CHAPTER 34

# Tumors Derived from Hematopoietic Cells and Tissue

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**Hematopoiesis** is the orderly process of blood cell proliferation and maturation. It is a continuum characterized by constant turnover of cells responsive to various stimuli including hypoxia, bleeding, and infection, and controlled by a number of humoral and cellular mediators (1). By such means the normal concentration of cellular elements in the peripheral blood is maintained.

Hematopoiesis begins with the **pluripotential stem cells** that are capable of differentiating into **myeloid stem cells** or **lymphoid stem cells** (Fig. 34.1) (2). Myeloid stem cells subsequently form three cell lines of colony forming units (CFU) which, in turn, transform into the precursors of erythrocytes, megakaryocytes, polymorphonuclear leukocytes, basophils, eosinophils, and monocytes-macrophages. Lymphoid stem cells give rise to T-lymphocytes, B-lymphocytes, and plasma cells.

The process of **erythropoiesis**, by which erythrocytes are formed, occurs in stages, involving the humoral regulator erythropoietin and the biosynthesis of hemoglobin (3). Megakaryocytes undergo a process of nuclear endoreduplication, cytoplasmic maturation, and fragmentation to yield platelets (4). Polymorphonuclear leukocytes or granulocytes (neutrophils, basophils, and eosinophils) share similar processes of nuclear configuration and the formation of cytoplasmic granules (5,6).

Monocytes, macrophages, and their precursors comprise the **mononuclear phagocyte system** (7,8). These cells were once thought to arise from reticular networks within the endothelium of blood vessels in several tissues (e.g., lungs, liver, spleen, and bone marrow) and were considered to constitute the reticuloendothelial system. In fact, these cells originate in the bone marrow from committed progenitors, are released into the blood as monocytes, and migrate to tissues where they differentiate into macrophages. Macrophages are designated by their location when fixed; they are called ''histiocytes'' in the tissues, ''Kupffer cells'' in the liver, ''lining cells'' in the spleen and lymph nodes, ''mesangial cells'' in the kidney, ''microglial cells'' in the central

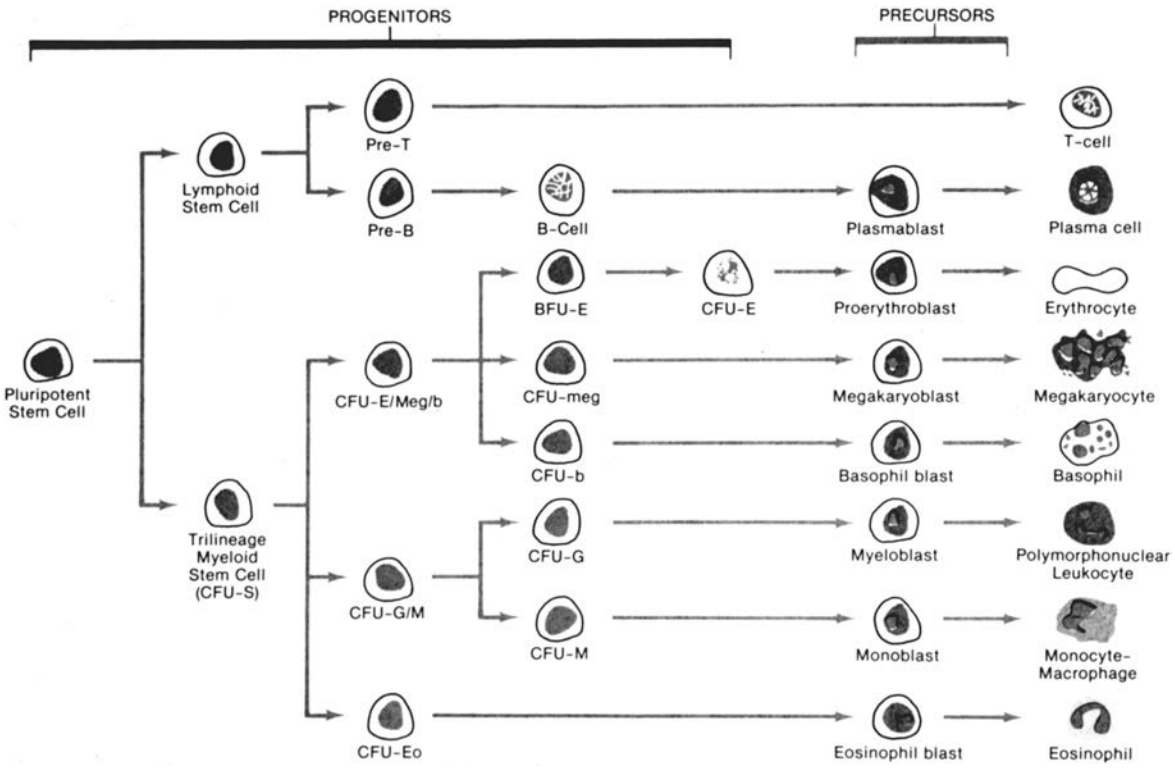



**Figure 34.1.** Schematic outline of the progenitor basis for hematopoiesis disease. (From Nathan DG. Approach to the patient with hematologic disease. In Bennett JC, Plum F, eds. Cecil Textbook of Medicine. Philadelphia: WB Saunders, 1996:817–821.)

nervous system (CNS), and ''osteoclasts'' in the bone. They are called ''wandering macrophages'' when they are in the pleural, peritoneal, and pericardial cavities or the alveoli of the lung.

The **lymphoid system** is the other major derivative of the pluripotential stem cell and is comprised of B-lymphocytes, T-lymphocytes, and plasma cells. Terminology was previously based on cell surface morphology (9). One type of lymphocyte had a smooth surface and was thymus-derived: the T-lymphocyte; the other lymphocyte had a ''hairy'' surface that was covered with microvilli and was derived from the bone marrow: the B-lymphocyte. In fact, both types have microvilli when they are in the peripheral circulation, and both are smooth in their final tissue sites (10).

Lymphocyte differentiation is complex. Precursors of B-lymphocytes originate in the bone marrow, spleen, and lymph nodes whereas T-lymphocytes arise in the bone marrow, travel to the thymus for further differentiation, and then migrate to the marrow, spleen, and lymph nodes. Once thought to develop independently, plasma cells derive from lymphocytes (10,11).

In the embryo and fetus, hematopoietic stem cells arise from the mesoderm (12), and hematopoiesis is both skeletal and extraskeletal (1). From birth, bone marrow provides the principal hematopoietic microenvironment. Medullary hematopoiesis is the rule, although normal marrow occasionally develops outside the skeleton. Usually, however, such extramedullary hematopoiesis occurs in disease, such as certain leukemias (1). Throughout the hematopoietic process, from progenitor cells to mature blood cells, glycoproteins known as hematopoietic growth factors or colony stimulating factors, influence proliferation, differentiation, and survival (13). The actions of human growth factors are complex and overlapping. Several human growth factor genes have

**Table 34.1**
**Classification of the Acute Leukemias**

| |
|---|
| Acute lymphocytic leukemia (ALL) |
| Early pre-B-cell ALL |
| Pre-B-cell ALL |
| B-cell ALL |
| T-cell ALL |
| Acute nonlymphocytic leukemia (ANLL) |
| Acute myelocytic leukemia, minimally differentiated (AML-MO) |
| Acute myelocytic leukemia without maturation (AML-M1) |
| Acute myelocytic leukemia with maturation (AML-M2) |
| Acute promyelocytic leukemia (APL, AML-M3) |
| Acute myelomonocytic leukemia (AMMoL, AML-M4) |
| Acute monocytic leukemia (AMoL, AML-M5) |
| Acute erythroleukemia (AEL, AML-M6) |
| Acute megakaryocytic leukemia (AMegL, AML-M7) |
| Biphenotypic (mixed lineage) leukemia. |

From Kinney MC, Lukens JN. Classification and differentiation of the acute leukemias. In: Lee RG, Foerster J, Lukens J, et al, eds. Wintrobe's Clinical Hematology. Baltimore: Williams & Wilkins, 1999; 2209–2240.

**Table 34.2**
**Chronic Myeloproliferative Disorders**

| |
|---|
| Polycythemia vera |
| Essential thrombocythemia |
| Agnogenic myeloid metaplasia |
| Chronic myelogenous leukemia |

**Table 34.3**
**REAL/WHO Classification of Non-Hodgkin's Lymphoma**

| |
|---|
| Indolent |
| B-cell CLL/small lymphocytic lymphoma |
| Marginal zone lymphoma |
| MALT |
| Splenic marginal zone lymphoma |
| Nodal marginal zone lymphoma |
| Lymphoplasmacytoid lymphoma/immunocytoma |
| Follicle center lymphoma, follicular type |
| Grade I (0–5 centroblasts/hpf) |
| Grade II (6–15 centroblasts/hpf) |
| Grade III (>15 centroblasts/hpf) |
| Aggressive |
| Diffuse, large cell lymphoma |
| Mediastinal large cell lymphoma |
| Primary effusion lymphoma |
| Mantle cell lymphoma |
| Burkitt's lymphoma/high-grade Burkitt's-like |
| Precursor B-cell leukemia/lymphoma |

been cloned, their actions analyzed, and their potential therapeutic applications demonstrated (14,15).

Any cell involved in hematopoiesis, regardless of its degree of differentiation, may proliferate excessively. In this chapter, we consider the neuro-ophthalmologic manifestations of hematologic proliferative disorders, including polycythemia vera, erythrocytosis, essential thrombocytosis, agnogenic myeloid metaplasia, leukemia, lymphoma, Hodgkin's disease, plasma cell dyscrasias, and the histiocytoses. Classification of these disorders requires diagnostic accuracy, reproducibility, and clinical relevance, and classification schemes continue to evolve due to a progressive understanding of tumor-cell physiology, immunotyping, and molecular genetic analyses. A variety of schemes have been used to classify hematologic malignancies including the French-American-British (FAB) and World Health Organization (WHO) classification of acute leukemias (16,17) and the Working Formulation 1982 (18), Revised European-American Classification of Lymphoid Neoplasms (REAL) 1994 (19), and the WHO classification of lymphomas 1999 (20). Classification of the acute leukemias is presented in Table 34.1, chronic myeloproliferative disorders in Table 34.2, and non-Hodgkin's lymphomas in Table 34.3. It is beyond the scope of this text to describe all aspects of these diseases in detail. The reader interested in pursuing this subject in more detail is advised to read one of the latest texts or monographs concerning hematologic malignancies.

## ERYTHROCYTOSIS AND POLYCYTHEMIA VERA

**Erythrocytosis** is characterized by elevation of the red blood cell count, hematocrit, and hemoglobin concentration; it may be absolute or apparent. **Absolute erythrocytosis** results from an increase in total red cell mass and may be further categorized as clonal and nonclonal. **Clonal erythrocytosis** results from a disorder intrinsic to the erythroid progenitor cells of the bone marrow, independent of erythropoietin, and is called **polycythemia (rubra) vera**. **Nonclonal** or secondary **erythrocytosis** results from an otherwise normal bone marrow excessively stimulated by erythropoietin elevated by physiologic demand or pathologic production. **Apparent erythrocytosis** is not accompanied by an increased red cell mass. Instead, it results from decreased plasma volume or an increased ratio of red cell mass to plasma volume (21).

**Polycythemia vera** is a malignancy of the hemopoietic system characterized by excessive proliferation of erythroid, myeloid, and megakaryocytic elements within the bone marrow, resulting in an increased red blood cell mass, low serum erythropoietin and, frequently, elevated peripheral granulocyte and platelet counts. The precise mechanism is unknown, but there is evidence that the increased proliferation of all three hematopoietic cell lines can be traced to a single abnormal clone that presumably developed at the level of the pluripotent stem cell (Fig. 34.1) (22–24). Such increased cell proliferation may involve abnormal myeloproliferative factors (25), increased sensitivity to erythropoietin (26), or absence of normal negative regulation of primitive progenitors (27). Polycythemia is one of the chronic myeloproliferative disorders. The others in this category include essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia (Table 34.2).

Polycythemia usually occurs in later life with a median age at presentation of 60 years (5). Rarely, the disorder is seen in children (28). There is a slight male preponderance and a propensity for the disease to occur with increased frequency in patients of Jewish ancestry.

### GENERAL CLINICAL MANIFESTATIONS

Headaches, light-headedness, weakness, perspiration, and epigastric discomfort are common symptoms of polycythemia vera. These symptoms apparently are related to increased blood viscosity and hypervolemia. Epistaxis, spontaneous bruising, and upper gastrointestinal hemorrhage are ascribed to the effects of hypervolemia and platelet dysfunction. Peptic ulcer disease and pruritus occur with increased frequency in patients with polycythemia vera, presumably from increased histamine release caused by excessive turnover of granulocytes, particularly basophils. The pruritus is often especially severe after a hot bath. Symptomatic bone pain and tenderness, particularly of the ribs and sternum, are occasionally severe and reflect panhyperplasia of the bone marrow.

Patients with polycythemia vera typically have a plethoric

or dusky, cyanotic appearance of the face, hands, feet, and mucous membranes. Mild hypertension occurs in about one-third of patients; ecchymosis is common; splenomegaly occurs in 50–80% of patients and results from extramedullary hematopoiesis; and hepatomegaly is present in 30–50% of patients (24). Arterial and venous thrombotic events result from a combination of hyperviscosity, thrombocytosis, and platelet dysfunction (29).

### Neurologic Manifestations

With increased blood volume and viscosity, it would be expected that both the brain and the eyes would show changes in patients with polycythemia vera, and such is the case. Neurological problems are common and occur in 50–80% of patients (30). Cerebral blood flow is greatly reduced at hematocrits above 53% (31), a phenomenon easily confirmed by transcranial Doppler measurements (32). The onset of symptoms may be acute or insidious and progressive (33). Psychiatric manifestations may be predominant features (34).

Transient ischemic attacks are experienced at some time during the course of the disease by most patients with polycythemia vera (35–37). Visual symptoms associated with such attacks include amaurosis fugax, photopsias, transient scotomas, photophobia, and other features similar to those that occur in patients with migraine. Cerebral infarction is common and may be associated with monocular blindness, cortical blindness, or homonymous visual field loss. Death from cerebral thrombosis occurs in 15% of patients with polycythemia (37). Infarction may result from occlusion of one of the large arteries in the neck (35,38–40) or from occlusion of one or more intracranial vessels (41). Thrombosis of the cerebral venous sinuses may occur in severe cases (39,42–44). This results in increased intracranial pressure (ICP) and papilledema when mild (42), and intractable seizures and obtundation when more severe. Subarachnoid and subdural hemorrhage may also occur, as may cerebral demyelination (45), infarction of the spinal cord, and peripheral neuropathy (46).

### Ocular Manifestations

The ocular abnormalities seen in patients with polycythemia vera are similar to those seen in patients with other hyperviscosity syndromes (47–49). Their severity is related to that of the polycythemia and its duration (50). Many patients develop engorgement of the conjunctival and retinal vessels. The associated ischemic disorders of the eye may become manifest as dilated, tortuous vessels, retinal hemorrhages, central retinal artery occlusion (CRAO), central retinal vein occlusion (CRVO), and anterior ischemic optic neuropathy (AION) (Fig. 34.2) (38,43,51). CRVO may be bilateral (52). As mentioned above, papilledema may result from the effects of thrombosis of the cerebral venous sinuses (43). Optic disc swelling may also result from local vascular changes related to hyperviscosity (53,54).

Diplopia may result from ischemic damage to one or more of the ocular motor nerves or from ischemia of the brainstem. Melamed et al. reported a patient with polycythemia who developed a cavernous sinus thrombosis with carotid artery occlusion (39). Ophthalmoplegia, ptosis, proptosis, and edema resolved with treatment. Hoyt described a 67-year-old woman with polycythemia vera who experienced sudden vertical double vision and was found to have monocular paresis of elevation of the left eye presumably caused by vascular occlusion in the rostral mesencephalon (Fig. 34.3) (55). A patient with polycythemia described by Lousea et al. had a one-and-a-half syndrome from an infarction of the pons (56).

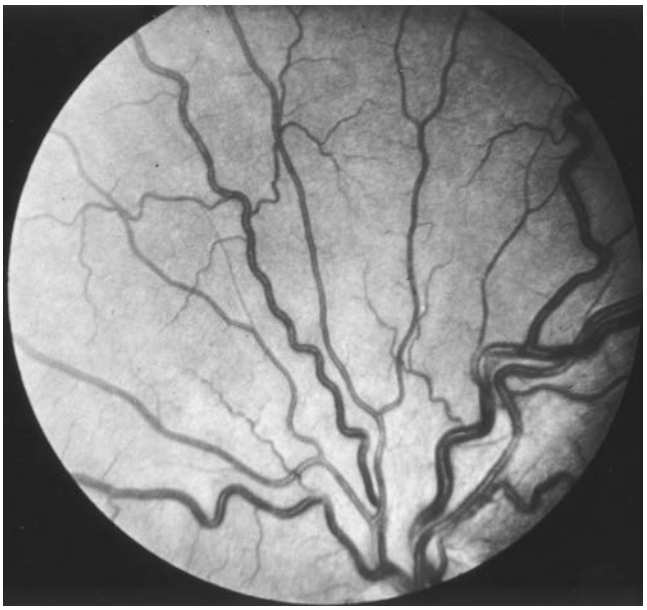


**Figure 34.2.** Dilated, tortuous retinal vessels in a patient with polycythemia vera.

## DIAGNOSIS

Criteria for the diagnosis of polycythemia vera were developed by the Polycythemia Vera Study Group (57) and include an increased red blood cell mass, normal arterial oxygen saturation, and splenomegaly. Patients without splenomegaly may also be diagnosed with polycythemia vera if, in addition to increased red blood cell mass and normal arterial oxygen saturation, there is thrombocytosis, leukocytosis, an increased granulocyte alkaline phosphatase, or an increased serum concentration of vitamin $B_{12}$ (58,59). Strict adherence to these criteria may, however, exclude patients in the early stages of the disease (60).

