Hematopoietic tumors

Oral pathology lecture 13 and 14

ASMAA SAMI JAWAD

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. 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

more males than females are affected. The myeloid leukemias generally affect an adult population.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.

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.

Oral candidiasis is often a complication of leukemia, involving the oral mucosa diffusely. **Herpetic infections** are the most common viral lesions.

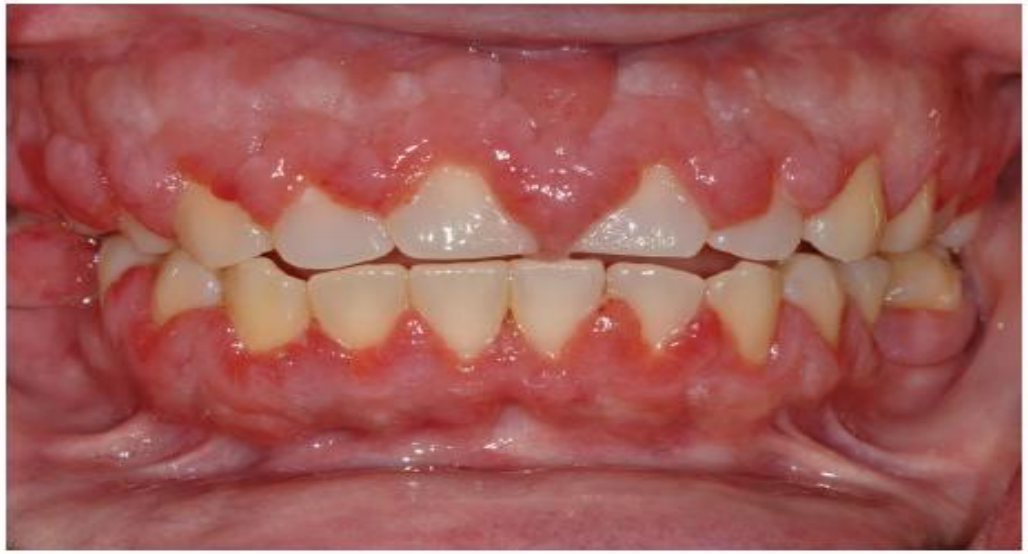
the leukemic cells infiltrate the oral soft tissues and produce a diffuse and nontender swelling that may or may not be ulcerated. This occurs with the myelomonocytic types of leukemia, and it may result in diffuse gingival enlargement or a prominent tumor like growth .

Histopathologic Features

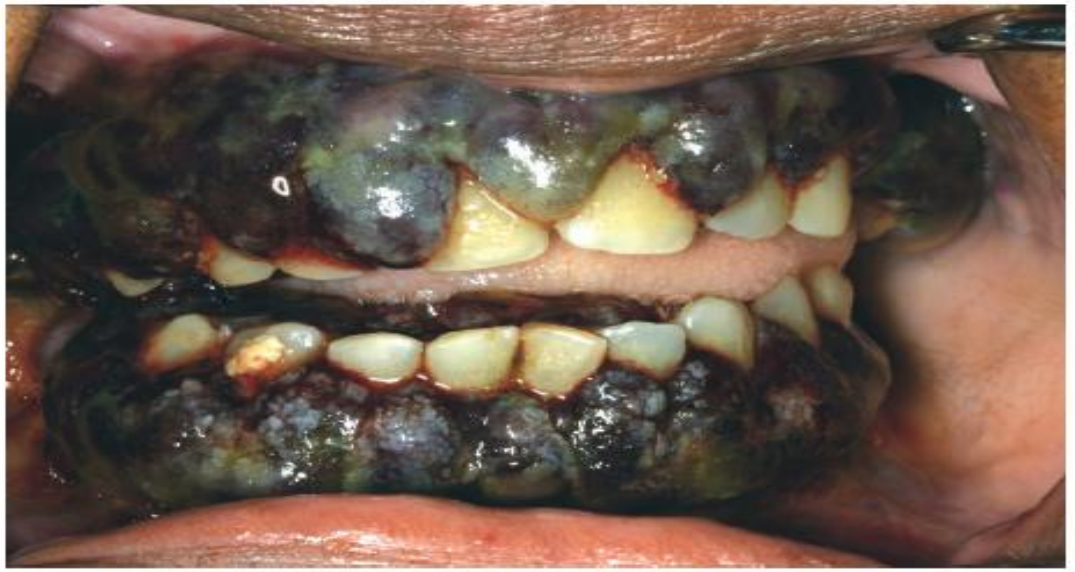
Microscopic examination of leukemia-affected tissue shows diffuse infiltration and destruction of the normal host tissue by sheets of poorly differentiated cells with either myelomonocytic characteristics or lymphoid features.

Treatment and Prognosis

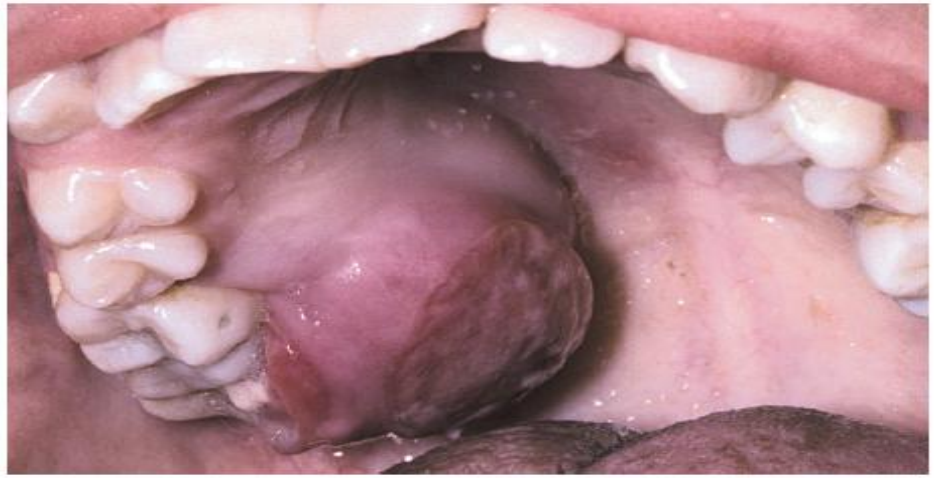
the treatment of a patient with leukemia typically consists of various forms of chemotherapy; the type of leukemia dictates the chemotherapeutic regimen. In most cases the purpose of chemotherapy is to destroy as many of the atypical cells as possible in a short time, thus inducing a remission .For this 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). 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 the condition 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 given patient. 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 with few 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 this form of Hodgkin lymphoma, numerous bizarre giant Reed-Sternberg cells are present, with few lymphocytes.

