown to be limited in its utility and accuracy.an international study group in the early 1990s devised a new method of categorizing the lymphomas, known as the REAL (revised European-American lymphoma) classification

Epstein-Barr virus (EBV) has been implicated to be an etiopathogenic agent in Burkitt lymphoma,a type of high grade, small, noncleaved B-cell lymphoma. Human herpesvirus 8 (HHV-8) has not only been associated with Kaposi sarcoma but also with primary body cavity lymphoma. Even bacteria have been shown to induce the formation of so-called mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach. Antibiotic treatment of Helicobacter pylori infection of the stomach lining often results in complete regression of this low-grade lymphoma.

Clinical and Radiographic Features

Non-Hodgkin lymphoma occurs primarily in adults, children may be affected, particularly by the more aggressive intermediate- and high-grade lymphomas. The condition most commonly develops in the lymph nodes, but so-called extranodal lymphomas are also found. With a nodal presentation, the patient usually is aware of a nontender mass that has been slowly enlarging for months. The lesion typically involves a local lymph node collection, such as the cervical, axillary, or inguinal nodes; one or two freely movable nodules are noticed initially. As the malignancy progresses, the nodes become more numerous and are fixed to adjacent structures or matted together. Gradually, the process involves other lymph node groups, and invasion of adjoining normal tissues occurs.

In the oral cavity, lymphoma usually appears as extranodal disease.the oral lesions of lymphoma are often a component of more widely disseminated disease. The malignancy may develop in the oral soft tissues or centrally within the jaws. Soft tissue lesions appear as nontender, diffuse swellings; they most commonly affect the buccal vestibule, posterior hard palate, or gingiva. Such swellings characteristically have a boggy consistency. The lesion may appear erythematous or purplish, and it may or may not be ulcerated

Patients who wear a denture that contacts the lesional site often complain that their denture does not fit because it feels too tight. Lymphoma of bone may cause vague pain or discomfort, which might be mistaken for a toothache. The patient may complain of paresthesia, particularly with a mandibular lesion (so-called numb chin syndrome).

Radiographs usually show an ill-defined or ragged radiolucency, although in the early stages, the radiographic changes may be subtle or nonexistent. If untreated, then the process typically causes expansion of the bone, eventually perforating the cortical plate and producing a soft tissue swelling. Such lesions have been mistaken for a dental abscess, although a significant amount of pain is not present in most cases.

Clinical staging to determine the extent to which the disease has spread is an important factor in assessing the prognosis for a particular patient. The staging evaluation should include a history, physical examination, complete blood count, liver function studies, CT scans of the thoracic, pelvic and abdominal regions, and bone marrow biopsy. PET/CT scans are also very useful in staging, but this technique often is available only at larger medical centers. PET/CT is also employed to assess response to treatment, in addition to staging.

Histopathologic Features

Non-Hodgkin lymphomas are histopathologically characterized by a proliferation of lymphocytic-appearing cells that may show varying degrees of differentiation, depending on the type of lymphoma. Low-grade lesions consist of well-differentiated small lymphocytes. High-grade lesions tend to be composed of less differentiated cells.

All lymphomas grow as infiltrative, broad sheets of relatively uniform neoplastic cells that usually show little or no evidence of lesional tissue necrosis .In some lesions, particularly those of B-lymphocyte origin, a vague semblance of germinal center formation may be seen (i.e., a nodular or follicular pattern). Other lymphomas show no evidence of such differentiation, and this pattern is termed diffuse. If the lymphoma arises in a lymph node, then the tumor destroys the normal architecture of the node. An extranodal lymphoma destroys the normal adjacent host tissue by infiltrating throughout the area. In the oral cavity, diffuse large B-cell lymphoma, which is considered to be a high-grade lymphoma, is the most common diagnosis.