## PROGNOSIS AND TREATMENT

Without treatment, polycythemia vera is associated with a high incidence of fatal thrombotic or hemorrhagic complications and a median survival of 18 months from the time of first symptoms or signs (61). Treatment designed to maintain peripheral blood counts and red blood cell mass at normal levels extends median survival to about 10 years (59,62–64). Mortality and morbidity are influenced by treatment modal-

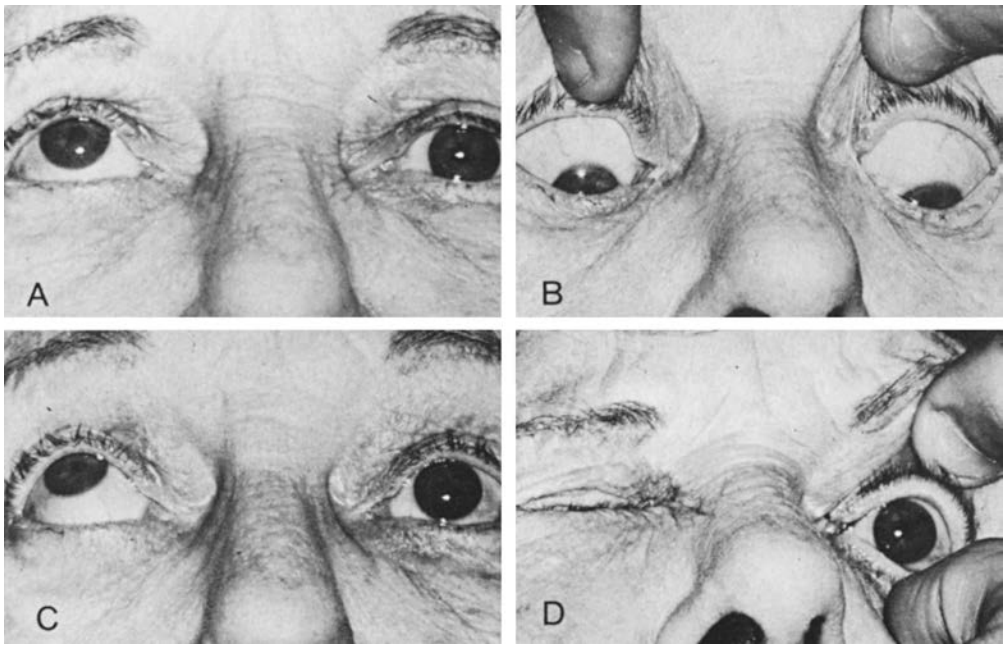



**Figure 34.3.** Double elevator palsy from mesencephalic stroke in a patient with polycythemia vera. *A*, When patient fixes with the paretic left eye, there is a 30-diopter right hypertropia. *B*, In downgaze, there is no significant paresis or deviation of the eyes. *C*, On attempted upgaze, there is marked limitation of elevation of the left eye. *D*, During forced eyelid closure, the left eye shows no Bell's phenomenon. (From Hoyt CS. Acquired ''double elevator'' palsy and polycythemia vera. J Pediatr Ophthalmol Strabismus 1978;15:362–365.)

ity. In untreated patients and in those treated with phlebotomy alone, thrombotic complications are most common, occurring in 41–60% of cases (65,66). Acute leukemia occurs in 1.5% of patients with polycythemia vera who are not treated with myelosuppression and in 10–13% of patients who are treated (67). The development of other neoplasms, hemorrhage, and myelofibrosis are other major causes of death (24). Postpolycythemic myeloid metaplasia, the spent phase of the disease, develops in 10–50% of patients (64,68).

The initial treatment of polycythemia vera is phlebotomy. Efforts are made to reduce the hematocrit to about 45%, a level at which complications of hypervolemia and hyperviscosity are minimized. Phlebotomy alone may be adequate to prevent the thrombotic complications of the disease while reducing the risk of the development of acute leukemia, particularly for patients under 50 years of age. Others argue that the addition of treatment for myelosuppression is preferable, in part because this approach can control the thrombocytosis that is often a major clinical feature of the disease. Factors found by the Polycythemia Vera Study Group to increase the risk of thrombosis in phlebotomy-only treated patients included older age, a history of thrombosis, and a high phlebotomy requirement (58). It is recommended that patients over 70 years be treated from the onset with phlebotomy and myelosuppressive therapy (24). Myelosuppression may be achieved using radioactive phosphorus, the alkylating agent busulfan, or the nonalkylating agent hydroxyurea (58,69,70). Leukemic induction by myelosuppressive agents is a serious risk. Hydroxyurea was previously thought to be nonleukagenic, but this assumption may be incorrect (71). Interferon is effective in some cases (72,73).

## ESSENTIAL THROMBOCYTHEMIA

**Essential thrombocythemia** (primary thrombocythemia, hemorrhagic thrombocythemia, idiopathic thrombocythemia) is a chronic myeloproliferative disorder in which the predominant laboratory feature is a persistent, striking thrombocytosis with elevation of the platelet count to values in excess of 1,000,000 per microliter (mL) (74–78). It is a clonal neoplasm. The median age at diagnosis is 60 years, and women are affected more commonly than men (79). Young adults are less commonly affected (80–82). Diagnostic criteria include a platelet count equal to or greater than $6 \times 10^5$/mL and the absence of conditions associated with reactive thrombocytosis (77). Most patients are asymptomatic at the time of diagnosis, although one-third have vasomotor complaints, including vascular headache, dizziness, visual disturbances, and erythrocelalgia (burning paresthesis of the palms and soles accompanied by erythema) (79,83,84). Other clinical manifestations of essential thrombocythemia result from thrombotic events, hemorrhagic events, or both. Some patients have easy bruising, epistaxis, unexplained gastrointestinal bleeding, and an excessive tendency to bleed postoperatively. Splenomegaly is found in fewer than 50% of patients at diagnosis (79) but in 80%

during the course of the disease (78). Other patients develop evidence of microvascular occlusion in the extremities, the heart, and—in about two-thirds of patients—the CNS (83,85–88).

The neurological complications of essential thrombocythemia include transient ischemic attacks, arterial and venous strokes, seizures, and radiculomyelopathy (43,89–96). In a series of 17 patients presenting with neurological or visual symptoms, symptoms included transient unsteadiness in 13, dysarthria in 8, and focal paresis in 7 (96). Levine et al. described a patient with recurrent amaurosis fugax and contralateral hemiparesis (97). Cerebral venous thrombosis also occurs, including superior sagittal sinus involvement with increased ICP (43,90,91,93,98).

Visual disturbances in patients with essential thrombocythemia are related to thrombotic, hemorrhagic, and possibly vasomotor phenomena. For example, patients may experience embolic retinal artery occlusions (99), amaurosis fugax (97,100), or CRVO (75,101–103). In the study performed by Jabaily et al., visual disturbances occurred in 6 of 33 patients and included scintillating scotomas, episodic dimming of vision, and amaurosis fugax (89). Murphy et al. reported that 10 of 37 patients with essential thrombocythemia had ''visual phenomena'' as part of their disease (75). Among 33 patients reported by Michiels et al., 10 had visual symptoms: transient monocular blindness in 3, scintillating scotoma in 3, scintillations followed by transient monocular blindness in 1, and blurred vision in 10 (96).

Patients with essential thrombocythemia have a normal life expectancy but approximately one-third have major thrombohemorrhagic complications (74,79,104). Definitive management is not established. Asymptomatic patients may be observed, and vasomotor symptoms may be treated with nonsteroidal anti-inflammatory drugs or platelet anti-aggregating agents (84). Thrombocytopheresis is an option in the acute setting. Chronic myelosuppression is usually attempted in older patients, patients who experienced thrombotic episodes, and patients with cardiovascular risk factors. Hydroxyurea is effective but associated with a long-term risk of leukemia. The safety and efficacy of interferon-alpha has been demonstrated in a controlled clinical trial (79,105–107). However, bilateral AION has occurred in a patient with essential thrombocytosis who was treated with interferon (108).

## AGNOGENIC MYELOID METAPLASIA (MYELOID METAPLASIA WITH MYELOFIBROSIS, IDIOPATHIC MYELOFIBROSIS)

### GENERAL CONSIDERATIONS

**Agnogenic myeloid metaplasia** is the most commonly used term for this neoplastic hematopoietic disorder, considered one of the chronic myeloproliferative disorders, and is characterized by extramedullary hematopoiesis and myelofibrosis. Myelofibrosis—fibrosis of the bone marrow—is not unique to this disease and may be seen in a variety of neoplastic and nonneoplastic disorders, both hematologic and nonhematologic. In agnogenic myeloid metaplasia, hematopoietic cell proliferation is clonal, and myelofibrosis is a secondary process, resulting from growth factor stimulation of adjacent polyclonal fibroblasts (109). Although the cause is unclear, current evidence points to involvement of a major putative cytokine, transforming growth factor-beta (TGF-β) (109–111).

Men are affected more commonly than women. The median age at diagnosis is 60 years (79,112) and children are very rarely affected (113). In 20–25% of cases, the diagnosis is made in asymptomatic patients (109,112). The primary symptoms include weakness and fatigue from anemia, weight loss, low-grade fever, a painful splenic mass, and easy bruising. Common signs include cutaneous petechiae or ecchymoses, splenomegaly, hepatomegaly, and pallor.

### DIAGNOSIS

The diagnosis of agnogenic myeloid metaplasia is based on symptoms and signs and is established by blood smear and bone marrow biopsy. Marked anemia is found in 50% of patients (109). The blood smear is characteristically leukoerythroblastic, reflecting bone marrow fibrosis, and the red cells show marked anisocytosis and poikilocytosis. Tear-drop-shaped erythrocytes reflect splenic extramedullary erythropoiesis. Nucleated red blood cells are common. In 50% of patients, the white blood cell count is elevated and may show all types of granulocytes (112). Bone marrow biopsy shows various degrees of fibrosis, increased megakaryocytes, distended sinusoids with intravascular hematopoiesis, and osteosclerosis (5). Bone marrow aspirate is nondiagnostic.

Neurological and visual dysfunction in patients with myeloid metaplasia is usually related to hemorrhagic or thrombotic events (109,114). In some patients, extramedullary hematopoiesis (EMH) occurs in the epidural space. When EMH occurs in the spinal epidural space, an acute or progressive myelopathy may develop (115,116). When EMH occurs intracranially, it may produce focal neurological symptoms and signs including seizures, increased ICP with papilledema, or diabetes insipidus (109,117–120). EMH at the orbital apex or in the bone of the optic canal may compress the optic nerve and posterior orbital tissues, producing proptosis, progressive visual loss, or both (121,122). Ocular symptoms may precede transformation of agnogenic myeloid metaplasia to acute leukemia (123).

### PROGNOSIS

Survival of patients with this disorder is poorer than for polycythemia vera and essential thrombocythemia; 4–5 years is the median (112,124). Poor prognostic features include age greater than 60 years, hepatomegaly, low hemoglobin, low or very high leukocyte count, and weight loss, among others (124). Transformation to an acute nonlymphocytic leukemia occurs in 5–15% of patients and is responsible for death in about 25% of patients (104,112). Other

causes of death are related to underlying cardiovascular disease that is affected adversely by anemia, thromboembolic events, and hemorrhage, including intracranial hemorrhage. There is no cure. Treatment is directed toward symptoms. Androgens, danazol, prednisone, and hydroxyurea are used for complications, including anemia, qualitative platelet defects, thrombocytopenia, thrombocytosis, leukocytosis, and organomegaly (109).

# LEUKEMIAS

The leukemias are a group of diseases characterized by the overproduction of abnormal leukocytic elements at their site of origin, with or without an increase of these cells in the circulating blood and infiltration of various viscera. The essential abnormality resides in the leukemic cell and consists of an inability of leukocyte progenitors to respond to the factors that normally regulate their proliferation and maturation. Leukemias thus clearly belong in the category of neoplastic diseases and may be considered a cancer of the hematopoietic system.

## GENERAL CONSIDERATIONS

Leukemia constitutes 3% of all cancers in the United States but is the leading cause of death due to cancer in the United States in persons younger than 35 years of age (125,126). The annual incidence of leukemia in the United States is 13.1 for males and 7.6 for females (127). Leukemias are usually classified by their predominant cell type, the degree of differentiation within that cell line, and whether the process is acute or chronic (see Table 34.1 for classification of acute leukemias) (18,128). Acute leukemia occurs most commonly in the first 5 years of life, predominates in boys, and is most often lymphocytic (129). Chronic leukemias occur in older patients, with chronic myelocytic leukemia usually developing in men 20–60 years of age and chronic lymphocytic leukemia affecting predominantly men between 45 and 60 years of age (5,130).

The cause of most leukemias is unknown. Although leukemias are generally considered acquired disorders, most patients with acute nonlymphocytic leukemia have a cytogenetic abnormality (131). Contributing factors include radiation, oncogenic viruses, genetics, and chemical exposure (5,125,132–134). Two rare forms of leukemia are associated with retroviruses, adult T-cell leukemia caused by human T-cell lymphotopic virus (HTLV-I), and hairy cell leukemia linked with HTLV-II (5,125,135,136) (see Chapter 58). In some congenital cases, leukemia is associated with another congenital syndrome, such as osteogenesis imperfecta, the Wiskott-Aldrich syndrome, or ataxia-telangiectasia (18). In addition, certain congenital cytogenic disorders, such as Down syndrome (trisomy 21), Klinefelter syndrome (XXY or mosaic), Patau syndrome (trisomy in group D), Bloom syndrome, and Fanconi syndrome, may predispose to leukemia (125).

## PATHOLOGY

The pathologic alterations in all types of leukemia may be divided into two types: (*a*) those that are produced by the proliferation of leukemic cells within the blood-forming organs, particularly the bone marrow, spleen, and lymph nodes; and (*b*) those that are produced by infiltration of leukemic cells in other organs. Fatigue, pallor, and headache ensue. The bone marrow is invariably hyperplastic and reddish gray, whereas the degree of cellular proliferation in, with consequent enlargement of, the lymph nodes and spleen varies with the different types of leukemia. In organs that become infiltrated during the leukemic process, it is common to observe destruction of normal tissue and replacement by masses of leukemic cells. Organs most likely to be affected include the liver, lungs, kidneys, and gastrointestinal tract.

A variety of mechanisms are responsible for the clinical findings in patients with leukemia. A reduction in the normal number of blood-forming elements may result in anemia, which causes tissue hypoxia, ischemia, and infarction; leukopenia, which can result in increased susceptibility to infection; and thrombocytopenia, which can lead to spontaneous hemorrhage with infarction. Systemic, neurologic, and ocular dysfunction may occur from vascular thrombosis caused by the tumor cells themselves. Finally, tumor cells may invade the walls of blood vessels, causing hemorrhage and allowing spread of the cells into the surrounding tissue.

## SYMPTOMS AND SIGNS

### Systemic

Patients with **acute leukemia** often experience a prodrome of weakness and malaise, followed by fever, tachycardia, and prostration. About one-third of patients present with symptoms of bleeding (125). Fever, pain in the bones and joints, petechiae, hemorrhages, and severe secondary infections are also common. Enlargement of the spleen occurs in most patients with acute leukemia, but it is usually only moderate, in which cases the spleen may not even be palpable. Similarly, some types of acute leukemia, particularly the lymphocytic variety, produce generalized lymphadenopathy, whereas other types produce no palpable adenopathy. Many are asymptomatic and diagnosed by hematologic studies performed for other reasons.