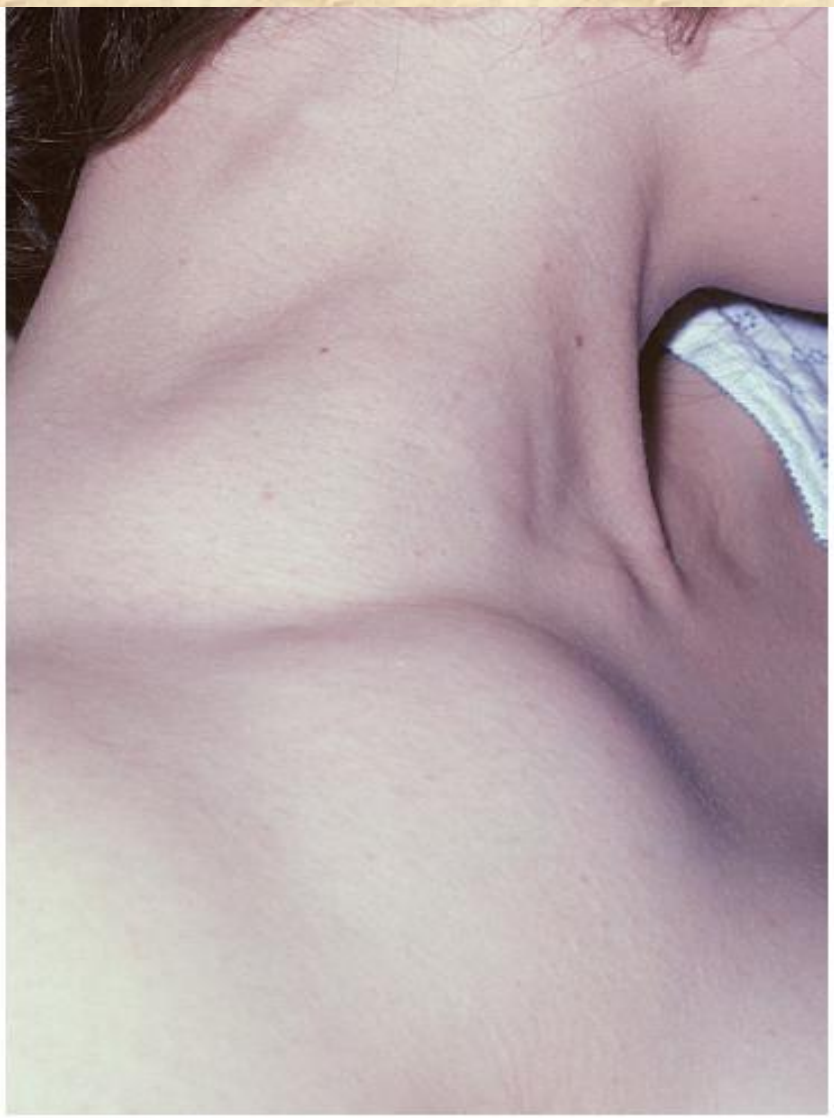
examples of Hodgkin lymphoma are encountered that really do not fit the criteria for any of the known subtypes, and these are designated as **unclassifiable.**

Treatment and Prognosis

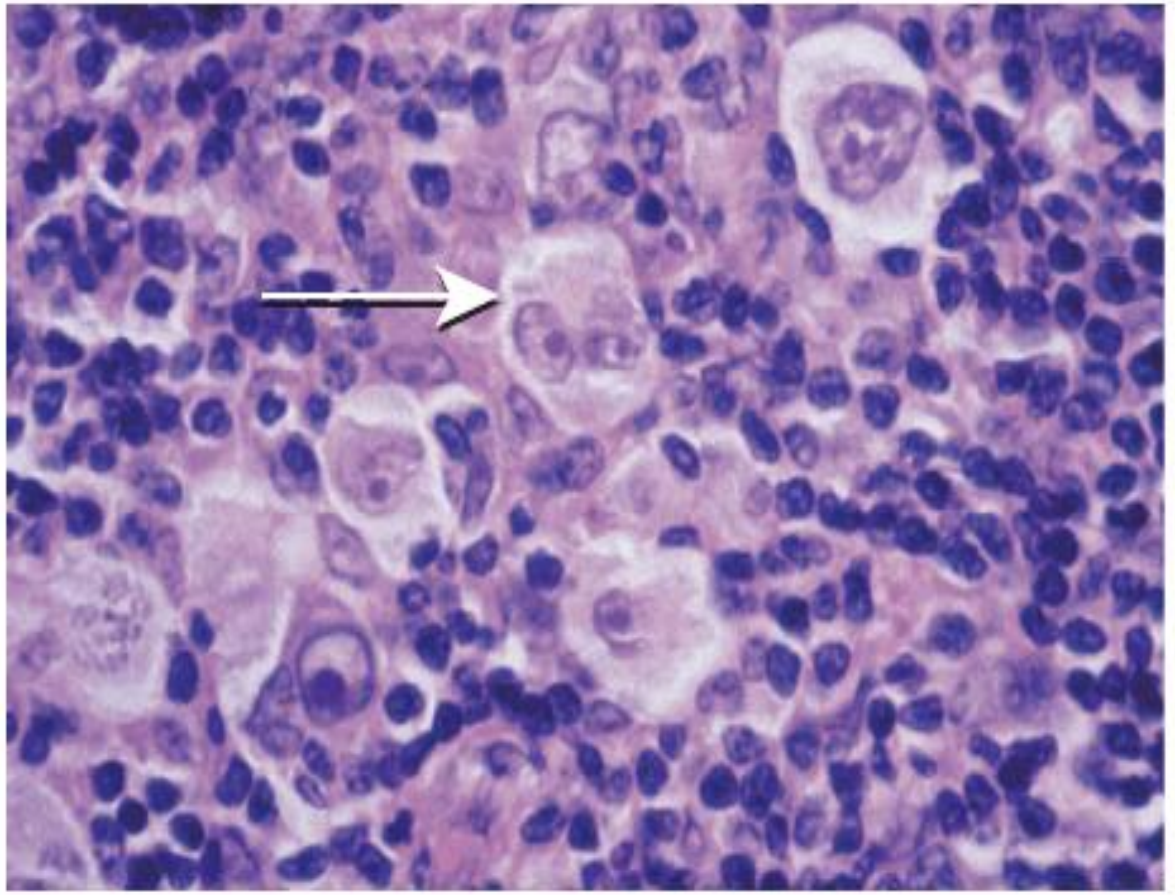
The treatment of Hodgkin lymphoma depends on the stage of involvement. combine less extensive radiotherapy fields with milder multiagent chemotherapy regimens to maximize disease control and minimize long-term complications of therapy.

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

the 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.



• **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. **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,and 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.