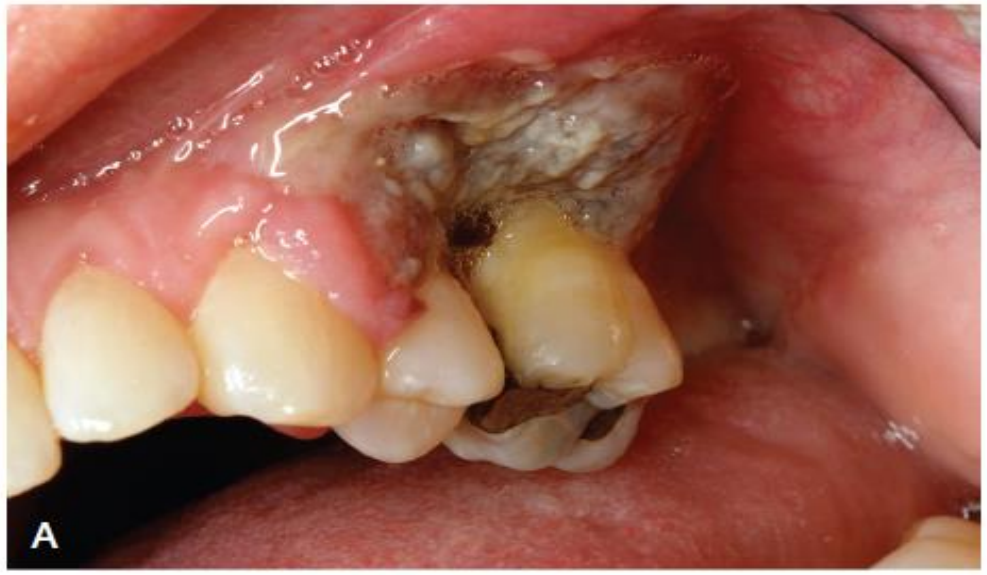
Treatment and Prognosis

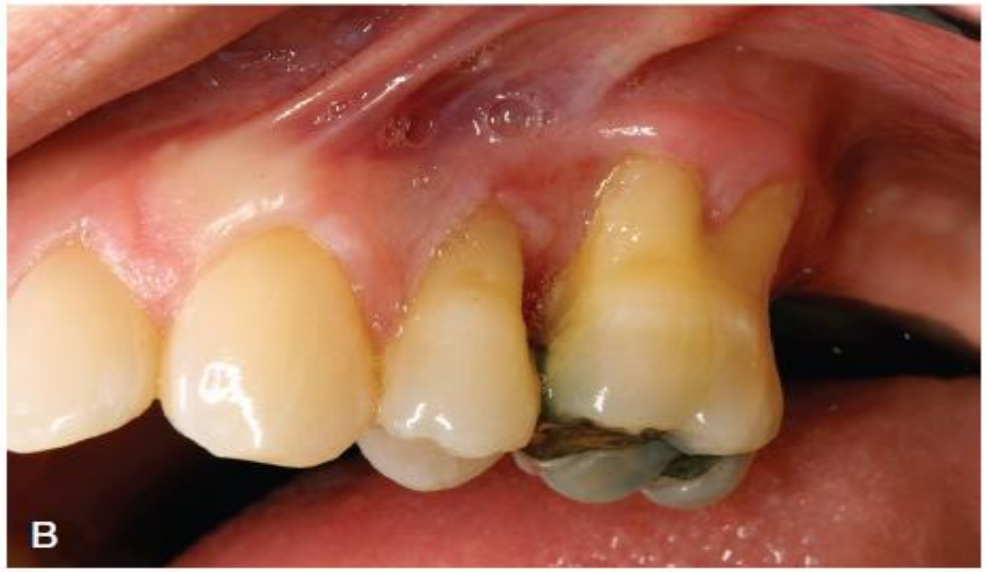
The treatment of a patient with non-Hodgkin lymphoma is based on several factors, including

- ❑ the type of lymphoma
- ❑ the stage and grade of the lymphoma
- ❑ the overall health of the patient
- ❑ the patient's pertinent past medical history.