Patients with **chronic leukemias** may have their disease for several years before symptoms and signs lead to the diagnosis (134). In some patients with chronic lymphocytic leukemia, the first sign may be enlargement of the lymph nodes, particularly in the cervical region. In other patients, such as those with chronic myelocytic leukemia, there is rarely any enlargement of the lymph nodes, and the first sign may be abdominal swelling from marked enlargement of the spleen. In all varieties of chronic leukemia, multiple organs eventually become affected, and patients may develop a variety of symptoms and signs. Anemia may result in easy fatigability, intolerance to heat, decreased appetite, weight loss, increased pulse rate, cardiac failure, and angina pectoris. Leukopenia may be associated with an increased number of viral and other infections and a longer recovery period after devel-

oping such infections. Thrombocytopenia may lead to petechiae, purpura, and hemorrhage. Enlargement of lymph nodes in the cervical region may cause cough and dyspnea, whereas enlargement of retroperitoneal lymph nodes may result in abdominal pain and distention as well as other gastrointestinal disturbances. Infiltration of the spleen may cause acute abdominal pain from splenic infarction. Replacement of bone marrow may cause local bone pain from involvement of the periosteum. Involvement of the gastrointestinal tract, particularly the stomach and ileum, may cause nausea, vomiting, diarrhea, and either occult or gross blood in the stool. Infiltration of the kidneys by leukemic cells may be associated with renal colic, pyuria, or renal failure, whereas infiltration of the lungs may produce dyspnea.

### Neurologic Complications

Neurological complications of leukemia are caused by a variety of different processes (137). First, neurologic injury may be caused by leukemic invasion of the leptomeninges, parenchyma, spinal cord, nerve roots, and peripheral nerves. Second, leukemia may cause cerebrovascular disorders, both hemorrhagic and ischemic, by obstructing intracranial vessels. Third, neurologic sequelae may result from the various forms of treatment of the disease. Fourth, some neurological disorders in patients with leukemia are paraneoplastic. In most cases, however, leukemic involvement of the CNS occurs from hematogenous spread or by direct invasion from adjacent affected bone marrow.

CNS leukemia is diagnosed by cerebrospinal fluid (CSF) analysis, requiring a minimum of five white blood cells per microliter and the presence of leukemic blast cells by cytospin technique (138). There is disagreement as to whether or not patients with fewer than five leukocytes per microliter are at increased risk for CNS relapse (139,140).

Since the advent of successful therapy of leukemia, the meninges have become the major site of leukemic relapse (138). With the advent of intrathecal chemotherapy and cranial irradiation as routine CNS prophylaxis, the incidence of meningeal leukemia has declined to approximately 10% (138,141,142). For those who suffer meningeal involvement following radiation therapy, however, prognosis is poor (143,144). Meningeal involvement occurs more commonly in acute lymphoblastic leukemia than in acute myeloblastic leukemia and is rare in the chronic lymphocytic leukemias (145).

Meningeal leukemia occurs when the meninges are infiltrated by leukemic cells from the arachnoid veins. These cells then enter the CSF, including the Virchow-Robin spaces, penetrate the pia-glial membrane, and may invade brain parenchyma (146,147). On histopathology, the meninges show diffuse and focal invasion of leukemic cells, often in a perivascular configuration. Meningeal leukemia may produce a variety of symptoms from single as well as multiple cranial neuropathies and may also cause increased ICP (141,148–153). Affected patients may thus develop headache, meningismus, nausea, vomiting, papilledema, increasing lethargy, and focal neurologic signs, including diplopia from ocular motor nerve paresis. Papilledema occurs in up to 50% of such patients (145). The cranial sutures may be split in young children. Cranial neuropathies may result from infiltration of leukemic cells or from compression. Among the most commonly involved are those with neuro-ophthalmologic impact, including the optic nerve, the oculomotor nerve (154), and the abducens nerve (145,155–157). Facial and vestibulocochlear neuropathies are also common, and the lower cranial nerves are occasionally affected. Spontaneous remission of such neurological complications is rare.

In most cases, leptomeningeal and parenchymal infiltration occurs at a relatively late stage of the disease after the diagnosis is established, but this is not always the case. In a series of 30 children with neurological presentations of malignancy, one-third had acute leukemia (158). Papilledema and ocular motor neuropathies may be presenting manifestations of acute lymphocytic leukemia (156,157, 159–162).

Leukemic involvement of the brain parenchyma is usually an extension of meningeal infiltration, but rare autopsy results document isolated leukemic parenchymal collections. These may be the result of a mechanism other than invasion from the meninges or from treatment that suppresses meningeal leukemic cells but spares those deep within the parenchyma (141,145). Parenchymal involvement is usually perivascular. More diffuse infiltration may be seen in hypothalamic presentations with symptoms of hyperphagia, obesity, and somnolence (145). Rarely, discrete tumor nodules are found (145,149,163,164). More rare are **chloromas**, also called granulocytic sarcomas and myeloblastomas. These are collections of immature myeloid cells that are more common in the chronic form of the disease (165) and that may also be seen in myeloproliferative disease. They may precede the onset of leukemia, be a harbinger of transformation from chronic to acute forms, or signal a relapse (165,166). Chloromas are usually single, but they may be multiple. They may arise in various locations in the CNS parenchyma and dura (167–170). They are isointense to white matter on magnetic resonance (MR) T1- and T2-weighted images (171) and are isointense to hypointense on computed tomographic (CT) imaging, enhancing with contrast (172).

Leptomeningeal infiltration can lead to infiltration of the intracranial portions of the optic nerves and optic chiasm. In most patients, visual loss may be slow and progressive, responding to radiation therapy, or extremely rapid. Zimmerman and Thoreson described a 25-year-old man with known acute granulocytic leukemia with progressive bilateral optic neuropathy (173). The patient died 2 months after the onset of visual symptoms. At autopsy, the optic chiasm was completely infiltrated by leukemic cells. Optic nerve involvement is discussed below.

Cerebrovascular disorders may produce neurological dysfunction in patients with leukemia. The majority are hemorrhagic, caused by invasion of blood vessel walls by leukemic cells, thrombocytopenia, sepsis, and disseminated coagulopathy (145,174). Blast crisis, extreme leukocytosis, and thrombocytopenia are predisposing factors (37). Intracranial hemorrhage contributes to mortality in 10–21% of leukemic patients (145). Cerebral ischemia is less common than hemorrhage and may result from arterial or venous obstruction.

In leukemic patients, cerebral venous thrombosis is the most common form of infarction, resulting in focal neurologic deficits, increased ICP, and papilledema (145). Arterial infarction may involve large vessels, cause lacunar events, or result from septic emboli (174).

Patients with leukemia may develop neurological dysfunction from the toxic effects of drugs used to treat the leukemia and from infections that occur in the CNS of patients who are debilitated or immunosuppressed. With conventional cranial radiotherapy, neurotoxicity is more often subacute and delayed, rather than acute (141). Intrathecal methotrexate may cause a chemical meningitis. A subacute leukoencephalopathy occurs in patients treated with methotrexate and is thought to be caused by direct toxicity of the drug (145,175–178). It is more commonly encountered when methotrexate is given in high doses intravenously and intrathecally and/or combined with cranial irradiation, and it occurs in up to 50% of children undergoing such therapy (141,179). Other drugs may produce a similar encephalopathy, a peripheral neuropathy, or both.

**Progressive multifocal leukoencephalopathy** (PML) is characterized by multifocal areas of coagulative necrosis of white matter, absence of inflammatory cellular reaction, and the presence of severe axon damage (175,180–182) (see Chapter 57). PML is seen most commonly in leukemia and lymphoma, but it occurs in a wide variety of conditions, especially states of immunodeficiency. It results from infection of oligodendrocytes by a papovavirus, the JC virus, whose replication is facilitated by an impairment of the host's cell-mediated defenses. The multiplying virus destroys oligodendrocytes and causes extensive demyelination of the white matter of the brain. When this process affects the visual sensory pathway, patients develop progressive visual dysfunction indicative of an optic neuropathy, a chiasmal process, or damage to the retrochiasmal visual fibers (181,183–185).

### Ocular Manifestations

Ocular findings are the initial manifestation in 3.6% of patients with acute childhood leukemia (161). Most ocular dysfunction in leukemia is related to direct invasion by neoplastic cells; however, as is the case with other organs, hematologic abnormalities associated with the leukemia and the sequelae of hyperviscosity also contribute significantly to visual morbidity. Between 17–35% of leukemia patients have ocular findings before starting chemotherapy, underscoring the recommendation that routine ophthalmic examination be performed at the time of diagnosis (161,162). Patients with acute myelocytic leukemia and acute lymphocytic leukemia are equally affected (186). The main sites of involvement are the orbit and adnexal tissues, the retina, the optic nerve, and the uveal tract (155,161,162,187–194).

### Involvement of the Orbit and Eyelid

All types of leukemia may involve the orbit; however, such involvement occurs more frequently in acute leukemia than in chronic leukemia (189,195,196). Leukemia is therefore a not infrequent cause of proptosis in children (Fig. 34.4). Various authors report that 2–11% of children with proptosis have some form of acute leukemia (190,197–199). The orbital involvement may be related to infiltration of soft tissue by leukemic cells, to hemorrhage, or to both.

Orbital infiltration in leukemia causes proptosis, diplopia, edema of the eyelids, chemosis of the conjunctiva, and moderate to severe pain, thus mimicking an orbital cellulitis (199–202). It usually occurs in patients with previously diagnosed leukemia, but in some cases, it is the first evidence of the disease (203,204).

Leukemic cells may infiltrate almost all of the structures in the orbit, including the extraocular muscles, fat, and lacrimal gland (186,189,191,199,205,206). Leukemic infiltration may even extend beyond the confines of the orbit into the paranasal sinuses (187). It is usually diffuse, but in some

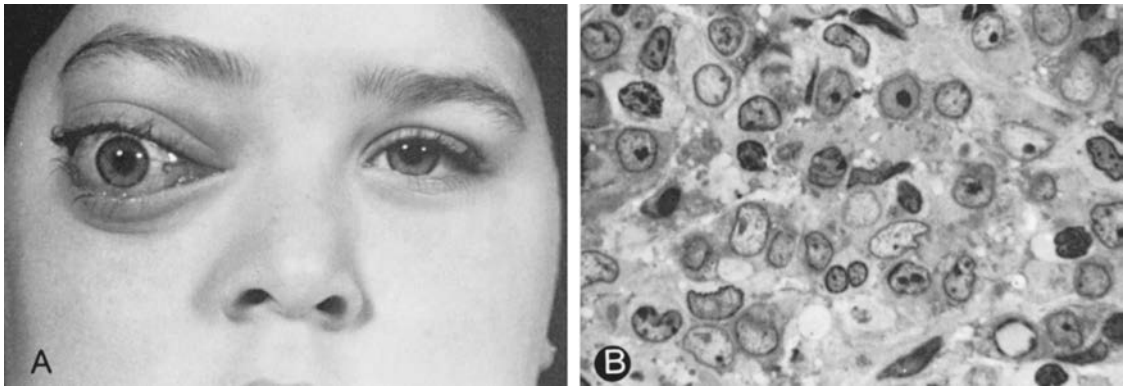



**Figure 34.4.** Orbital chloroma (granulocytic sarcoma). *A*, Right proptosis in a young girl with a granulocytic sarcoma (chloroma). She had no evidence of a peripheral blood or bone marrow leukemia at the time her proptosis occurred. Eventually, however, she developed evidence of leukemia. *B*, Histopathologic appearance of granulocytic sarcoma shows the blastic nature of the tumor cells. The nucleoli are obvious. Just below the *center* of the photograph is a bilobed cell with early myelocytic differentiation. (From Jakobiec FA, Font RL. Orbit. In Spencer WH, ed. Ophthalmic Pathology: An Atlas and Textbook. Philadelphia: WB Saunders, 1986:2459–2860.)

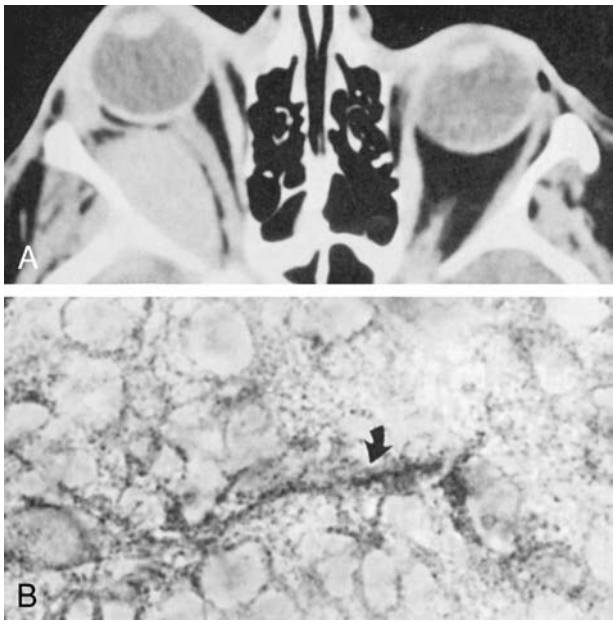



**Figure 34.5.** Orbital chloroma (granulocytic sarcoma). *A*, Axial computed tomographic scan shows a well-circumscribed mass in the right orbit along the lateral orbital wall, displacing the lateral rectus muscle and the optic nerve medially. Note that the lacrimal gland is enlarged, probably from leukemic infiltration. *B*, Immunohistochemical staining for myeloperoxidase (*arrow*), the enzyme produced by the tumor cells in a chloroma. (From Watkins LM, Remulla HD, Rubin PAD. Orbital granulocytic sarcoma in an elderly patient. Am J Ophthalmol 1997;123:854–856.)

patients, the infiltration produces a relatively well-circumscribed mass of leukemic cells. Although such a mass can accompany any form of leukemia and can be observed in patients with chronic leukemia after long periods of remission, it occurs most often in patients with acute myelogenous leukemia. In such patients, the mass may have a characteristic greenish appearance caused by the pigmented enzyme myeloperoxidase and is called, as noted above, a granulocytic sarcoma or chloroma (Figs. 34.4 and 34.5) (207–215). The cause of granulocytic sarcoma is unknown, but cellular immune deficiency may play an important role (210). Granulocytic sarcomas may appear at any time during the course of the leukemia and, like diffuse infiltration, may even occur months or even years before there is any evidence of other systemic disease (190,207,209,216). In patients with leukemia, bilateral involvement of the orbits is not uncommon. It is usually a poor prognostic sign (190,217,218).

### Involvement of the Optic Nerve

In the past, leukemic infiltration of the orbital portion of the optic nerve (like that of the intracranial portion) occurred in the late stages of the disease, usually as a preterminal phenomenon. Since the advent of sophisticated chemotherapeutic regimens and the use of prophylactic CNS irradiation in the treatment of leukemia, the prognosis for long-term survival has improved so dramatically that leukemic invasion of the optic nerve is not uncommon and should be considered a treatable cause of vision loss (219). Clinical evidence of infiltration of the orbital portion of the optic nerve occurs primarily in children and adults with acute leukemia, especially those with the acute lymphocytic variety (148,155,220–229). Histopathologically, however, optic nerves from patients with acute leukemia are only slightly more likely to show evidence of leukemic infiltration than are nerves from patients with chronic leukemia (189). Although active bone marrow disease as well as involvement of the CNS are usually present at the time the infiltration becomes evident (187), optic nerve infiltration may be the first manifestation of recurrence leukemia (227,229–232) or relapse (233).

Leukemic infiltration of the optic nerve may produce two distinct clinical patterns (190). In one pattern, the prelaminar and laminar portions of the optic nerve are infiltrated (234); in the second pattern, the infiltration is retrolaminar (235). Infiltration of the optic disc occurs less frequently than does retrolaminar infiltration (189).

When the optic disc is infiltrated, the appearance is that of a fluffy, whitish infiltrate within the substance of the disc (Fig. 34.6) (218,226). The infiltrate is usually associated with disc swelling and hemorrhage. In this setting, the visual acuity is usually normal or only minimally reduced, although if the infiltration, swelling, or hemorrhage extend into the macula, significant impairment of central vision may occur (223).

Leukemic infiltration of the retrolaminar portion of the optic nerve is associated with a variable degree of optic disc swelling. The fluffy appearance that is characteristic of optic disc invasion is absent in such cases (Fig. 34.7), but an associated retinopathy that includes evidence of both arterial and venous occlusion may be present (236). Although leukemic infiltration of the retrolaminar portion of the optic nerve may be compatible with normal visual function, there is usually moderate to severe loss of vision.

Because both patterns of leukemic infiltration of the optic nerve are associated with some degree of optic disc swelling, they must be differentiated from papilledema. In many cases, this is extremely difficult, not only because in all three settings there is optic disc swelling associated with minimal if any visual loss, but also because it is not unusual for optic nerve infiltration to occur simultaneously with meningeal infiltration and increased ICP (148,160), particularly in the setting of treatment of acute promyelocytic leukemia with all-trans retinoic acid (237–239). For this reason, in all patients who present with optic disc swelling in the setting of leukemia, neuroimaging studies and a lumbar puncture must be performed. Both CT scanning and MR imaging typically show generalized enlargement of the affected optic nerve often associated with a cuff of enhancement surrounding the nerve that represents leukemic cells (Fig. 34.8). Ocular echography may also be helpful in this setting, showing an enlarged optic nerve with a negative 30° test, indicating that the nerve itself is enlarged (229,240).