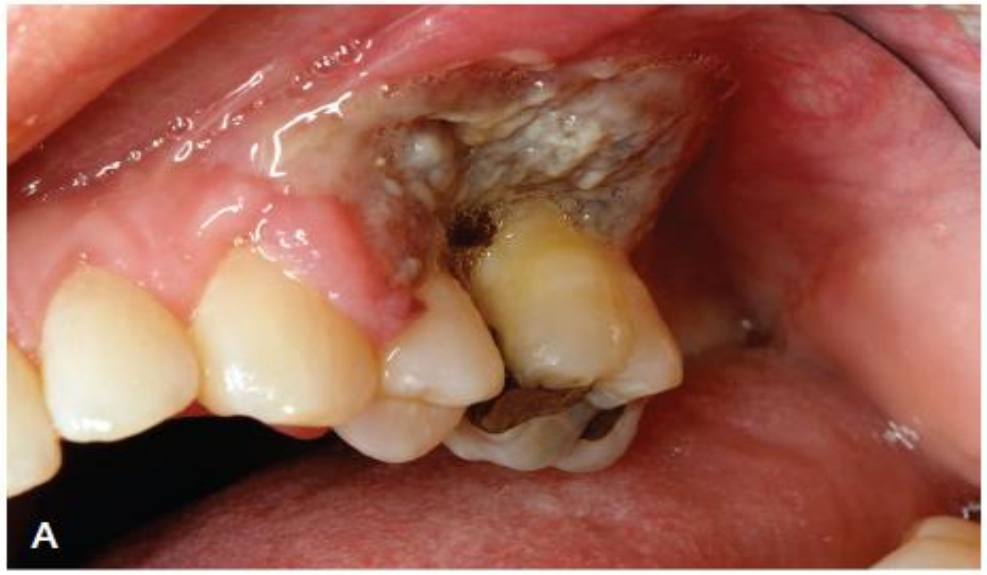
Treatment and Prognosis

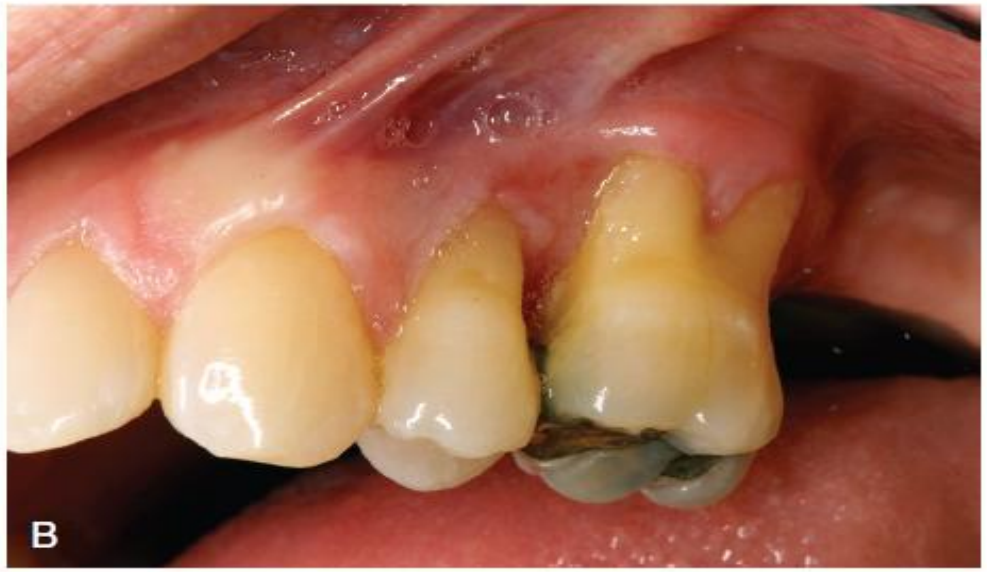
The treatment of a patient with non-Hodgkin lymphoma is based on several factors, including

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

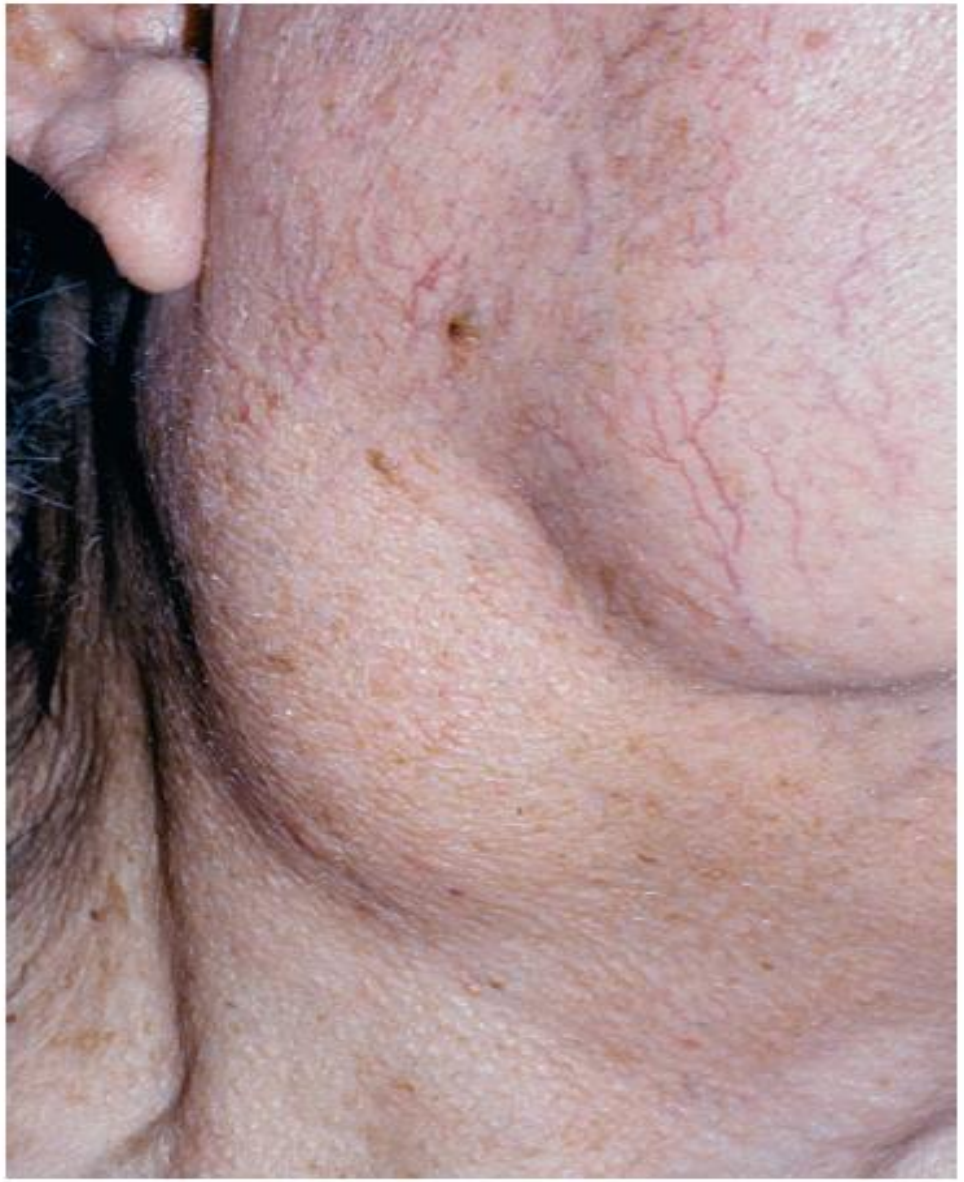
The patient's health must be considered because many of the chemotherapeutic regimens are quite debilitating. Surgical management is not usually indicated. Because most non-Hodgkin lymphomas are of B-cell differentiation, many treatment strategies now incorporate monoclonal antibodies directed against 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.