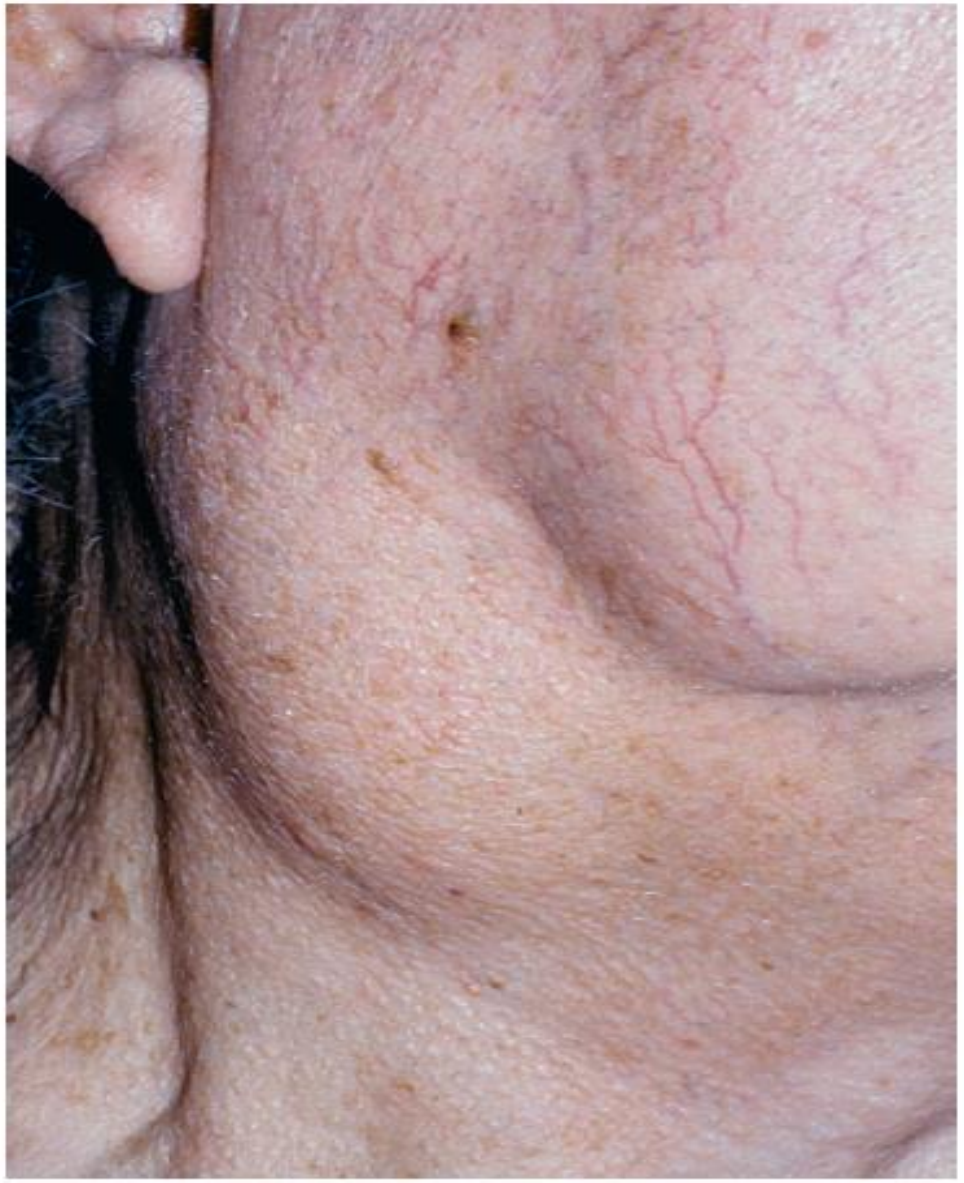
The patient's health must be considered because many of the chemotherapeutic regimens are quite debilitating. Surgical management is not usually indicated. Because most non-Hodgkin lymphomas are of B-cell differentiation, many treatment strategies now incorporate monoclonal antibodies directed against CD20, a B-cell surface antigen, as part of the chemotherapeutic regimen for both low-grade and high-grade lymphomas. Rituximab is one of the more commonly used agents.

Low-grade (indolent) lymphomas are the most controversial in terms of treatment. Some authorities recommend no particular treatment because these tumors are slow growing and tend to recur despite chemotherapy. low-grade lymphomas arise in older adults and the median survival without treatment is 8–10 years, many oncologists in the past would opt for a "watch and wait" strategy, treating the patient only if symptoms develop. **For high-grade (aggressive) lymphomas,** the treatment of localized disease may consist of radiation plus chemotherapy.