The treatment of leukemia is discussed below; however, it is appropriate here to emphasize that the optimum treatment for infiltration of the optic nerve is prompt local irradia-

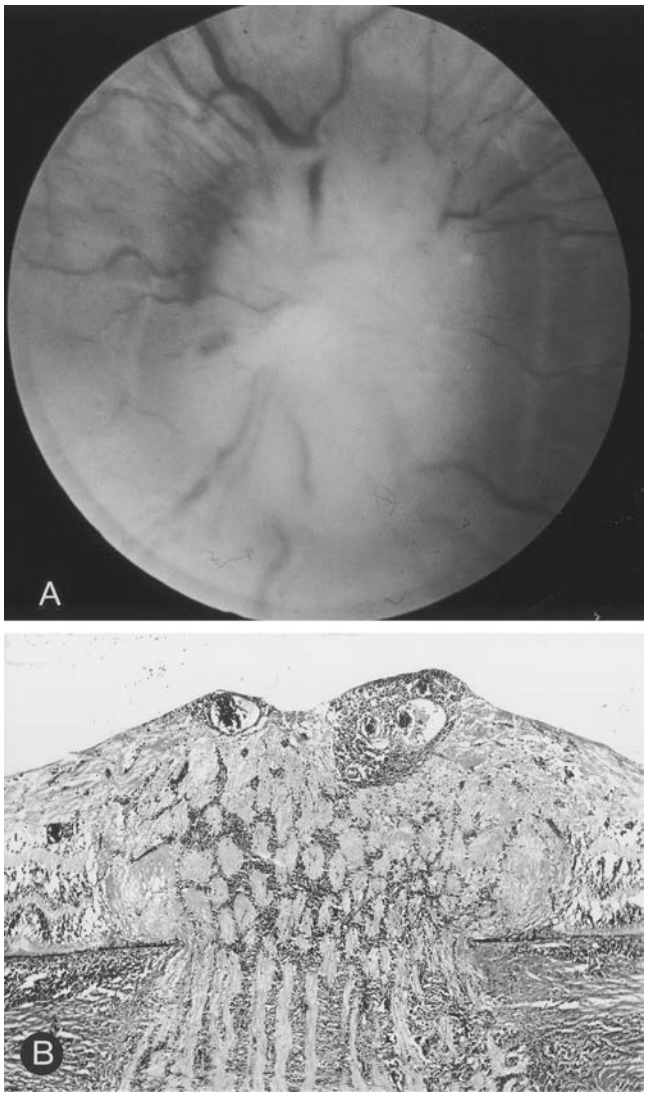



**Figure 34.6.** Leukemic infiltration of the optic disc. *A*, Clinical appearance of leukemic infiltration of the optic disc in a 10-year-old boy who was thought to be in remission from acute leukemia when he developed blurred vision in his right eye. Note fluffy, white appearance of disc and peripapillary retina. *B*, Histopathologic appearance of leukemic infiltration of the optic disc in a 19-month-old boy with acute monocytic leukemia diagnosed at age 8 months. Autopsy disclosed diffuse infiltration of the central nervous system. The optic disc shows extensive leukemic infiltration mainly in a perivascular location. Note elevation of optic disc. (Courtesy of Dr. W. Richard Green.)

tion (241). This is typically performed urgently and followed by intrathecal as well as systemic chemotherapy. Patients who receive about 2000 cGy to the posterior globe and orbit usually show a rapid resolution of their disc swelling and infiltration that may be accompanied by improvement in vision.

In addition to infiltration, neovascularization of the optic disc occurs in patients with acute leukemia, particularly the lymphocytic type (242–244).

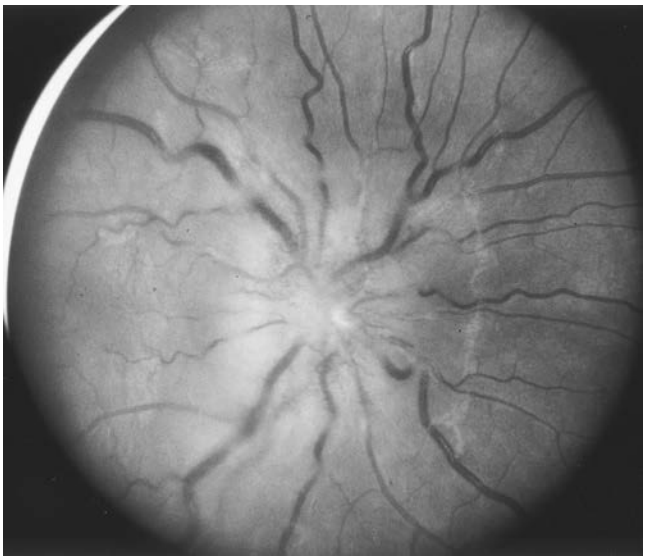


**Figure 34.7.** Unilateral optic disc swelling in an 11-year-old boy with acute leukemia. The patient had no visual complaints but was noted to have swelling of the right optic disc during a routine ocular examination. There were no vitreous cells. The patient underwent a complete evaluation including lumbar puncture and bone marrow aspiration and was found to be in remission. It was assumed that the disc swelling was caused by leukemic infiltration of the retrolaminar portion of the right optic nerve. The patient therefore underwent radiation therapy to the right orbit and had complete resolution of disc swelling.

### Involvement of the Retina

Leukemic retinopathy occurs in both acute and chronic leukemia, although it is more common in the acute forms (51,199,245–247). The retinopathy is characterized by multiple hemorrhages, exudates, and abnormalities of the retinal vasculature (Fig. 34.9). Of 120 patients with leukemia studied prospectively in one study, retinal hemorrhages were observed in 29, cotton-wool spots in 19, white-centered hemorrhages in 13, CRVO in 5, vitreous hemorrhage in 3, and localized choroidal hemorrhage in 1 (199).

The hemorrhages are often numerous and are most common in the posterior pole. When they are located in the macula, they cause decreased central vision. Otherwise, they are almost always asymptomatic. They are usually intraretinal and are either round or flame-shaped, but some are subhyaloid. Some of the intraretinal hemorrhages are characterized by a white spot in their center (Fig. 34.10). These hemorrhages, called **Roth spots**, occur in a variety of conditions, including anemia, endocarditis, and systemic infection. In patients with leukemia, the white spot may represent cellular debris, emboli, or leukemic cells (Fig. 34.11) (245,248). The intraretinal hemorrhages that develop in patients with leukemia may occur at all levels of the retina, but they are most often in the inner layers, accompanied by focal destruction of surrounding tissue (51,189,199). The evidence for direct correlation between retinal hemorrhages and the degree of anemia and thrombocytopenia is conflicting (249–251). Both hard and soft exudates may occur. In

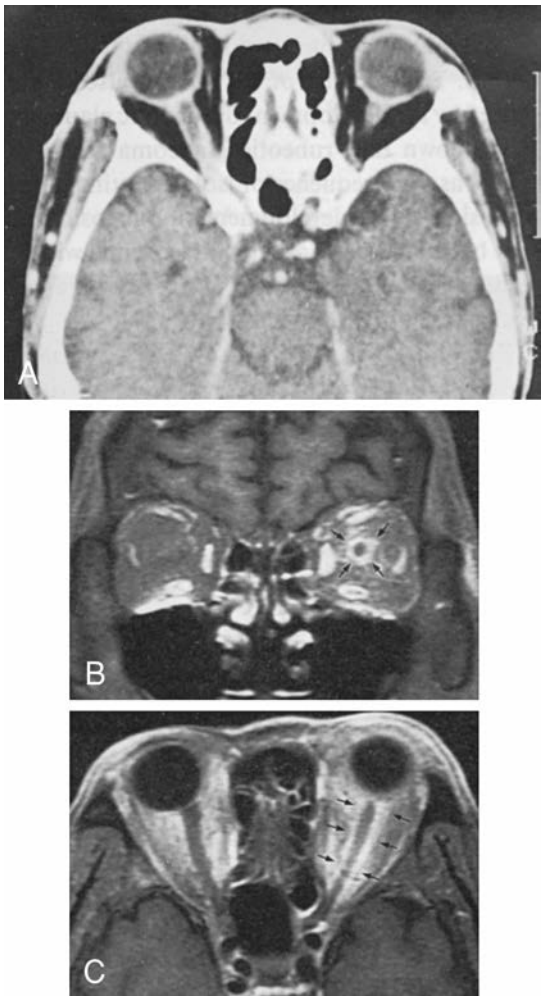



**Figure 34.8.** Neuroimaging appearance of optic nerve infiltration in leukemia. *A*, Computed tomographic scan, axial view, after intravenous injection of iodinated contrast material shows diffuse enlargement of the orbital portion of the right optic nerve. Note enhancement along border of nerve, similar to the tram-track sign often seen in optic nerve sheath meningiomas. *B and C*, T1-weighted coronal and axial magnetic resonance images after intravenous injection of paramagnetic contrast material in another patient with leukemic infiltration of the optic nerve. *B*, Coronal image shows a ring of enhancement around the left optic nerve (*arrows*). *C*, In the axial image, the leukemic infiltrate appears as a bright signal within the subarachnoid space and leptomeninges of the left optic nerve (*arrows*). (*A,* From Ishikawa A, Kiyosawa M, Tamai M, et al. Leukemic optic nerve involvement complicating antral retinal artery occlusion. Neuroophthalmology 1991;11:209–213. *C,* From Horton JC, Garcia EG, Becker EK. Magnetic resonance imaging of leukemic invasion of the optic nerve. Arch Ophthalmol 1992;110:1207–1208.)

some cases, the soft exudates represent nerve fiber layer infarcts, whereas in other cases, they are composed of collections of leukemic cells.

Perhaps the most typical feature of leukemic retinopathy is tortuous, dilated retinal veins. The dilation is often irregular in caliber and thus gives a sausage-like appearance to the affected vessels. Both arteries and veins appear somewhat

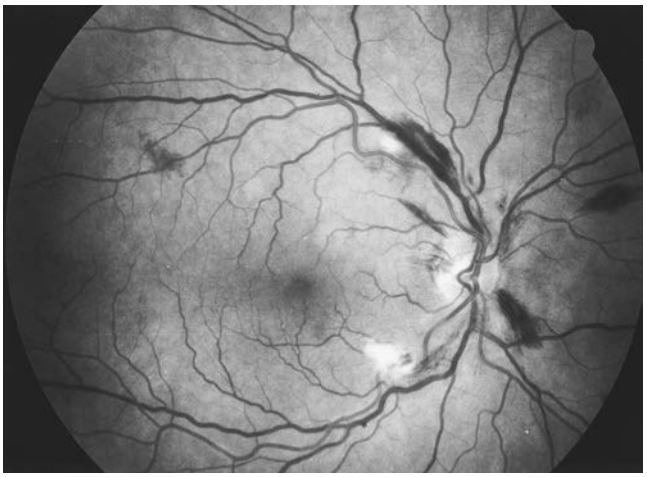


**Figure 34.9.** Leukemic retinopathy. Note multiple intraretinal hemorrhages and exudates. (Courtesy of Dr. Andrew Schachat.)

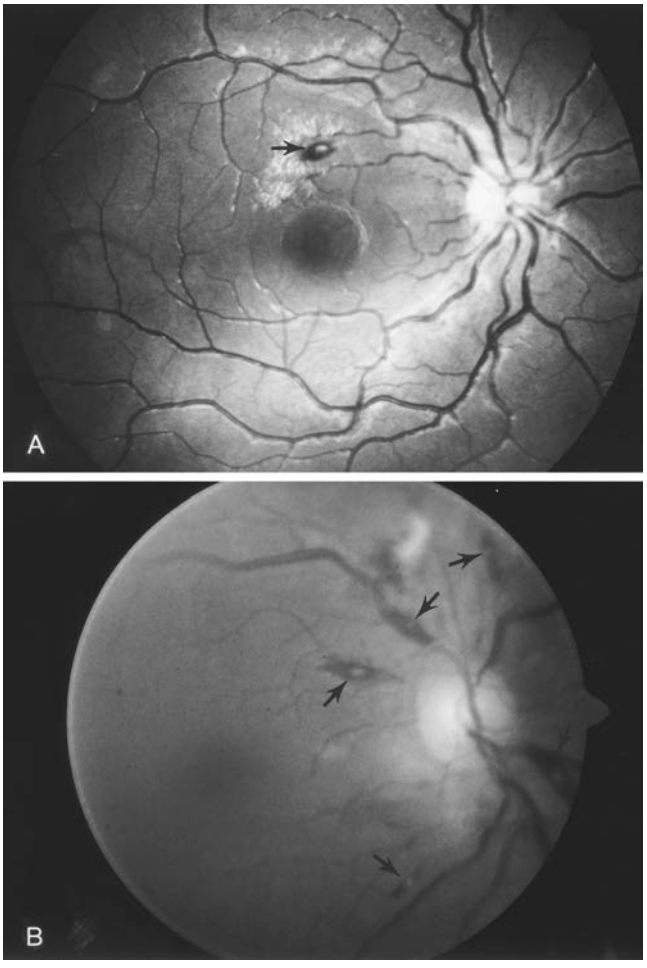



**Figure 34.10.** Roth spots in leukemia. These lesions consist of an intraretinal hemorrhage with a white spot in the center. *A*, Single Roth spot (*arrow*) in a patient with chronic leukemia. *B*, Multiple Roth spots (*arrows*) in a patient with acute leukemia. The view of the ocular fundus is hazy because of a diffuse vitreous hemorrhage.

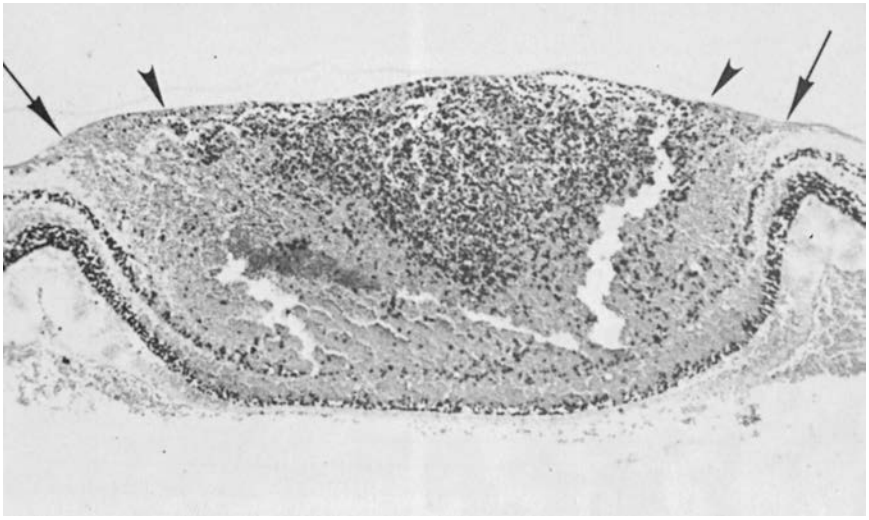


**Figure 34.11.** Histopathologic appearance of Roth spot in acute leukemia. Photograph shows an intraretinal hemorrhage (*between arrows*) with a central area of leukemic cells (*between arrowheads*). (From Green WR. Retina. In Spencer WH, ed. Ophthalmic Pathology: An Atlas and Textbook. Philadelphia, WB Saunders, 1985: 589.)

yellow, reflecting the decreased red cell and increased white cell count. The retinal vessels are often sheathed, and this is thought to represent perivascular infiltration by leukemic cells. Branch retinal artery infarction and CRAO may also occur (225,252,253).

As is the case with optic nerve infiltration, leukemic retinopathy is usually observed when the patient is in relapse. It is thought to be related in most instances to the vascular occlusions, severe anemia, and thrombocytopenia that occur either from the leukemia itself or from its treatment (191,249,250).

Nodular retinal infiltrates may occur in patients with leukemia (249,254). The infiltrates appear as gray-white nodules of varying size, usually associated with surrounding areas of hemorrhage. They occur most frequently in patients with a markedly elevated leukocyte count, a high proportion of blast cells, and fulminant disease. They are thus associated with a poor prognosis (192).

Retinal neovascularization, including optic disc neovascularization, may also develop in patients with chronic leukemia (242–244). In almost all cases, the neovascularization is associated with occlusion of peripheral retinal vessels and dropout of retinal capillaries (244,255–258). Most cases of retinal neovascularization in the setting of leukemia occur in patients with marked leukocytosis, thrombocytosis, or both. Increased blood viscosity leads to a reduction in blood flow producing dropout of capillaries, microaneurysms in the peripheral retina and, eventually, proliferative retinopathy (190).

Retinal detachment and other disturbances of the retina, other than those described previously, may occur in patients with leukemia (259–262).

### Involvement of the Vitreous

The internal limiting membrane usually acts as a barrier to infiltration of the vitreous by leukemic cells (254); however, such infiltration occasionally occurs (189,252,263,264). Terson syndrome occurs in rare cases (265).