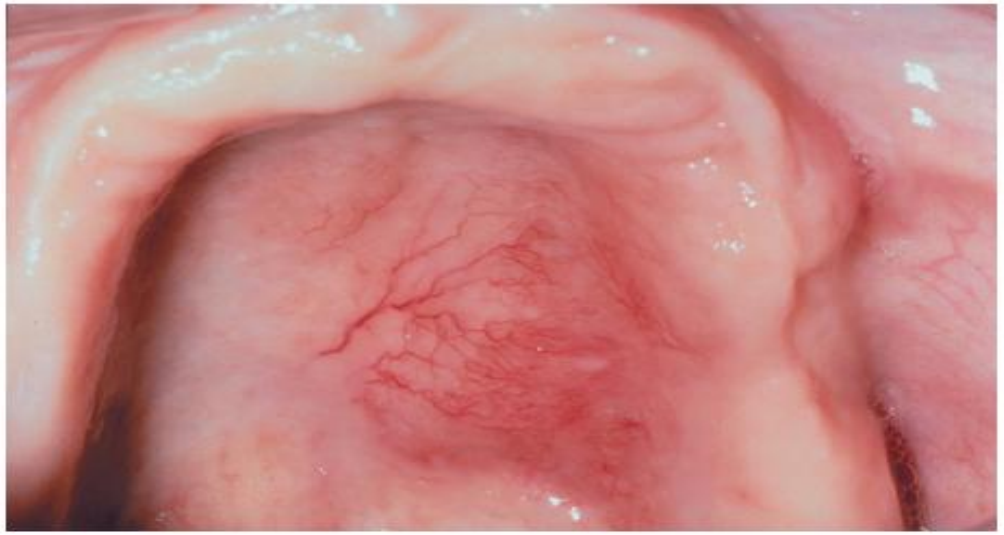




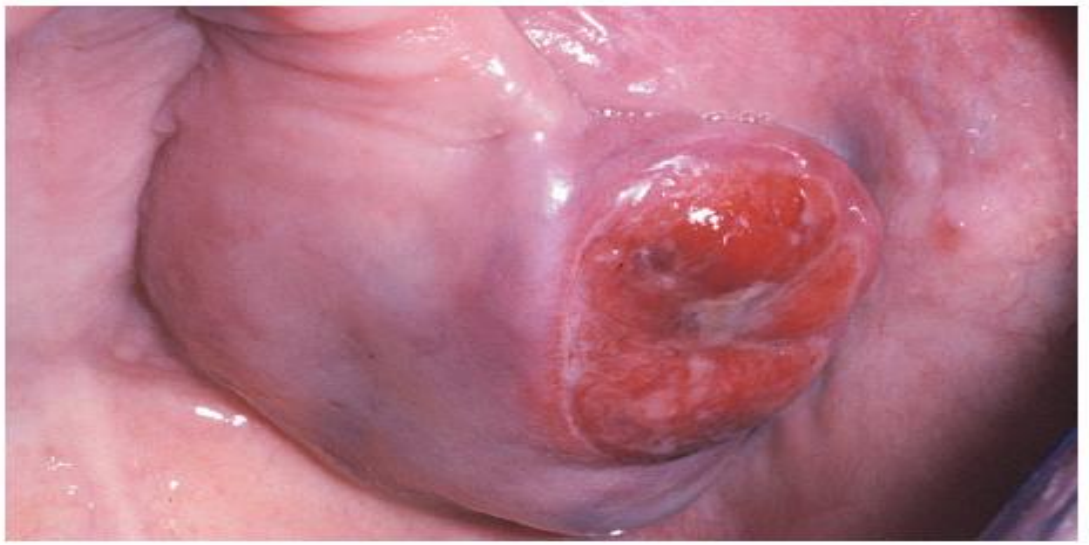
• **Fig. 13.27 Epstein-Barr Virus (EBV)-Associated Lymphoproliferative Disorder. A,** This 42-year-old woman, treated for autoimmune hepatitis with mycophenolate mofetil, developed painful gingival ulcers. **B,** Resolution of the lesion after immune suppression was stopped and rituximab therapy was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



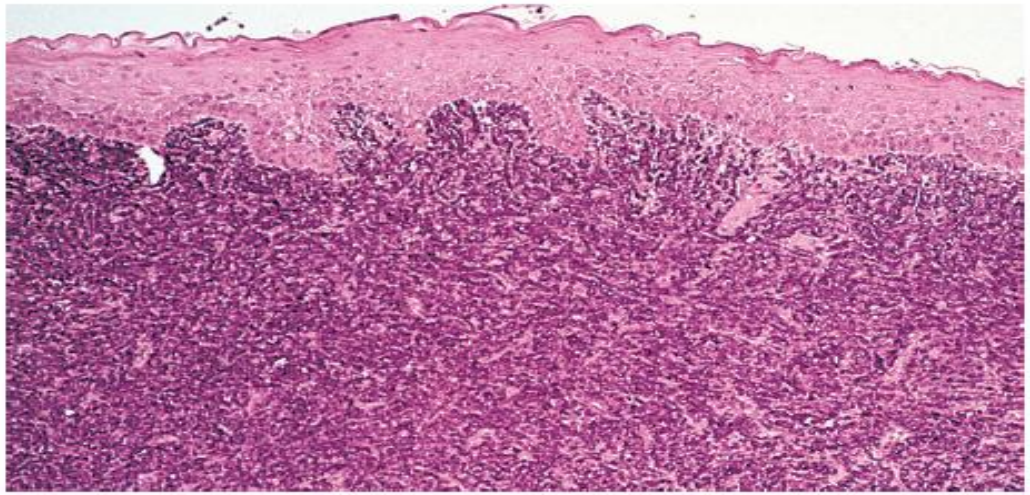
• **Fig. 13.28 Non-Hodgkin Lymphoma.** The matted, nontender lymph node enlargement in the lateral cervical region represents a common presentation of lymphoma.



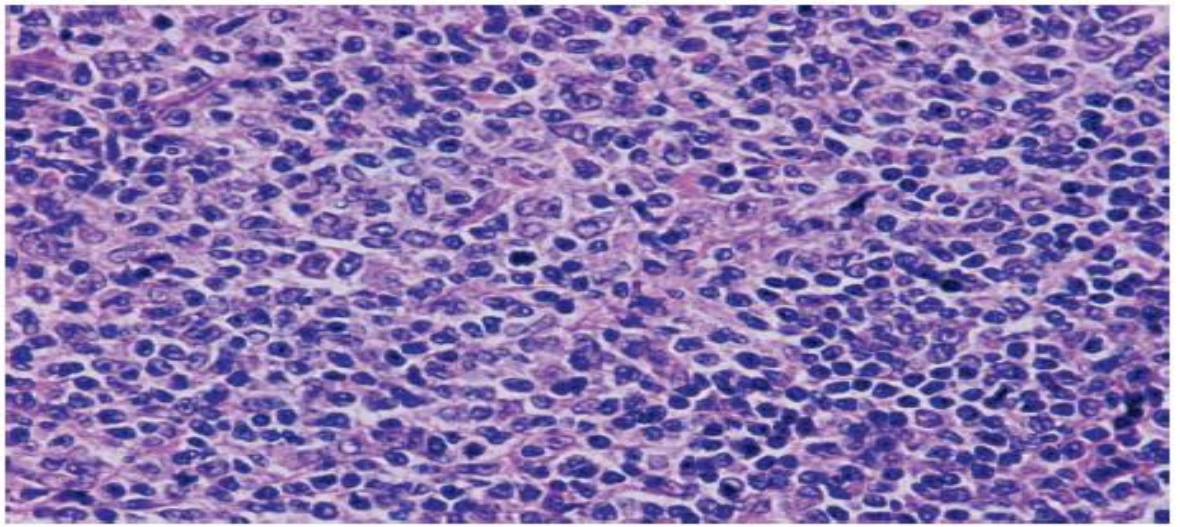
• **Fig. 13.29 Non-Hodgkin Lymphoma.** One of the frequent locations of extranodal lymphoma in the head and neck area is the palate, where the tumor appears as a nontender, boggy swelling. Note the overlying telangiectatic blood vessels, a feature often seen with malignancy.