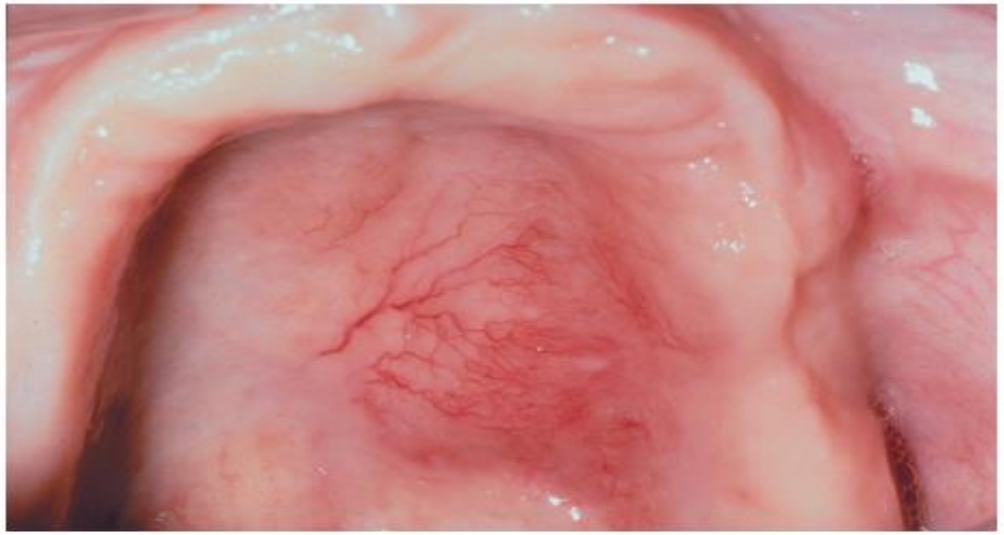




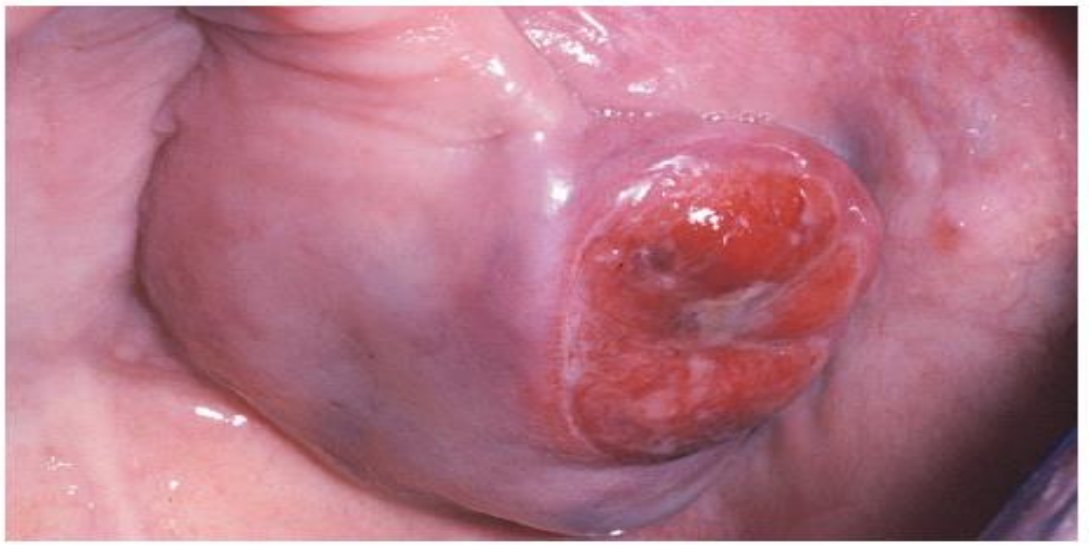
• **Fig. 13.27 Epstein-Barr Virus (EBV)-Associated Lymphoproliferative Disorder. A,** This 42-year-old woman, treated for autoimmune hepatitis with mycophenolate mofetil, developed painful gingival ulcers. **B,** Resolution of the lesion after immune suppression was stopped and rituximab therapy was initiated.