### Involvement of the Uveal Tract

Infiltration of the anterior segment by leukemic cells occurs in rare patients. It usually occurs in patients with acute leukemia but may also occur in patients with chronic leukemia (189). In some patients, usually children, a spontaneous hypopyon-hyphema is the first evidence of the disease (266–269), whereas in other patients with known leukemia, involvement of the iris and anterior segment is the first or only evidence of relapse of the disease (270–276). The condition is characterized by conjunctival injection, symptoms of acute iridocyclitis, and a hypopyon that may be tinged with blood (268,269). There may be elevated intraocular pressure (187,262,276). Infiltration of the iris may be diffuse or nodular. Diffuse infiltration discolors the iris, which appears to be covered by a whitish-gray film, and it produces hyperchromia or hypochromia iridis when the process is unilateral (Fig. 34.12). If there is nodular infiltration, the nod-

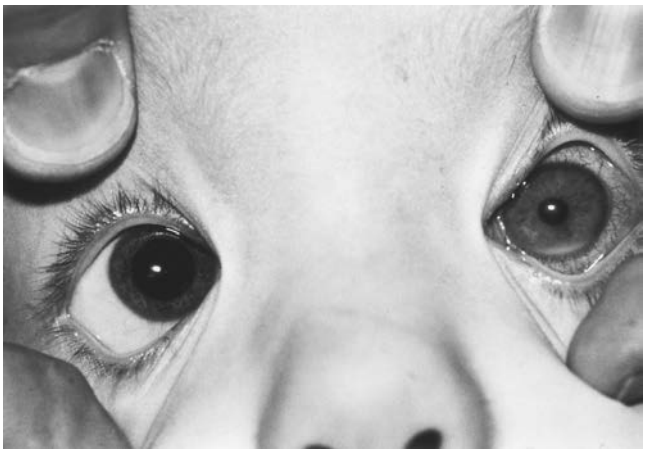


**Figure 34. 12.** Hypochromia iridis with hypopyon in a young child with acute leukemia. The lighter color of the left iris results from diffuse infiltration by leukemic cells. (Courtesy of Dr. Andrew Schachat.)

ules appear as ill-defined densities that usually extend to the pupillary margin (277).

The diagnosis of anterior segment involvement by leukemia can be confirmed by paracentesis with cytologic examination of the aqueous humor (278). The condition can be treated effectively with low-dose irradiation to the anterior portion of the globe.

The choroid is commonly infiltrated by leukemic cells during the course of both acute and chronic leukemia. In fact, Leonardy et al. found the choroid to be the most frequently involved site (31.1%) of ocular involvement in an autopsy series of leukemic patients (191). Abnormalities that are visible during ophthalmoscopy, however, are rare (189). Nevertheless, some patients develop generalized serous detachment of the retina, retinal pigment epithelium, or both, associated with diffuse infiltration of the choroid by leukemic cells (189,245,252,261,262,279–281). Others develop localized choroidal masses with overlying retinal and RPE detachment, and rare patients develop pigmentary changes in the RPE from interference of the blood supply to the RPE by leukemic cells that infiltrate the choroid (259,260,282).

#### Involvement of the Cornea and Sclera

Because the cornea is normally avascular, direct invasion by leukemic cells would not be expected (283,284). Leukemia can, however, induce formation of a sterile ring ulcer with iritis and pannus (285). This lesion, also called an ''immune ring,'' may occur before the diagnosis of leukemia is made; therefore, a patient with a corneal ring ulcer should be evaluated for leukemia as well as for other causes (286).

Infiltration of the sclera or episclera by leukemic cells is usually found at autopsy and rarely produces any clinical symptoms or signs (189,287). The cells are most often present in the episclera, with a perivascular distribution.

#### Involvement of the Conjunctiva

Involvement of the conjunctiva most often occurs in patients with lymphocytic leukemia (189), but it also occurs in other types. Cellular invasion occurs at all levels of the substantia propria. It may be diffuse or patchy, although it tends to concentrate around blood vessels (288). In some cases the involvement consists of visible nodules with surrounding injection resembling areas of focal episcleritis, whereas in others there is only slight swelling of the conjunctiva, and in still others there is diffuse and substantial swelling leading to limitation of eye movements. As with other ocular manifestations of leukemia, conjunctival involvement may occur at any time during the course of the disease and may even be its first sign (189,287,289,290).

#### Other Ocular Manifestations

Uncommon ocular manifestations of leukemia include anterior segment necrosis, which may be spontaneous (291) or may occur after retinal or strabismus surgery (292). Dacryocystitis may be caused by infiltration and obstruction of the lacrimal drainage system by leukemic cells (189,293). Open-angle glaucoma may occur from infiltration of the trabecular meshwork by leukemic cells with resultant obstruction of normal pathways of aqueous humor outflow (294,295).

Because patients with leukemia are immunosuppressed from their disease or from chemotherapy, they are susceptible to infections caused by saprophytic organisms. These organisms may be viral, fungal, protozoan, or bacterial (5,296–298). These infections and their effects on the eye and the CNS are described in Volume 3.

### THERAPY AND PROGNOSIS

Treatment of leukemia includes the use of chemotherapy, immunotherapy, and radiotherapy. The precise combination and nature of modalities used varies with the type of leukemia and changes with the increasing understanding of the pathogenesis and immunobiology of leukemia (299–305).

The prognosis for patients with leukemia depends on the type and extent of the leukemia, the age and sex of the patient, the presence or absence of an associated chromosome abnormality, and the degree of immunocompromise (304–310). It should be emphasized, however, that the prognosis for all types of leukemia is continually improving with advancements in therapeutic modalities. The physician interested in obtaining current information on the therapy and prognosis for patients with leukemia should consult a hematologic oncologist.

## LYMPHOMAS

These tumors probably represent clonal expansions of cells transformed at various stages in the differentiation of T- or B-lymphocytes (311). The lymphomas thus share a common cytogenealogy with the lymphocytic leukemias and with plasma cell dyscrasias (Fig. 34.1). They also share a number of prominent clinical features, including lymphadenopathy, splenomegaly, and a variety of hematologic and immunologic abnormalities. The classification of the lymphomas, like that of the leukemias, is constantly changing as more is learned about their immunologic characteristics (18,312); however, the standard general classification recognizes two main groups: Hodgkin's disease and the non-Hodgkin's lymphomas (Table 34.3). The latter is a more heterogenous grouping that encompasses more than ten disorders, including the nodular lymphocytic lymphomas and more aggressive neoplasms such as diffuse large-cell lymphoma (previously called reticulum cell sarcoma or diffuse histiocytic lymphoma) and Burkitt's lymphoma (311). In this section, we discuss the neuro-ophthalmologic manifestations of both groups of lymphomas.

### HODGKIN'S DISEASE

In 1832, Hodgkin described the autopsy findings in seven patients who died with generalized lymph node enlargement and splenomegaly. Subsequently, Wilks referred to the disorder as **Hodgkin's disease** and emphasized that it was characterized by ''a gradual progressive enlargement of the lym-

phatic glands beginning usually in the cervical region and spreading throughout lymphoid tissue of the body, forming nodular growths in the internal organs, resulting in anemia and usually a fatal cachexia'' (313). The characteristic histopathologic abnormality in this disorder is a polycellular infiltrate composed of giant (Reed-Sternberg) cells, lymphocytes, plasma cells, monocytes, eosinophils, and neutrophils, all of which are associated with a variable degree of fibrosis and necrosis.

The origin of the Reed-Sternberg cells is unclear. Most authors believe that they result from abnormal differentiation along the macrophage-phagocyte pathway (311). Results of studies using T- and B-lymphocyte surface markers conflict as to the cytogenealogy of these cells (314). They are characteristic of, but not unique to, Hodgkin's disease (315).

Based on the number and appearance of Reed-Sternberg and background inflammatory cells, four subtypes of Hodgkin's disease have been distinguished histopathologically: lymphocyte predominant, nodular sclerosis, mixed cellularity, and lymphocyte depleted (311). Each type has a different natural history and response to therapy.

The cause of Hodgkin's disease is unknown. A wide variety of microorganisms are suggested as possible causes, particularly the Epstein-Barr virus (EBV) (316–318). Geographic and familial studies implicate genetic, infectious, and environmental factors.

### General Considerations

Hodgkin's disease occurs in patients of all ages, but there is a bimodal incidence, with the first peak between 15 and 35 years of age and the second after age 50 (315). Males are affected nearly twice as often as females. Patients with acquired immunodeficiency syndrome (AIDS) appear to have an increased risk of developing Hodgkin's disease (319–321).

### Symptoms and Signs

The manifestations of Hodgkin's disease are highly variable. They may be systemic or referable primarily to one or more organ systems. It is convenient to group these features as they relate to solid tumor masses, hematologic abnormalities, and immunologic disturbances.

#### Systemic

The most common presenting complaints are of painless, progressive, asymmetric enlargement of cervical lymph nodes. The size of the enlarged lymph nodes often fluctuates. Somewhat less frequent are the symptoms that result from compression of various adjacent structures by expanding tumor masses. For example, cough, dyspnea, dysphagia, and cervicofacial and upper extremity edema may result from a mediastinal mass impinging on the tracheobronchial tree, esophagus, or superior vena cava. Similarly, discomfort in the lower back or abdomen, edema of the lower extremities, or dysfunction of the urinary or gastrointestinal tract may result from retroperitoneal tumor, and pain in the left flank may result from an enlarged spleen.

Almost all patients with Hodgkin's disease have nontender, rubbery, matted, or lobulated subcutaneous masses. These are lymph nodes that are infiltrated by the pathologic cellular process. The masses are not attached to the overlying skin. Palpable splenomegaly is present in less than 50% of patients (315).

Constitutional symptoms are encountered frequently during the course of Hodgkin's disease and, in fact, may be the initial manifestation of the disease. Some patients initially develop fever, weakness, pruritus without rash, and cachexia without any obvious evidence of lymphoma on physical examination. In such patients, the diagnosis of Hodgkin's disease may not be made until CT scanning or MR imaging identifies multiple, enlarged retroperitoneal or mediastinal nodes, or a laparotomy is performed.

Hematologic abnormalities are observed in the majority of patients with Hodgkin's disease and are present at the time of initial diagnosis in about 30% of patients. The most frequent finding is a normochromic, normocytic anemia, most often the result of decreased erythropoiesis. The white cell count is often moderately increased, and both granulocytosis and monocytosis may be present. Eosinophilia, usually less than 10%, occurs in about 10–20% of cases. Thrombocytosis occasionally occurs, and large bizarre platelets may be observed. Reed-Sternberg cells are occasionally identified in bone marrow aspiration and biopsy specimens at the time of diagnosis and also may be seen in the peripheral blood smear.

A number of immunologic abnormalities occur in patients with progressive Hodgkin's disease (322). These patients, like those with leukemia, are more susceptible to infections with viral, bacterial, and fungal organisms. In untreated patients, natural killer cell cytotoxicity is depressed. Interleukin-2 is abnormally produced, and there is increased sensitivity to suppressor monocytes and T-suppressor cells.

#### Neurological and Ocular Disorders

Neurological disturbances in patients with Hodgkin's disease may result from involvement of the intracranial portion of the CNS, the spinal cord, or the peripheral nervous system (PNS). According to some authors, involvement of the nervous system in patients with Hodgkin's disease occurs in 13–15% of all cases (323), although a review of 2,185 patients with Hodgkin's disease found only 12 (0.5%) who developed neurological symptoms, signs, or both (324). This discrepancy may be related to increasingly early diagnosis and treatment of this condition. Most examples of neurological involvement are **secondary**, occurring from discrete or diffuse metastases via meningeal vessels or from direct tumor extension (325–327).

When involvement of the meninges is primarily intracranial, single or multiple cranial neuropathies with and without papilledema commonly occur. In addition, single or multiple tumor nodules may implant on the meninges and enlarge, ultimately compressing and invading the substance of the brain and producing focal neurological defects (Fig. 34.13) (327,328). Such lesions may also invade the adjacent bones of the skull.

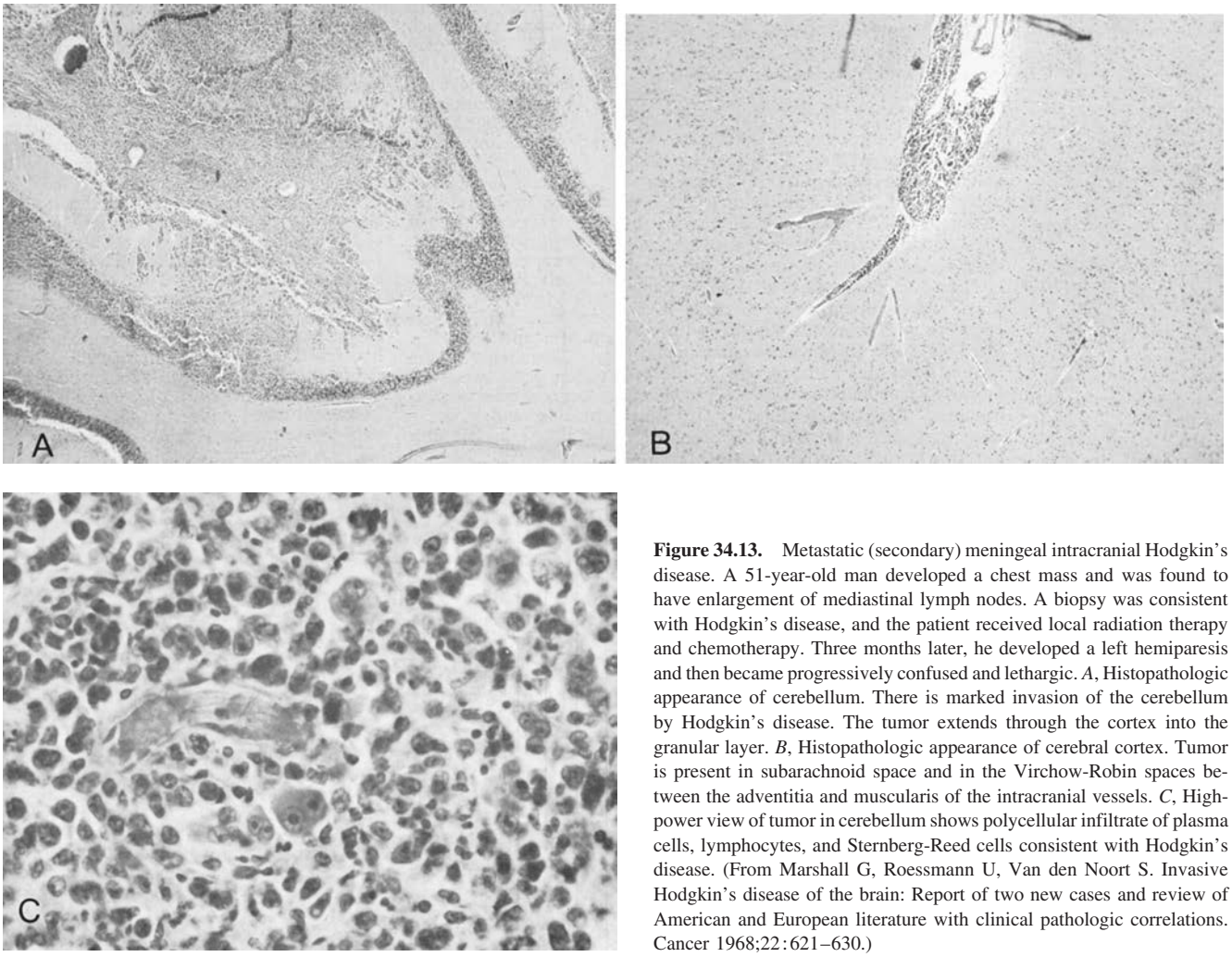



**Figure 34.13.** Metastatic (secondary) meningeal intracranial Hodgkin's disease. A 51-year-old man developed a chest mass and was found to have enlargement of mediastinal lymph nodes. A biopsy was consistent with Hodgkin's disease, and the patient received local radiation therapy and chemotherapy. Three months later, he developed a left hemiparesis and then became progressively confused and lethargic. *A*, Histopathologic appearance of cerebellum. There is marked invasion of the cerebellum by Hodgkin's disease. The tumor extends through the cortex into the granular layer. *B*, Histopathologic appearance of cerebral cortex. Tumor is present in subarachnoid space and in the Virchow-Robin spaces between the adventitia and muscularis of the intracranial vessels. *C*, High-power view of tumor in cerebellum shows polycellular infiltrate of plasma cells, lymphocytes, and Sternberg-Reed cells consistent with Hodgkin's disease. (From Marshall G, Roessmann U, Van den Noort S. Invasive Hodgkin's disease of the brain: Report of two new cases and review of American and European literature with clinical pathologic correlations. Cancer 1968;22:621–630.)

In patients with involvement of the spinal meninges and nerve roots, pain, weakness, and numbness of the trunk and extremities usually occur. When the cervical or high thoracic portions of the spinal cord are involved, a central or preganglionic Horner syndrome may occur, although this syndrome (as well as other myelopathic signs) may also result from destruction and collapse of vertebrae or from compression of the cord and nerve roots by enlarged paraspinal lymph nodes (329,330). Spinal cord compression occurs in 3–8% of patients with Hodgkin's disease (331,332).