• **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.

BURKITT LYMPHOMA

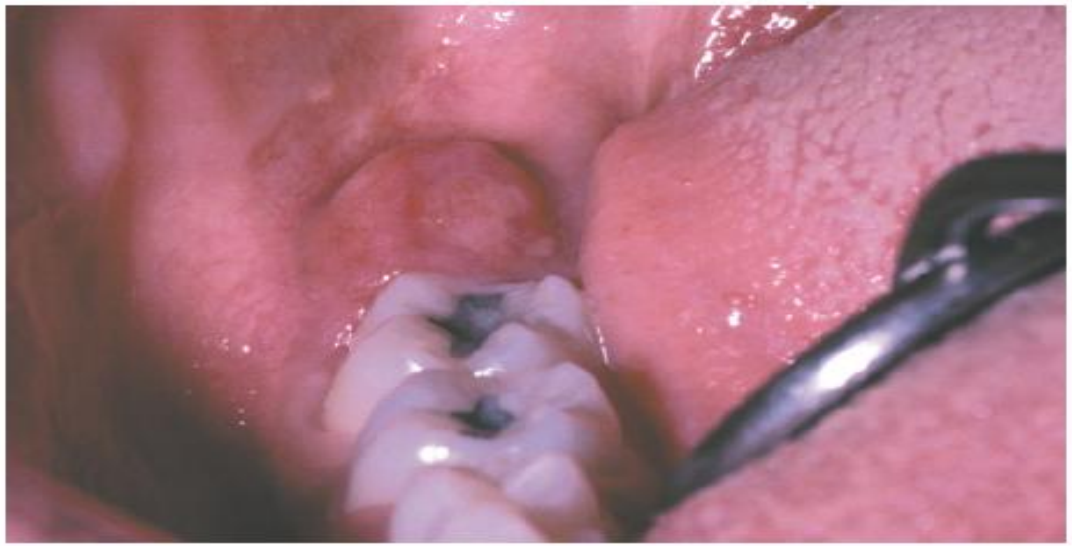
Burkitt lymphoma is a malignancy of B-lymphocyte origin that represents an undifferentiated lymphoma. the pathogenesis of endemic Burkitt lymphoma is related to EBV because more than 90% of the tumor cells show expression of EBV nuclear antigen, and affected patients have elevated antibody titers to EBV. Malarial infection somehow plays a role in endemic Burkitt lymphoma as well.

Clinical and Radiographic Features

As many as 50%–70% of the cases of endemic Burkitt lymphoma present in the jaws. The malignancy usually affects children (peak prevalence, about 7 years of age) who live in Central Africa, and a male predilection is usually reported. The posterior segments of the jaws are more commonly affected, and the maxilla is involved more often than the mandible (a 2:1 ratio). Sometimes all four quadrants of the jaws show tumor involvement.The tendency for jaw involvement seems to be age related; nearly 90% of 3-year-old patients have jaw lesions, in contrast to only 25% of patients older than age 15. Sporadic Burkitt lymphoma tends to affect patients over a greater age range with the abdominal region is typically affected, jaw lesions also have been reported in sporadic Burkitt lymphoma

The growth of the tumor mass may produce facial swelling and proptosis. Pain, tenderness, and paresthesia are usually minimal, marked tooth mobility may be present because of the aggressive destruction of the alveolar bone. Premature exfoliation of deciduous teeth and enlargement of the gingiva or alveolar process may also be seen.

The radiographic features are consistent with a malignant process and include a radiolucent destruction of the bone with ragged, ill-defined margins. Patchy loss of the lamina dura as an early sign of Burkitt lymphoma.

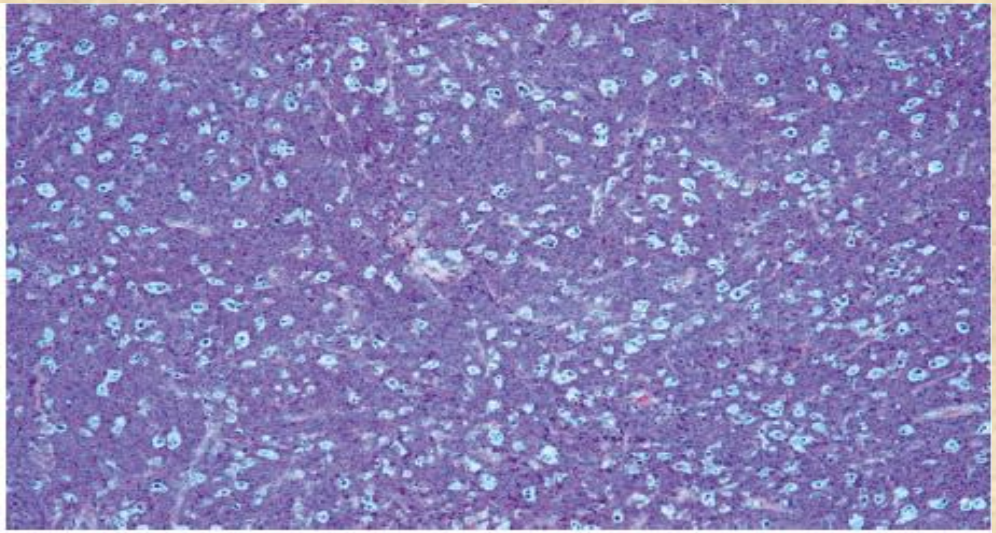


• **Fig. 13.37 Burkitt Lymphoma.** This patient had documented American Burkitt lymphoma involving the abdominal region. The retromolar swelling represents oral involvement with the malignancy.