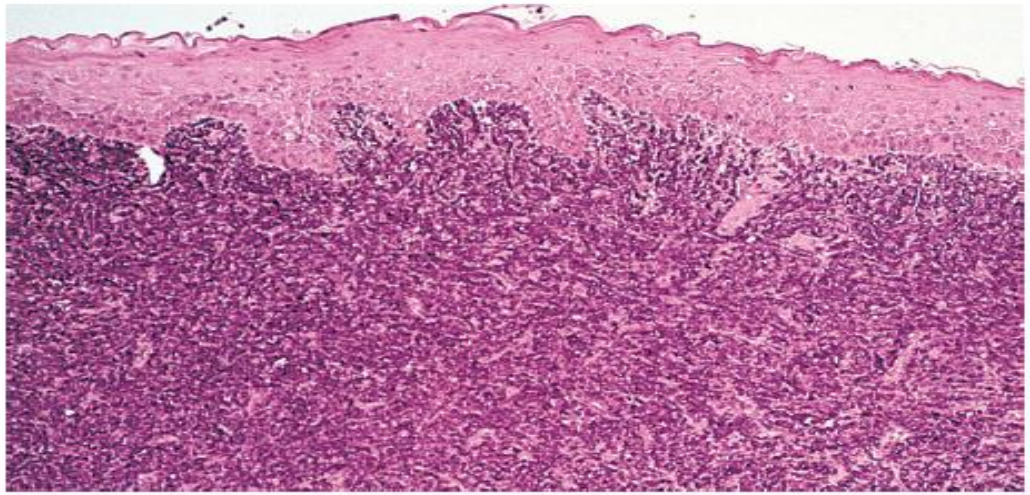
• **Fig. 13.28 Non-Hodgkin Lymphoma.** The matted, nontender lymph node enlargement in the lateral cervical region represents a common presentation of lymphoma.



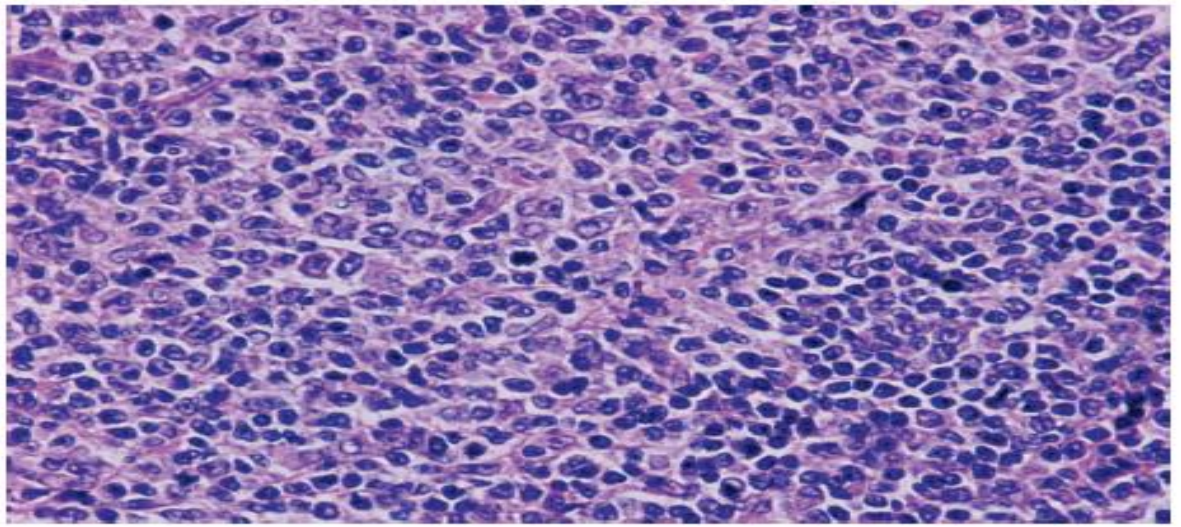
• **Fig. 13.29 Non-Hodgkin Lymphoma.** One of the frequent locations of extranodal lymphoma in the head and neck area is the palate, where the tumor appears as a nontender, boggy swelling. Note the overlying telangiectatic blood vessels, a feature often seen with malignancy.



• **Fig. 13.30 Non-Hodgkin Lymphoma.** Ulcerated mass of the left posterior maxilla.



• **Fig. 13.31 Non-Hodgkin Lymphoma.** This low-power photomicrograph shows a diffuse infiltration of the subepithelial connective tissue by lymphoma.



• **Fig. 13.32 Non-Hodgkin Lymphoma.** This high-power photomicrograph shows lesional cells of lymphoma, consisting of a population of poorly differentiated cells of the lymphocytic series with minimal cytoplasm.