Single or multiple intracranial masses may develop in patients with systemic Hodgkin's disease. These lesions may be located anywhere within the cranial vault (324, 327,333–340). In such cases, the symptoms and signs are related to the location and size of the lesion. They include focal or generalized seizures, focal neurological signs, confusion, mental deterioration, and coma. Visual disturbances in such cases include visual hallucinations, unilateral or bilateral visual loss from invasion of the optic nerves, visual field defects indicating chiasmal dysfunction, or homonymous hemianopic field defects from damage to the postchiasmal visual sensory pathway (341–343). A cavernous sinus syndrome with multiple cranial nerve pareses may occur (Fig. 34.14) (340), but diplopia and ptosis may also result from invasion of the brainstem and disruption of the cranial nerve nuclei or their fascicles.

Peripheral neuropathy affects some patients with Hodgkin's disease. Among 302 patients with neurological abnormalities caused by Hodgkin's disease, Williams et al. found 81 patients (26.8%) with involvement of the PNS (340a). The most common disturbances were caused by damage to the brachial plexus. Other patients had Horner syndrome from damage to the oculosympathetic pathway or paralysis of the diaphragm from damage to the phrenic nerve. As is the case with CNS dysfunction, involvement of the PNS is usually a secondary phenomenon in patients in whom systemic Hodgkin's disease has previously been diagnosed.

Evidence of central (and occasionally peripheral) nervous system dysfunction in patients with Hodgkin's disease generally appears late in the course of the disease. Nevertheless, such dysfunction may occur as the initial and only manifestation of the process, months or years before any other evi-

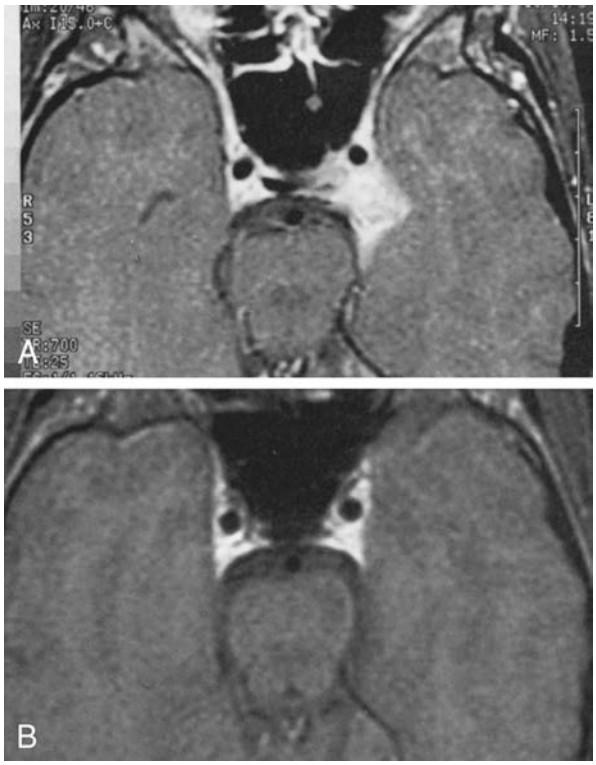



**Figure 34.14.** Cavernous sinus syndrome in Hodgkin's disease. The patient was a 28-year-old man with known Hodgkin's disease who developed left facial pain and a left abducens nerve paresis. *A*, Axial magnetic resonance (MR) image after intravenous injection of paramagnetic contrast material shows enlargement and enhancement of the left cavernous sinus. It was assumed that the patient had Hodgkin's disease in the cavernous sinus, and he was treated with radiation therapy. *B*, One month after completion of radiation therapy to the cavernous sinus, a repeat axial MR image shows a normal-appearing cavernous sinus with no abnormal enhancement. The patient subsequently developed other evidence of recurrent Hodgkin's disease. (From Kasner SE, Galetta SL, Vaughn DJ. Cavernous sinus syndrome in Hodgkin's disease. J Neuroophthalmol 1996;16:204–207.)

dence of Hodgkin's disease appears (338,339,344,345). Zimmerman collected 14 examples of Hodgkin's disease confined to the brain as verified by complete necropsies (207). Most of these tumors were circumscribed but not encapsulated. Some, however, invaded the brain diffusely. The circumscribed masses were often hemorrhagic and necrotic. They could be found in any of the cerebral lobes, as well as in the basal ganglia, hypothalamus, tuber cinereum, optic chiasm, brainstem, and cerebellum.

In some instances, a patient has constitutional symptoms or laboratory evidence compatible with Hodgkin's disease, but the diagnosis is not suspected until the CNS lesion is biopsied or, if that lesion is incorrectly diagnosed, not until months or even years later (328). This is particularly true when visual loss is the primary disturbance. Miller and Iliff described a described a 43-year-old man who was systemically well at the time that he began to experience bilateral progressive loss of vision (342). A complete systemic examination was unremarkable except for an eosinophilia of 14%. The patient ultimately underwent a left frontal craniotomy with exploration of the chiasmal region at which time the intracranial portion of the left optic nerve was found to be markedly thickened with a reddish mass bulging along its medial aspect adjacent to the optic chiasm, which pathologically was interpreted to be a ''spongioblastoma.'' The patient progressively deteriorated over several months, subsequently died, and at autopsy had extensive systemic infiltration by Hodgkin's lymphoma of the bone marrow, spleen, liver, both kidneys, and both adrenal glands. Reexamination of the original biopsy material obtained from the left optic nerve and chiasm revealed an infiltrate consisting of abnormal lymphocytes, atypical giant cells, eosinophils, and Reed-Sternberg cells consistent with Hodgkin's lymphoma.

In addition to visual loss from damage to parts of the visual sensory pathway and diplopia from damage to the ocular motor nuclei, fascicles, and nerves, Hodgkin's disease may produce visual symptoms from involvement of ocular structures, although this is uncommon. Ocular abnormalities associated with Hodgkin's disease include uveitis and retinopathy (329,346–348), keratitis sicca with bilateral enlargement of the parotid glands, and keratitis with vascularization. Barr and Joondeph (349) described a patient with retinal phlebitis as the initial clinical finding in Hodgkin's disease. Green et al. reported nine pairs of eyes obtained at autopsy from patients with Hodgkin's disease (348). Five were normal, but one showed retinal infarcts, and two showed infiltration of the choroid. One additional patient also had monocytic leukemia involving the choroid.

Orbital involvement is a rare complication of Hodgkin's disease (350). The majority of cases occur in patients with known Hodgkin's disease and consist of infiltration of the eyelids, subconjunctival space, conjunctiva, soft tissues of the orbit, and lacrimal gland (351–353). In some cases, however, involvement of the orbit is the first sign of the disease (330).

Siatkowski et al. reported a 21-year-old man who developed a left optic neuropathy associated with ipsilateral orbital pain after being in clinical remission of Hodgkin's disease for 2 years (354). The left optic disc showed moderate swelling with a few peripapillary hemorrhages (Fig. 34.15*A*). MR imaging showed diffuse enhancement of the nerve following intravenous administration of gadolinum-DTPA (Fig. 34.15*B*). The CSF was under normal pressure, had a normal concentration of protein and glucose, and contained no cells on standard or cytopathologic examination. Because of the suspicion of lymphomatous infiltration of the optic nerve, the patient was treated with 2000 cGy radiation, intravenous methylprednisolone, and oral prednisone. Over the next 6 weeks, vision improved, and the disc swelling resolved. Biopsy of a cervical lymph node revealed evidence of recurrent Hodgkin's disease.

Patients with AIDS are at higher risk for developing Hodgkin's lymphoma. As in patients without AIDS, the disorder may present with a variety of manifestations. For example, Park and Goins (265) reported a patient with AIDS in whom orbital and sinus involvement was the initial presentation of Hodgkin's disease.

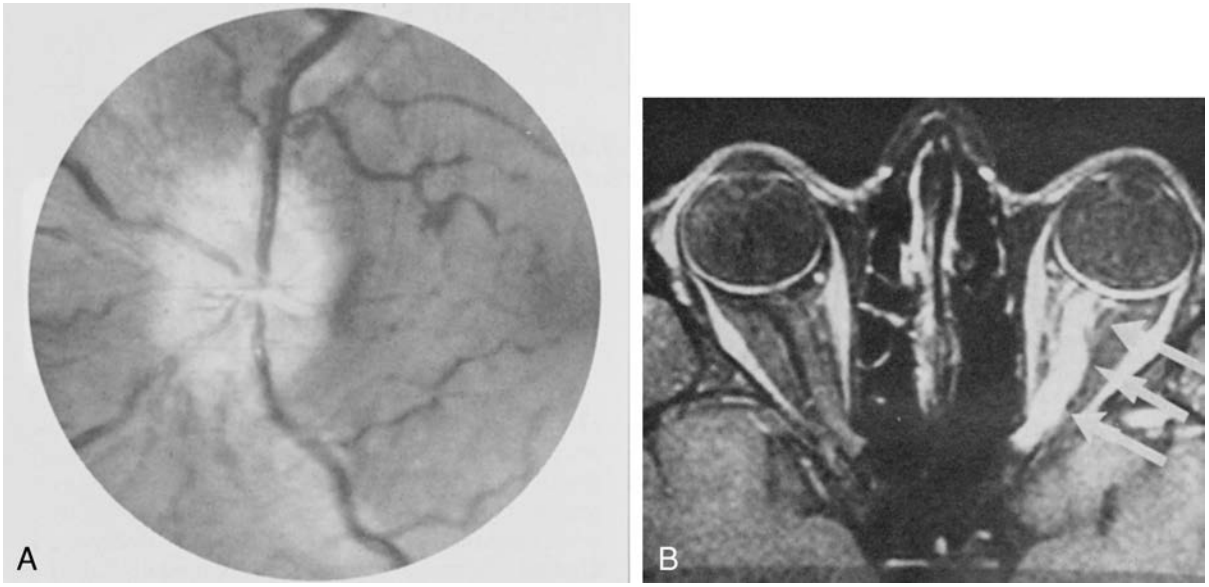



**Figure 34.15.** Anterior optic neuropathy caused by infiltration of the optic nerve in Hodgkin's disease. The patient was a 21-year-old man with known Hodgkin's disease thought to be in remission when he developed progressive loss of vision in the left eye. *A*, The left optic disc is moderately swollen. *B*, T1-weighted, fat-suppressed, axial magnetic resonance image after intravenous injection of gadolinium-DTPA shows marked enlargement and enhancement of the orbital portion of the left optic nerve (*arrows*). (From Siatkowski RM, Lam RL, Schatz NJ, et al. Optic neuropathy in Hodgkin's disease. Am J Ophthalmol 1992;114:625–629.)

The neurological and visual dysfunctions that occur in patients with Hodgkin's disease are not always related to the direct effects of the disease. Some patients with Hodgkin's disease develop infections or inflammations related to their debilitated and often immunosuppressed state. These include cryptococcal meningitis, aspergillosis, cytomegalic inclusion disease, herpes zoster, PML, and granulomatous angiitis of the CNS (185,355–358).

Patients with Hodgkin's disease (and patients with other lymphomas) may develop neurologic dysfunction, visual dysfunction, or both from **paraneoplastic disorders**. These disorders, which include encephalitis, encephalomyelitis, cerebellar degeneration, peripheral sensory and motor neuropathies, acute and chronic dysautonomia, cancer-associated retinopathy, and optic neuropathy, occur in a wide variety of malignancies and are thought to be caused by immune-mediated remote effects of the cancer (359–365). Kay et al. (366) reported a patient who developed opsoclonus-myoclonus syndrome after treatment of Hodgkin's disease by chemotherapy and autologous bone marrow transplantation. These authors speculated that chemotherapy resulted in breakdown of lymphomatous tissue and the production of antineuronal antibodies. A patient described by Abrey (367) developed myasthenia gravis characterized by ptosis, diplopia, generalized weakness, and dysphagia in the setting of extrathymic Hodgkin's disease. When the Hodgkin's disease was treated with antineoplastic therapy, the myasthenia gravis completely resolved, suggesting a paraneoplastic etiology.

### Treatment

Treatment of Hodgkin's disease, like that of other lymphomas and the leukemias, is constantly advancing. Treatment results in a cure in more than 70% of newly diagnosed patients (311). Surgical, medical, and radiation therapy are all used, either singly or in combination. Treatment is based in part on the stage of the disease at the time of diagnosis. Stage I Hodgkin's disease involves one lymph node region or one extralymphatic site. In stage II, there is involvement of two or more lymph node regions on one side of the diaphragm. Stage III disease affects lymph node regions on both sides of the diaphragm with or without localized involvement of one extralymphatic site. Stage IV Hodgkin's disease is defined as diffuse or disseminated involvement of extranodal sites (368). Each of these stages is further categorized by the designations ''X'' or ''A,'' depending on the presence (''X'') or absence (''A''), of constitutional symptoms, including unexplained fever, night sweats, or unintentional weight loss of more than 10% of body weight over the preceding 6 months, and ''B'' or ''E,'' indicating the presence of bulky disease (''B'') or involvement of a single extranodal site (''E'') (311). As a general rule, patients with stage I or II Hodgkin's disease are treated with radiation therapy alone, whereas patients with stage III or IV Hodgkin's disease are treated with a combination of radiation therapy and chemotherapy.

### Prognosis

The prognosis for patients with Hodgkin's disease continues to improve as new regimens to treat the disease are devel-

oped. Patients who survive 10 years or more without evidence of recurrent tumor appear to be cured and have the same death rate as healthy persons of the same age and sex (311). The 10-year survival rate for patients with Hodgkin's disease that is treated in an early stage is 95%, whereas it is 70% for patients with advanced Hodgkin's disease (369). Unfortunately, many patients with Hodgkin's disease still succumb to their illness. The prognosis is influenced by tumor bulk, patient age, histopathologic subtype, anatomic stage, presence or absence of constitutional symptoms, and immune status of the patient (368–371). In addition, relapses may occur after 10–20 years, and microscopic evidence of Hodgkin's disease may be present in long-term survivors who die from other causes (372). This finding suggests that in at least some patients with Hodgkin's disease, clinical cure may represent a state of equilibrium between the host and the tumor. Finally, patients who are otherwise successfully treated for Hodgkin's disease may develop long-term complications of radiation therapy and, to a lesser extent, chemotherapy and surgery. These complications include thyroid dysfunction, radiation-induced pulmonary disease, radiation-induced cerebritis and myelitis, chemotherapy-induced peripheral neuropathy, avascular necrosis of the long bones, pericarditis and other cardiac abnormalities, gonadal dysfunction, life-threatening infections (from removal of the spleen), abnormalities of the immune system, and secondary malignancies (373–375).

## NON-HODGKIN'S LYMPHOMAS

The non-Hodgkin's lymphomas are generally considered together even though they differ considerably in their biologic behavior, with some having a rather indolent course and others being more aggressive. Different classifications emphasize the clinical, immunologic, or histopathologic features of these somewhat diverse neoplasms (376,377). Histological classifications emphasize the overall microscopic pattern of the tumor (follicular or nodular versus diffuse; differentiated versus undifferentiated), the size and shape of the primary tumor cell (small versus large; cleaved versus noncleaved; convoluted versus nonconvoluted), the immunologic type of the tumor cell (T versus B), and the level of malignancy of the tumor (low, intermediate, or high grade). Although none of these approaches is perfect, partly because there is a significant inter- as well as intra-observer variation in the classification of any given tumor, the Revised European-American Classification of Lymphoid Neoplasms (REAL) (1994) (19) and the WHO classification of lymphomas (1999) (20) are widely accepted (Table 34.3). In this chapter, three main types of the non-Hodgkin's lymphomas are discussed based on their neuro-ophthalmologic significance: diffuse large-cell lymphoma, Burkitt's lymphoma, and other lymphocytic and lymphoblastic lymphomas, both diffuse and follicular.

### Diffuse Large-Cell Lymphoma (Diffuse Histiocytic Lymphoma, Reticulum Cell Sarcoma, Microgliomatosis)

Diffuse large-cell lymphoma is the category currently used for the hematopoietic neoplasm once thought to be composed of reticulum cells, histiocytes, or microglia. Previously, this tumor was called reticulum cell sarcoma, histiocytic lymphoma, and microgliomatosis (131,338,378). In fact, the tumor arises from lymphocytes. Diffuse large-cell lymphoma is subdivided into two types. One is of follicular center origin (B-cell transformation); the other is of an immunoblastic cell type (B- and T-cell origin).

Diffuse large-cell lymphoma occurs most frequently in persons between 40 and 60 years of age, although the age range of patients is broad (311,379). In some series, men and women are equally affected, whereas in others, women are affected twice as often as men. The tumor (particularly in its primary CNS form) occurs with increased frequency in patients with AIDS (380–383). Patients receiving organ transplants are also at risk (384). Diffuse large-cell lymphoma may take three forms: a systemic form, a primary CNS form, and an isolated intraocular form.

#### Systemic Diffuse Large-Cell Lymphoma

The **systemic** form of diffuse large-cell lymphoma arises in the lymph nodes, bone marrow, or viscera. Patients usually have no constitutional symptoms. Instead, the initial manifestations of the disorder are related to a painless, asymmetric, regional enlargement of lymph nodes, particularly in the cervical area. About one-third of patients become symptomatic because of extranodal tumor masses that most often arise in the nasopharynx or oropharynx, tonsils, skin, gastrointestinal tract, or bones. Presenting complaints may also relate to enlarging mediastinal or retroperitoneal tumors.