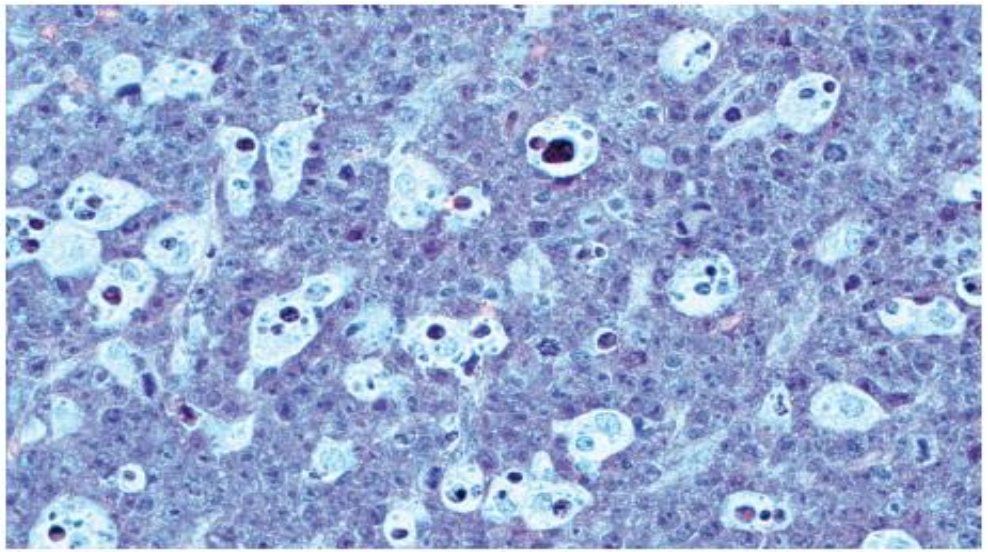
Histopathologic Features

Burkitt lymphoma histopathologically represents an undifferentiated, small, noncleaved B-cell lymphoma. The lesion invades as broad sheets of tumor cells that exhibit round nuclei with minimal cytoplasm. Each tumor nucleus often has several prominent nucleoli, and numerous mitoses are seen. Immunohistochemical studies using markers that identify proliferating cells (e.g., Ki-67) typically indicate that almost 100% of the tumor cells are in the process of replicating.

On viewing the lesion on low-power magnification, a classic "starry-sky" pattern is often appreciated—a phenomenon that is caused by the presence of macrophages within the tumor tissue.These macrophages have abundant cytoplasm, which microscopically appears less intensely stained in comparison with the surrounding process.Thus these cells tend to stand out as "stars" set against the "night sky" of deeply hyperchromatic neoplastic lymphoid cells.



• **Fig. 13.39 Burkitt Lymphoma.** This low-power photomicrograph shows the classic "starry-sky" appearance, a pattern caused by interspersed histiocytic cells with abundant cytoplasm ("stars") set against a background of malignant, darkly staining lymphoma cells ("night sky").



• **Fig. 13.40 Burkitt Lymphoma.** This high-power photomicrograph demonstrates the undifferentiated, small, dark lesional cells with numerous histiocytes.

Treatment and Prognosis

Burkitt lymphoma is an aggressive malignancy that usually results in the death of the patient within 4–6 months after diagnosis if it is not treated. In the past the prognosis for Burkitt lymphoma was poor, with a median survival time of only 10.5 months.

recently, intensive,multiagent chemotherapeutic protocols, which emphasize the use of high doses of cyclophosphamide, have shown an 85%–95% event-free (no evidence of recurrence) survival rate 3–5 years after treatment for younger patients, particularly those with relatively early, stage I or II disease.

Adults tend to be less tolerant of intensive multiagent chemotherapy;however, the addition of the monoclonal antibody, rituximab, to a less aggressive multiagent chemotherapeutic regimen can improve the 3-year.

PLASMACYTOMA

The plasmacytoma is a unifocal, monoclonal, neoplastic proliferation of plasma cells that usually arises within bone.Infrequently, it is seen in soft tissue,the term extramedullary plasmacytoma is used. Some investigators believe that this lesion represents the least aggressive part of a spectrum of plasma cell neoplasms that extends to multiple myeloma. the plasmacytoma is important because it may ultimately give rise to multiple myeloma.

Clinical and Radiographic Features

The plasmacytoma usually is detected in an adult male, age 55 years. The male-to-female ratio is approximately 2:1. Most of the lesions present centrally within a single bone, and the spine is the most commonly involved site. The initial symptoms often relate to swelling or bone pain;but some lesion is detected on routine radiographic examination. The extramedullary plasmacytoma appears as a relatively nondescript, well-circumscribed, nontender soft tissue mass. A slightly stronger male predilection is seen with this lesion, approaching a 3:1 male-to-female ratio. 25% of extramedullary plasmacytomas develop in the head and neck region, in the tonsils,the nasopharynx, the paranasal sinuses, the nose, and the parotid gland.

Radiographically, the lesion may be seen as a well-defined, unilocular radiolucency with no evidence of sclerotic borders or as a ragged radiolucency similar to the appearance of multiple myeloma . No other lesions should be identifiable by a skeletal survey using MRI, PET/CT, and careful physical examination.

Histopathologic Features

Sheets of plasma cells show varying degrees of differentiation. Immunohistochemical studies demonstrate that these plasma cells are monoclonal.

As many as 25%–50% of these patients also show a monoclonal gammopathy on evaluation by serum protein immunoelectrophoresis, although the amount of abnormal protein is much less than that seen with multiple myeloma.

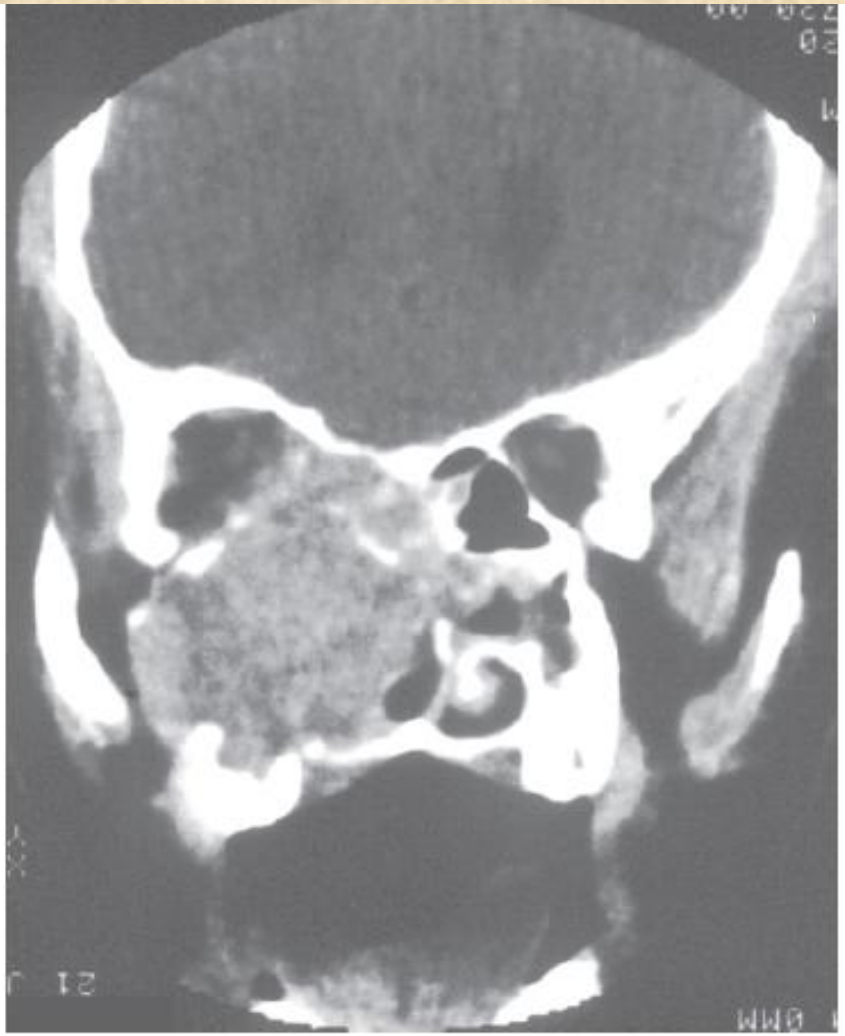
Solitary plasmacytoma also differs from multiple myeloma in that no evidence of plasma cell infiltration should be seen by a random bone marrow biopsy, and the patient should not show signs of anemia, hypercalcemia, or renal failure.