On examination, the palpable peripheral masses are usually nontender, matted, and free of attachment to the overlying skin. Generalized lymphadenopathy is uncommon, and splenomegaly is present in only about 20% of cases.

Hematologic abnormalities are uncommon in patients with the systemic form of diffuse large-cell lymphoma, particularly in its early stages. In the late stages, however, some patients develop a normochromic, normocytic anemia, and other evidence of bone marrow failure may ultimately appear.

The CNS is frequently affected in the systemic form of diffuse large-cell lymphoma, and there is some evidence that this is the most common subtype to affect the CNS secondarily (385,386). The CNS is involved in approximately 10% of the general population with non-Hodgkin's lymphoma (386) and up to 25% in those non-Hodgkin's lymphoma patients with AIDS. In most cases, the diagnosis is known at the time that neurological symptoms and signs appear; however, in some cases, the neurological dysfunction is the initial evidence of disseminated disease (385,386). CNS manifestations most often result from leptomeningeal spread of tumor, but some patients develop intracerebral metastases, and others have symptoms from infiltration or compression of the spinal cord (387–392). Systemic large-cell lymphoma may also present as a cavernous sinus syndrome (393). In rare cases, neurological symptoms and signs result not from direct invasion or compression of neural tissue by the tumor but from occlusion of cerebral blood vessels by tumor cells (394–396).

The most common neurological symptoms and signs are

cranial neuropathies, particularly ocular motor and facial nerve pareses. Wilkins and Samhouri (397) described a 62-year-old man with diffuse large-cell lymphoma, stage II, who was being treated with combination chemotherapy when he developed isolated bilateral oculomotor nerve pareses sparing the pupils and unassociated with any other neurological abnormalities. The patient underwent brainstem irradiation in conjunction with chemotherapy and experienced slight improvement in his condition; however, about 2 months after the onset of symptoms, he died suddenly from a pulmonary embolus. Postmortem examination disclosed generalized lymphatic and visceral infiltration by diffuse large-cell lymphoma. Although the brainstem, spinal cord, and meninges appeared normal on gross inspection, microscopic examination revealed lymphomatous infiltration of both oculomotor fascicles and the subarachnoid portion of both oculomotor nerves (Fig. 34.16). The oculomotor nuclei were uninvolved. No additional nervous system involvement was found except for lymphoma cells throughout the intracranial and spinal leptomeninges.

Raz et al. documented 18 cases of cranial neuropathy among 24 patients with involvement of the CNS by malignant lymphoma (385). In 15 of these patients, the lymphoma was of the diffuse large-cell type. Recht et al., on the other hand, found cranial nerve involvement in 36% of 90 patients with CNS lymphoma (391). The most commonly affected nerve was the facial nerve, which was involved in 16 patients. The oculomotor nerve was involved in two patients, the abducens nerve in six, and the trochlear nerve and optic nerve in one each. Other neurologic symptoms and signs that occur in patients with the systemic form of diffuse large-cell lymphoma and involvement of the CNS include headaches, change in mentation, nausea, vomiting, papilledema, seizures, radicular pain, hemiparesis, hemianopia, nystagmus, and disturbance of gait. Symptoms and signs of compression of the spinal cord include back and neck pain, paraplegia, a sensory level, bowel or bladder dysfunction, and weakness of the upper extremities.

Visual loss as well as neurological dysfunction may occasionally occur in patients with the systemic form of diffuse large-cell lymphoma. In most cases, visual dysfunction consists of a homonymous field defect from damage to the postchiasmal visual sensory pathway or diplopia from involvement of the ocular motor system anywhere from the brainstem to the orbit. Orbital involvement is rare, occurring in 1.3% of patients in one large series (398). It is also rare in patients with AIDS (399). When the orbit is involved, the clinical syndrome is one of progressive proptosis, eyelid swelling, diplopia, and a variable degree of pain (400–404). When the tumor is anterior, extensive, or both, a mass may be palpated. When the tumor is posterior, vision may be lost from compression or infiltration of the orbital portion of the optic nerve (148). Loss of central vision from optic neuropathy (with and without optic disc swelling) may also occur in patients with the systemic form of diffuse large-cell lymphoma (Fig. 34.17). In most of these cases, a diagnosis has

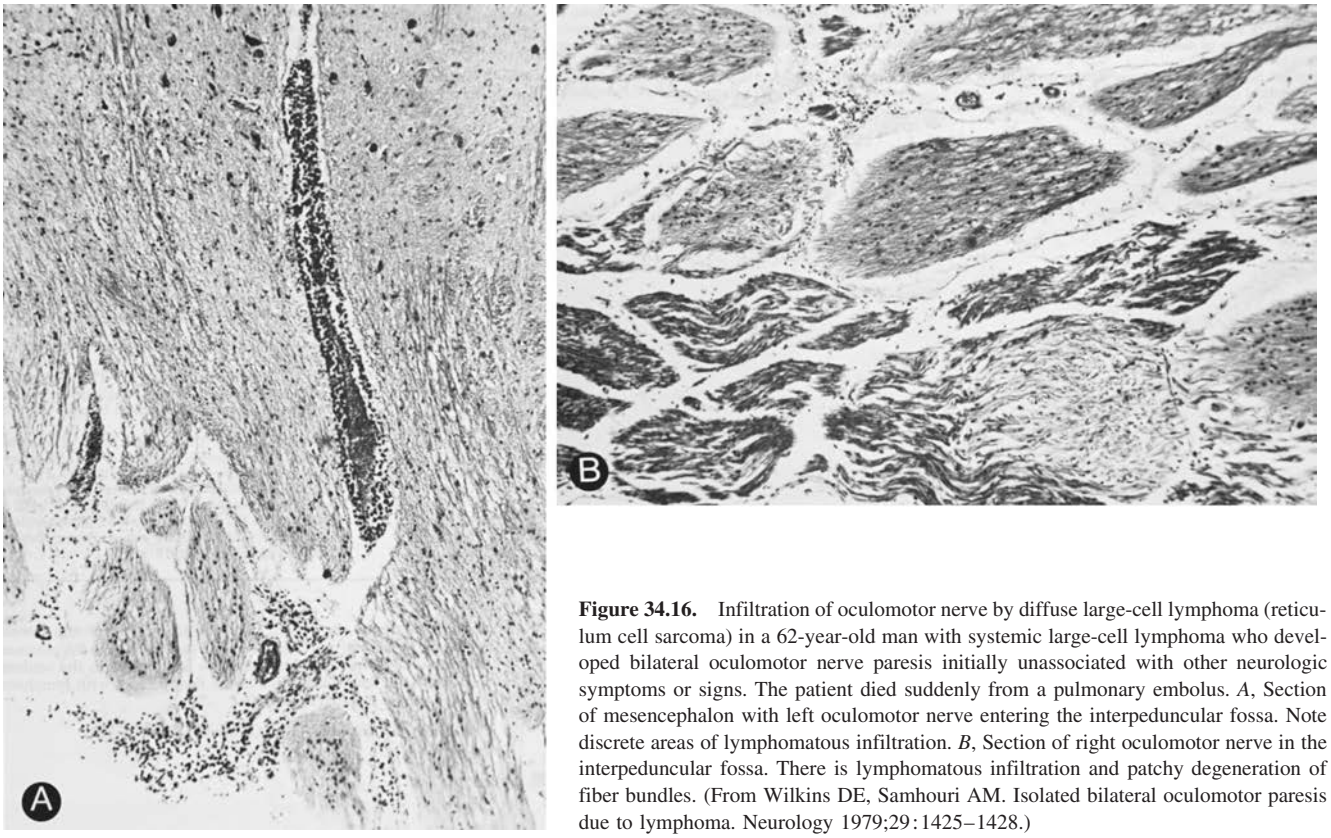



**Figure 34.16.** Infiltration of oculomotor nerve by diffuse large-cell lymphoma (reticulum cell sarcoma) in a 62-year-old man with systemic large-cell lymphoma who developed bilateral oculomotor nerve paresis initially unassociated with other neurologic symptoms or signs. The patient died suddenly from a pulmonary embolus. *A*, Section of mesencephalon with left oculomotor nerve entering the interpeduncular fossa. Note discrete areas of lymphomatous infiltration. *B*, Section of right oculomotor nerve in the interpeduncular fossa. There is lymphomatous infiltration and patchy degeneration of fiber bundles. (From Wilkins DE, Samhouri AM. Isolated bilateral oculomotor paresis due to lymphoma. Neurology 1979;29:1425–1428.)

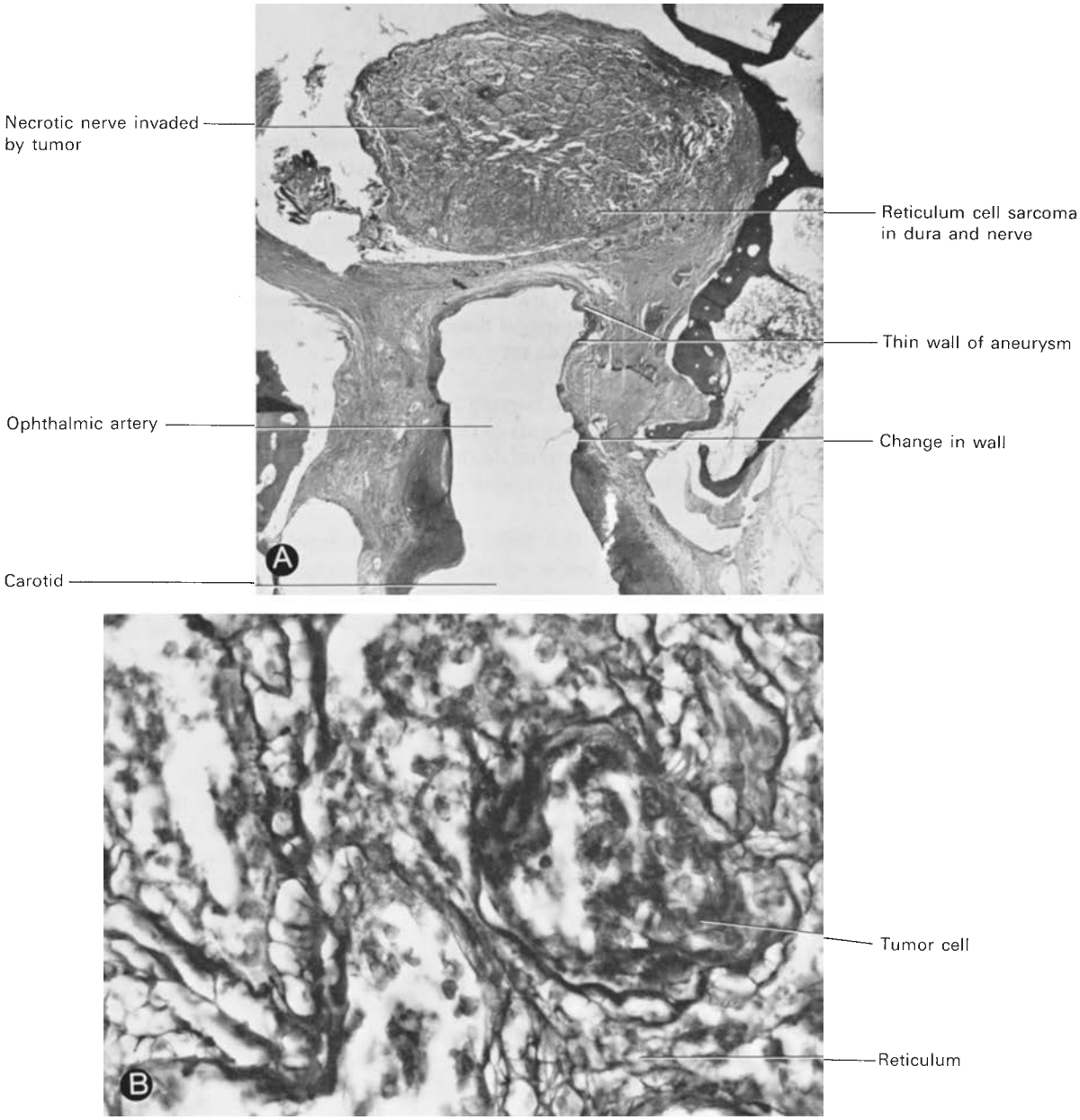



**Figure 34.17.** Infiltration of left optic nerve by diffuse large-cell lymphoma (reticulum cell sarcoma) in a 64-year-old woman who suddenly lost vision in her left eye. The left optic disc was slightly hyperemic, and she was initially thought to have optic neuritis. She was treated with systemic corticosteroids, but within 2 weeks the left eye was completely blind. She subsequently developed a left oculomotor nerve paresis and a left abducens nerve paresis. She then became systemically ill and died about 3 weeks after the onset of her visual symptoms. At autopsy, she was found to have extensive systemic diffuse large-cell lymphoma. *A*, Coronal section through the left optic nerve at the intracranial end of the optic canal shows the nerve to be necrotic and infiltrated by tumor. The tumor extends into the dura on the right. The left internal carotid artery and ophthalmic artery are inferior to the nerve, and the wall of the ophthalmic artery contains a small aneurysm which does not compress the nerve. *B*, High-power view of the left optic nerve shows marked necrosis and infiltration by tumor cells consistent with diffuse large-cell lymphoma. (From Walsh FB, Shewmake BJ. An unusual case of reticulum cell sarcoma. Am J Ophthalmol 1972; 74:741–743.)

already been established (405), whereas in rare instances, visual loss is the first and only sign of systemic disease. Optic neuropathy in systemic lymphoma is quite rare. It was observed in none of the 21 patients described by Griffin et al. (325), in 1 of 13 patients described by Bunn and colleagues (388), and in 2 of 105 patients reported by MacIntosh et al. (390). In a series of 205 patients with secondary optic nerve malignancy, Christmas et al. (406) found four due to lymphoma.

The systemic form of large-cell lymphoma can affect the eye as well. When ocular involvement with systemic lymphoma occurs, the uveal tract is most often affected (348,407). This manifestation typically appears as uveitis (408), is usually bilateral, and may be the first sign of systemic disease (409–411). Ocular involvement occurs most often, however, in patients with the primary CNS form of the disease.

The diagnosis of the systemic form of diffuse large-cell lymphoma is usually established by the results of biopsy of involved tissue, most often enlarged lymph nodes. Once the diagnosis is made, the disease is staged by the same criteria used in Hodgkin's disease (412). The treatment then depends on the stage of the process. The disorder is seen most frequently in patients with AIDS (382,413–417). Patients with low-grade disease are usually treated with radiation therapy. Patients with intermediate- and high-grade lymphoma are usually treated with combination chemotherapy, although radiation therapy may also be used, particularly in patients with bulky tumors (418,419). The median survivals for patients with low-grade, intermediate-grade and high-grade disease are 6.5 years, 2.5 years, and 1.5 years, respectively (311). Patients with involvement of the CNS and AIDS have a much worse prognosis.

### Primary CNS Large-Cell Lymphoma

Primary CNS lymphoma affects just over 1,000 patients each year in the United States. The incidence of primary CNS large-cell lymphoma increased threefold from the 1960s to the 1990s (420), in large part because of the emergence of AIDS; however, the incidence also increased in nonimmunocompromised persons, and the reason for this increase is unclear (421). This form of lymphoma is generally a disease of older adults, but it also occurs in young persons, most of whom are immunodeficient (415,420,422, 423). In immunocompetent patients, the male to female ratio is 3:2, but among patients with AIDS, males make up more than 90% of patients (382,415).

The etiology of primary CNS large-cell lymphoma is unknown. EBV is implicated in patients with AIDS (415,417,424–426), but the tumor also occurs in organ transplant patients and in patients with the Wiskott-Aldrich syndrome, also immunocompromised conditions (382,427). That a primary lymphoma develops in this setting is unusual because the CNS does not have lymphatics. The great majority of primary CNS lymphomas are B-cell tumors (428,429). There are, however, rare reports of primary CNS T-cell lymphomas (430).

The lesions of primary CNS large-cell lymphoma are intrinsic. They are located deep within the parenchyma of the brain but also involve the leptomeninges (207,382,415,429, 431–435). Parenchymal lesions are multifocal in 50% of patients without immunodeficiency and in nearly all patients with AIDS (432,433,436–439). Primary CNS lymphoma limited to the meninges is rare (434,440).

About 75% of primary CNS lymphomas involve the cerebral hemispheres, but the cerebellum, basal ganglia, and thalamus may also be affected (382,438,441). Most patients present with evidence of increased ICP or with focal neurologic signs indicating a mass lesion. Parenchymal involvement may be extensive (Fig. 34.18). Other common presenting features include memory loss, personality change, and confusion (382,415,432,437,442,443). Seizures are a rare manifestation. Paraparesis, quadriparesis, sensory symptoms and signs, or a combination of these manifestations occur when the spinal cord is the primary site of involvement (444).