Treatment and Prognosis

Plasmacytomas are usually treated with radiation therapy, and typically a dose of at least 40 Gy(Gray) is delivered to the tumor site. A few lesions have been surgically excised with good results, although this is not the preferred treatment in most instances.

PET/CT is typically used to determine the efficacy of therapy, based on the marked reduction in metabolic activity at the tumor site. Unfortunately, when patients with plasmacytoma of bone are observed on a long-term basis, most will eventually develop multiple myeloma.

From 65%–85% show evidence of disseminated disease by 10 years after their initial diagnosis. virtually all of these patients will develop multiple myeloma by 15 years following their diagnosis. Extramedullary plasmacytoma seems to have a much better prognosis, with less than 30% of these patients showing progression to multiple myeloma and 70% having a 10-year disease-free period after treatment.



• **Fig. 13.45 Plasmacytoma.** This computed tomography (CT) scan depicts a solitary plasmacytoma involving the left maxillary sinus and nasal cavity.

MULTIPLE MYELOMA

Multiple myeloma is a relatively uncommon malignancy of plasma cell origin that often appears to have a multicentric origin within bone. The cause of the condition is unknown, sometimes a plasmacytoma may evolve into multiple myeloma. This disease makes up about1% of all malignancies and 10%–15% of hematologic malignancies.

If metastatic disease is excluded, then multiple myeloma accounts for nearly 50% of all malignancies that involve the bone.The abnormal plasma cells that compose this tumor are typically monoclonal. Because the neoplasm develops from a single cell, all of the daughter cells that comprise the lesional tissue have the same genetic makeup and produce the same proteins. These proteins are the immunoglobulin components that the plasma cell would normally produce, although in the case of this malignant tumor the immunoglobulins are not normal or functional. The signs and symptoms of this disease result from the uncontrolled proliferation of the tumor cells and the uncontrolled manufacture of their protein products.

Clinical and Radiographic Features

Multiple myeloma is typically a disease of adults, with men being affected slightly more often than women. The median age at diagnosis is between 60 and 70 years, and it is rarely diagnosed before age 40. the disease occurs twice as frequently in blacks as whites.

1.Bone pain, particularly in the lumbar spine, is the most characteristic presenting symptom. Some patients experience pathologic fractures caused by tumor destruction of bone.

They may also complain of

2. fatigue as a consequence of anemia.
3.Petechial hemorrhages of the skin and oral mucosa may be seen if platelet production has been affected.

4.Fever may be present as a result of neutropenia with increased susceptibility to infection.

5. Metastatic calcifications may involve the soft tissues and are thought to be caused by hypercalcemia secondary to tumor-related osteolysis

Radiographically, multiple well-defined, punched-out radiolucencies or ragged radiolucent lesions may be seen in multiple myeloma. These may be especially evident on a skull film. any bone may be affected, and the jaws involved in 30% of cases. The radiolucent areas of the bone contain the abnormal plasma cell proliferations that characterize multiple myeloma.

Renal failure may be a presenting sign in these patients because the kidneys become overburdened with the excess circulating light chain proteins of the tumor cells.These light chain products,which are found in the urine of30%–50%of patients with multiple myeloma, are called Bence Jones proteins, according to the British physician.

Approximately 10%–15% of patients with multiple myeloma **show deposition of amyloid in various soft tissues of the body**, due to the accumulation of the abnormal light chain proteins. 3% of newly diagnosed multiple myeloma patients presented with oral mucosal amyloid deposition.

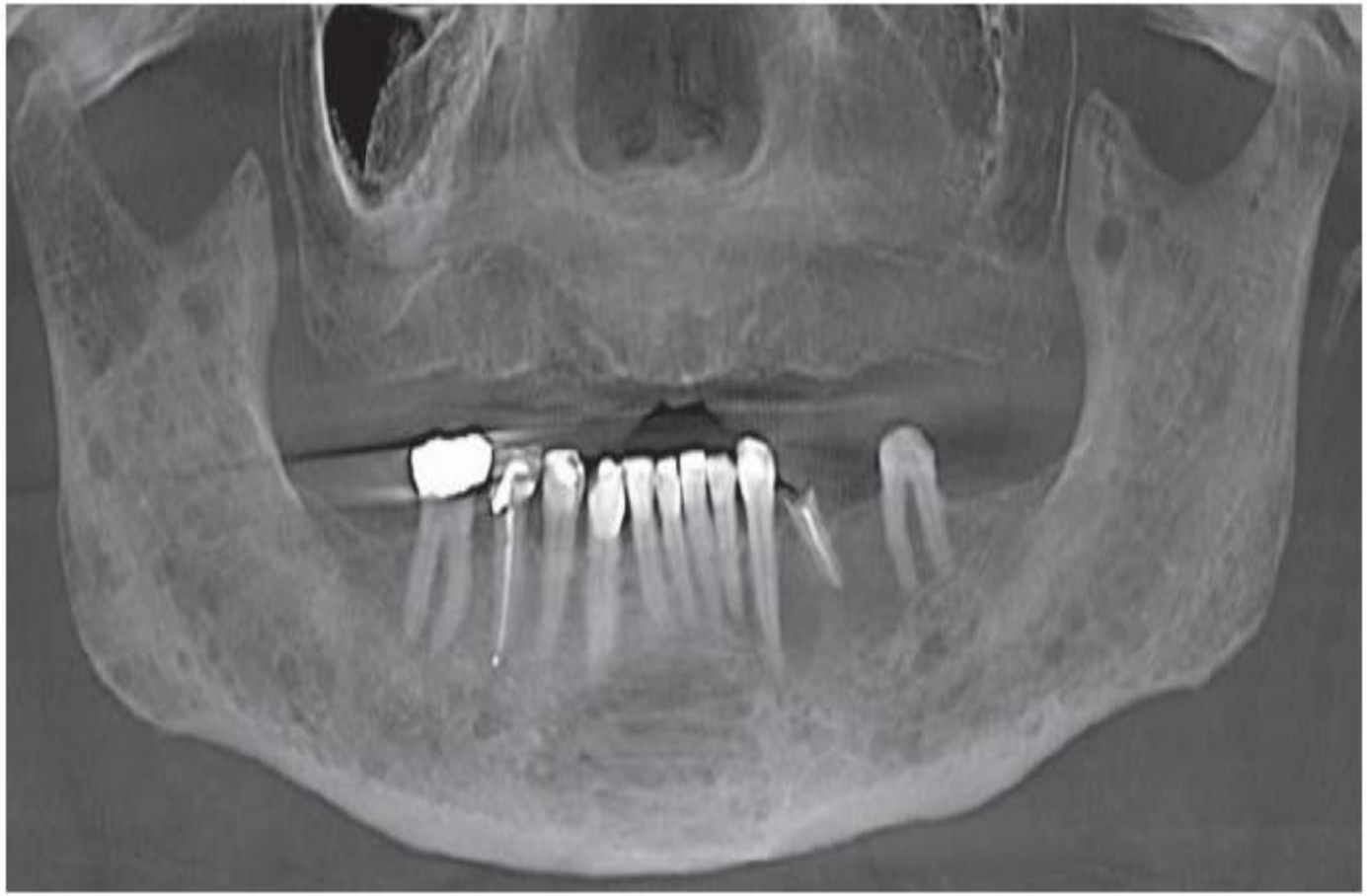
The tongue is the oral site that is most common affected Another area that is commonly affected is **the periorbital skin**.

Histopathologic Features

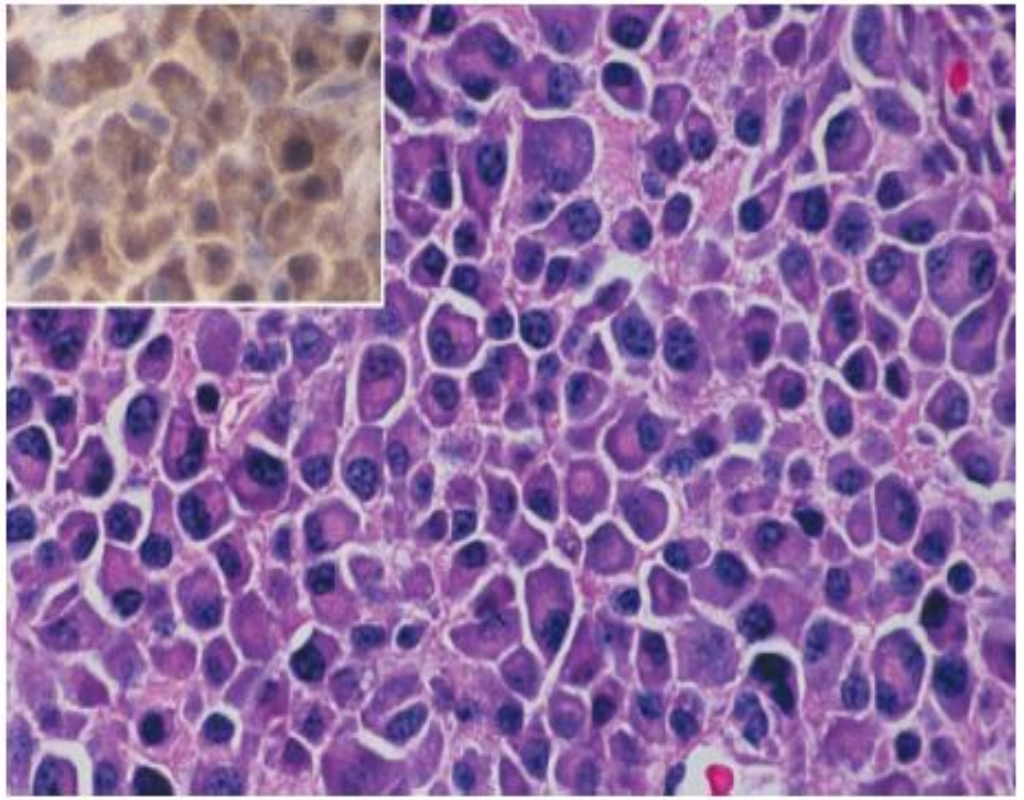
Histopathologic examination of the lesional tissue in multiple myeloma shows diffuse, monotonous sheets of neoplastic, variably differentiated, plasmacytoid cells that invade and replace the normal host tissue. Mitotic activity may be seen with some frequency.The monoclonality of the plasma cell population can be demonstrated using antibodies directed against the lambda and kappa light chain components of the immunoglobulin molecule. **In a neoplastic proliferation of plasma cells**, virtually all of the lesional cells will mark with only one of these antibodies. In contrast, **a reactive plasma cell infiltrate** will show a mixture of lambda- and kappa-producing plasma cells.

deposition of amyloid may be observed in association with the neoplastic cells which appear homogeneous, eosinophilic ,and relatively acellular. It stains metachromatically with crystal violet and shows an affinity for Congo red, demonstrating apple-green birefringence on viewing with polarized light.

Diagnosis The serum and urine protein immunoelectrophoresis should show the presence of myeloma protein (M protein). This represents the massive over-production of one abnormal immunoglobulin by the neoplastic clone of plasma cells, thus this feature is **termed monoclonal gammopathy.**



• **Fig. 13.43 Multiple Myeloma.** Multiple myeloma affecting the mandible. The disease produced multiple, small, "punch-out" radiolucencies. (Courtesy of Dr. Matthew D'Addario.)



• **Fig. 13.44 Multiple Myeloma.** This high-power photomicrograph reveals sheets of malignant plasma cells with eccentric nuclei and stippled nuclear chromatin. Immunohistochemical studies *(inset)* show a uniform reaction of the lesional cells for antibodies directed against kappa light chains, indicating a monoclonal neoplastic proliferation.

Treatment and Prognosis

The goals of treatment related to multiple myeloma include:

- ❑ **controlling the malignancy**
- ❑ **making the patient comfortable**
- ❑ **prolonging the patient's survival.**

A. Initial control of multiple myeloma consist of chemotherapy. Several combinations of chemotherapeutic agents are available, and the choice of regimen to depends on the cytogenetic profile of their myeloma cells. The cytogenetic profile identifies the presence or absence of any of several chromosomal translocations, deletions, or trisomies of patient's tumor, which predicts a low-, standard-, intermediate- or high-risk of progression of the malignancy.

B. the drugs that are used to treat this disease typically include :

1. **a corticosteroid (usually dexamethasone or prednisone) in addition to one or more other drugs, such as an**
2. **alkylating agent(cyclophosphamide),**
3. **an immune-modulating agent (thalidomide),**
4. **A proteasome inhibitor (bortezomib), or a monoclonal antibody.**

Usually the malignancy responds to the multidrug therapy.

C. autologous stem cell transplantation is then performed. More aggressive chemotherapeutic regimens, as well as allogeneic bone marrow transplantation, may be considered in otherwise healthy patients under the age of 55–65 years, but these individuals comprise a minority of multiple myeloma patients.

D. Radiation therapy is useful only as palliative treatment for painful bone lesions. Any one of several bisphosphonate medications can be prescribed to reduce the possibility of myeloma-related fracture with its attendant pain, but these medications do not increase survival.