Patients with the primary CNS form of diffuse large-cell lymphoma occasionally present only with visual symptoms and signs. Although any part of the visual sensory or ocular motor systems may be involved, the most common ocular presentation is that of apparent uveitis (409,427,441, 445–450). The incidence of ocular involvement is as high as 10–20% at diagnosis (451,452). Most patients are adults. Both eyes are usually affected, although one eye may become involved first. The typical patient develops mild decreased vision or ''floaters'' in one or both eyes and has a

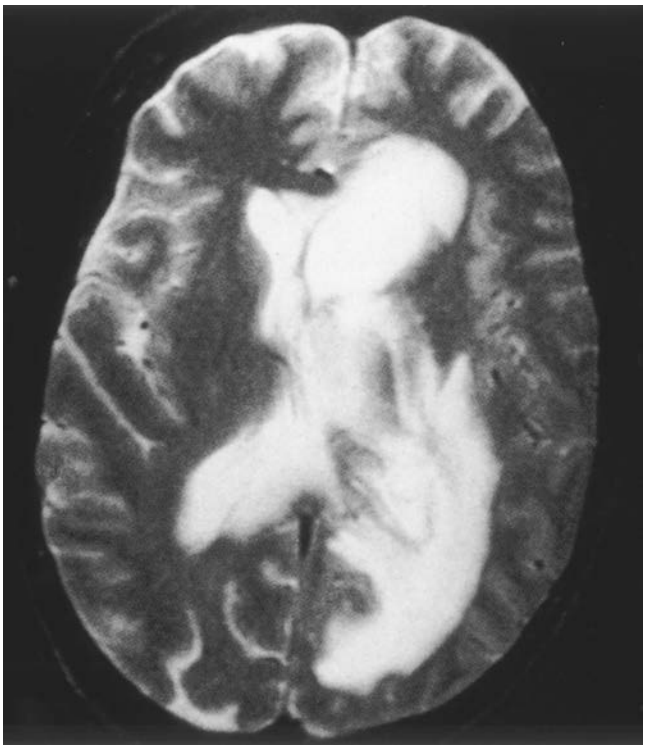


**Figure 34.18.** Neuroimaging appearance of a primary intracranial large-cell lymphoma. Axial T2-weighted magnetic resonance image shows extensive infiltration of the left cerebral hemisphere with surrounding edema.

mild to moderate unilateral or bilateral uveitis that is unassociated with pain or redness. The uveitis always involves the vitreous (407,441,447,448,453–461), but there may also be cells in the anterior chamber and even a hypopyon in rare cases (409,462–464). Regardless of its location, the cellular reaction may consist of fine cells or large gray-white cell clumps. In the anterior chamber, the cells may form keratic precipitates on the endothelium of the cornea that mimic the so-called ''mutton-fat'' keratic precipitates seen in patients with granulomatous uveitis (Fig. 34.19).

The uveitis that occurs in patients with primary CNS lymphoma is usually unassociated with any other ocular abnormalities; however, some patients eventually develop or are even found at the time of initial presentation to have yellow-orange infiltrates beneath the retina or the RPE (453, 456,465–468) (Fig. 34.20). Aspiration biopsy of these lesions reveals malignant cells and can be used to diagnose the disease if vitrectomy is unsuccessful (469). Other patients develop exudative retinal detachments, retinal vasculitis, branch and central retinal artery occlusions, retinal and vitreous hemorrhages, or retinal necrosis (447,462,463,468,470, 471). In time, neovascular glaucoma may develop (472,473).

Although most patients have normal-appearing optic discs when their ''uveitis'' is first discovered, some patients have optic disc swelling. The swelling may be caused by associated hypotony, by infiltration of the disc by lymphoma cells, or occasionally by concomitantly increased ICP (in which case it is papilledema). In this last setting, the patient usually has other symptoms of hydrocephalus.

The visual status of patients with the uveitis associated with primary CNS lymphoma varies considerably. Some patients have excellent vision, but others have vision commensurate with substantial involvement of the neurosensory retina and RPE. Still others have variably reduced vision that is unexplained by the apparent uveitis. In these patients, the loss of vision is usually caused by infiltration of one or both optic nerves by lymphoma cells. When the optic discs of such patients appear normal, the posterior orbital, intracanalicular, or intracranial portion of the affected nerves is infiltrated. When only one nerve is affected in this manner, there is invariably an ipsilateral relative afferent pupillary defect which, of course, cannot be explained by the ''uveitis.''

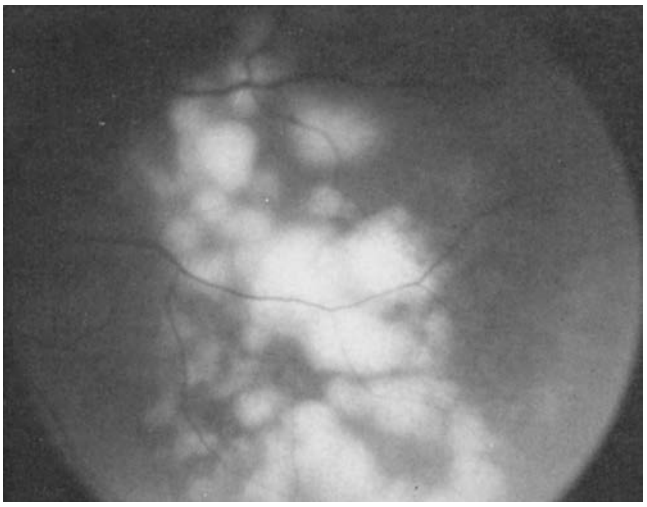


**Figure 34.20.** Clinical appearance of choroidal infiltration by primary CNS large-cell lymphoma in a 65-year-old woman who initially complained of bilateral blurred vision and was found to have a uveitis involving the vitreous cavity in both eyes. At the time of initial examination, these lesions were not present. The patient was treated with topical corticosteroids for her uveitis. When she returned one month later, the uveitis had improved, but the choroidal lesions were evident. Large, confluent, hypopigmented areas that do not obscure the retinal vessels are present in the posterior pole. Some of these areas are slightly elevated. The patient had a negative evaluation for lymphoma at this time, but later developed CNS large-cell lymphoma.

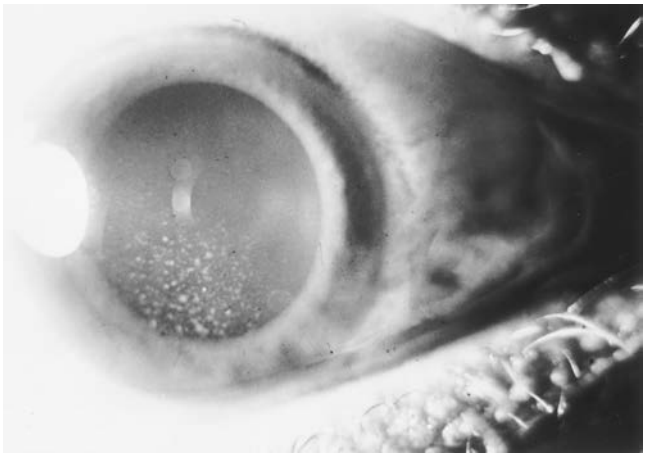


**Figure 34.19.** Large, keratic precipitates on the endothelium of the cornea in a 46-year-old woman with fever, malaise, and cervical lymphadenopathy. She then developed decreased vision in the right eye and was found to have marked ray and cell in the anterior chamber, hypopyon, and vitreous cells. The patient was eventually found to have the systemic form of diffuse large-cell lymphoma. At autopsy, both eyes were infiltrated by neoplastic cells. (From Barr CC, Green WR, Payne JW, et al. Intraocular reticulum-cell sarcoma: Clinicopathologic study of four cases and review of the literature. Surv Ophthalmol 1975;19:224–239.)

In patients who present only with evidence of what appears to be a chronic uveitis, the correct diagnosis usually is not suspected initially. Instead, the patients often are treated with topical or, occasionally, systemic corticosteroids. Such patients typically do not respond to this therapy, although occasionally there is a rapid improvement in vision, reduction in cellular reaction, or both. This improvement is short-lived, however, whether or not corticosteroid therapy is maintained. Eventually, further visual loss occurs, associated with evidence of further ocular involvement and the development of neurological symptoms and signs.

Some patients who present with the uveitic syndrome described earlier have evidence of other neurological diseases caused by CNS lymphoma at the time of the ocular presentation; however, in most patients, the intraocular involvement precedes clinical, neuroimaging, and even laboratory evidence of CNS lymphoma by months to years (409,447,474, 475). Specifically, the CSF usually shows no signs of malig-

nancy. In such patients, the diagnosis must be suspected clinically and verified by aspiration from the anterior chamber or vitreous or by vitrectomy (see Primary Ocular Lymphoma section below) (445,447,448,450,453,464,476–479).

In patients with suspected large-cell lymphoma, the finding of only normal-appearing lymphocytes in an aqueous or vitreous aspirate or a vitrectomy specimen does not eliminate the diagnosis. Cell marker studies performed on such cells usually identify them as a monoclonal strain of B-cells, which is indicative of malignancy rather than inflammation (409,447,480–483). As noted previously, in patients with subretinal lesions associated with vitreous opacities, a subretinal aspiration biopsy may establish the diagnosis of an intraocular lymphoma when vitrectomy fails to do so (469).

Although intraocular involvement is responsible for the majority of visual disturbances in patients with the primary CNS form of diffuse large-cell lymphoma, vision loss may occur from chiasmal or optic nerve involvement. The tumor may initially infiltrate the optic chiasm, producing a progressive chiasmal syndrome (484) (Fig. 34.21). Optic nerve involvement is not uncommon (Fig. 34.22) (275,390,447,458) and may be the presenting symptom of the disorder (485,486). In some cases, the optic disc on the affected side appears normal, and a diagnosis of retrobulbar neuritis is assumed until visual loss progresses or other neurological symptoms and signs develop (487,488). In other cases, there is concomitant orbital involvement with painless proptosis and swelling of the eyelids (461,489). In still other patients, visual loss is associated with optic disc swelling in the affected eye but no vitreous reaction (Fig. 34.23), suggesting infiltration of the intraorbital portion of the optic nerve (453,490). This presentation also may initially be confused with optic neuritis (in this case, a papillitis), particularly when the patient is given systemic corticosteroids and shows a dramatic response.

Patients with primary CNS lymphoma may develop diplopia from ocular motor nerve pareses (491) or from damage to brainstem ocular motor pathways (491). In some cases, spontaneous remission of an ocular motor neuropathy has been observed in the course of the disease. Galetta et al. described a 72-year-old man who initially developed an acute right abducens nerve paresis that spontaneously resolved (492). One month later, he developed recurrent diplopia, and an examination revealed an almost complete right oculomotor nerve paresis with involvement of the pupil. MR imaging showed enlargement and enhancement of the sub-

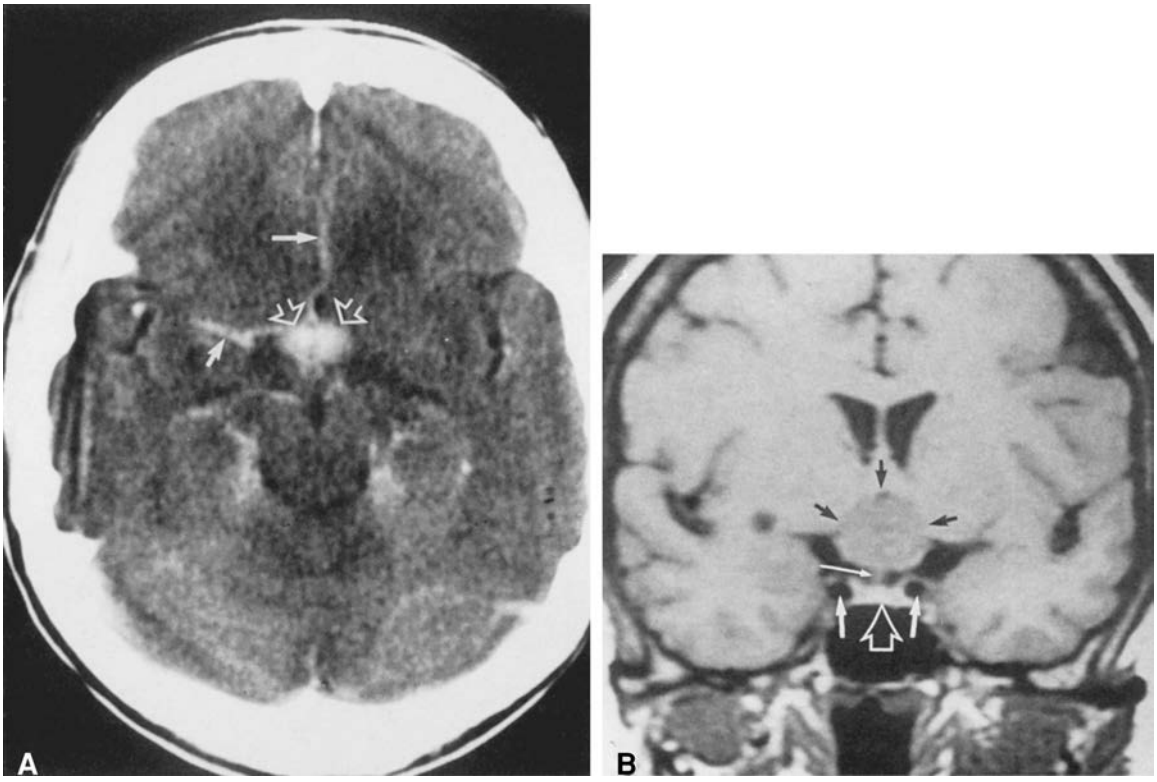



**Figure 34.21.** Primary large-cell lymphoma of the optic chiasm. The patient was a 58-year-old woman with progressive loss of vision. *A*, Axial computed tomographic scan after intravenous injection of iodinated contrast material shows an enhancing mass in the suprasellar region (*open arrows*). Right middle cerebral artery (*short arrow*) and left anterior cerebral artery (*long arrow*) are also seen. *B*, T1-weighted coronal magnetic resonance image shows marked enlargement of the optic chiasm (*black arrows*). The infundibulum (*thin white arrow*), pituitary gland (*open arrow*), and intracavernous carotid arteries (*thick white arrows*) appear normal. A biopsy of the lesion established the diagnosis. (From Gray RS, Abrahams JJ, Hufnagel TJ, et al. Ghost-cell tumor of the optic chiasm: Primary CNS lymphoma. J Clin Neuroophthalmol 1989;9:98–104.)

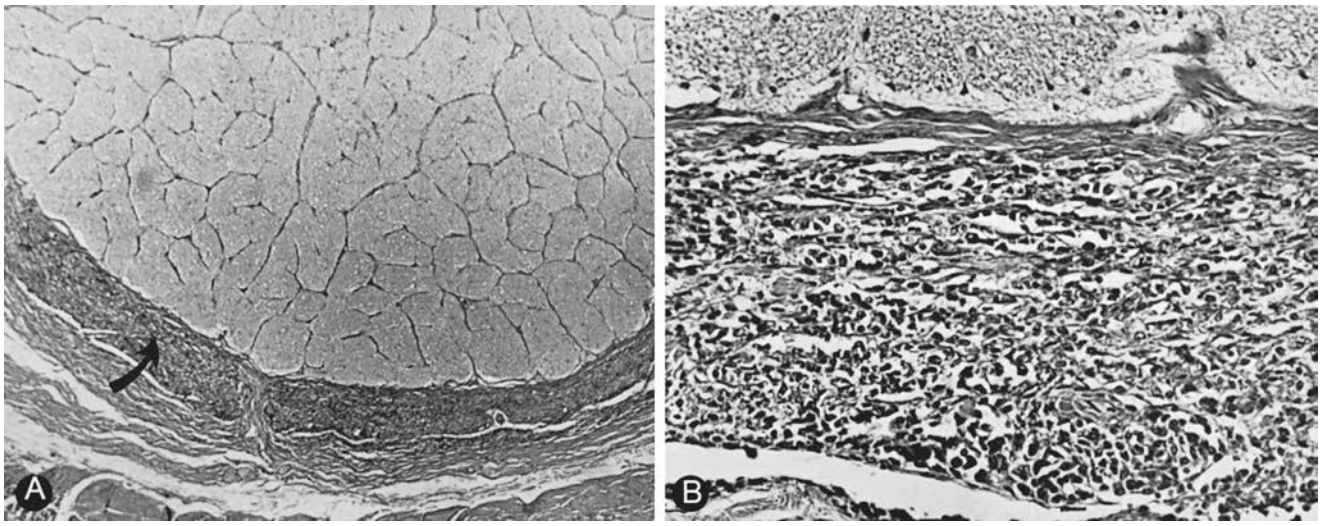



**Figure 34.22.** Infiltration of optic nerve sheath by diffuse large-cell lymphoma. Cross section of the posterior portion of right optic nerve shows lymphoma filling the subarachnoid and subdural spaces and infiltrating the pia-arachnoid. *A*, Low-power view. *Arrow* points to tumor in the subdural space. *B*, High-power view shows tumor cells infiltrating the pia-arachnoid. (From Hogan MJ, Spencer WH, Hoyt WF. Primary reticuloendothelial sarcomas of the orbital and cranial meninges: Ophthalmologic aspects. Am J Ophthalmol 1966;61:1146–1158.)

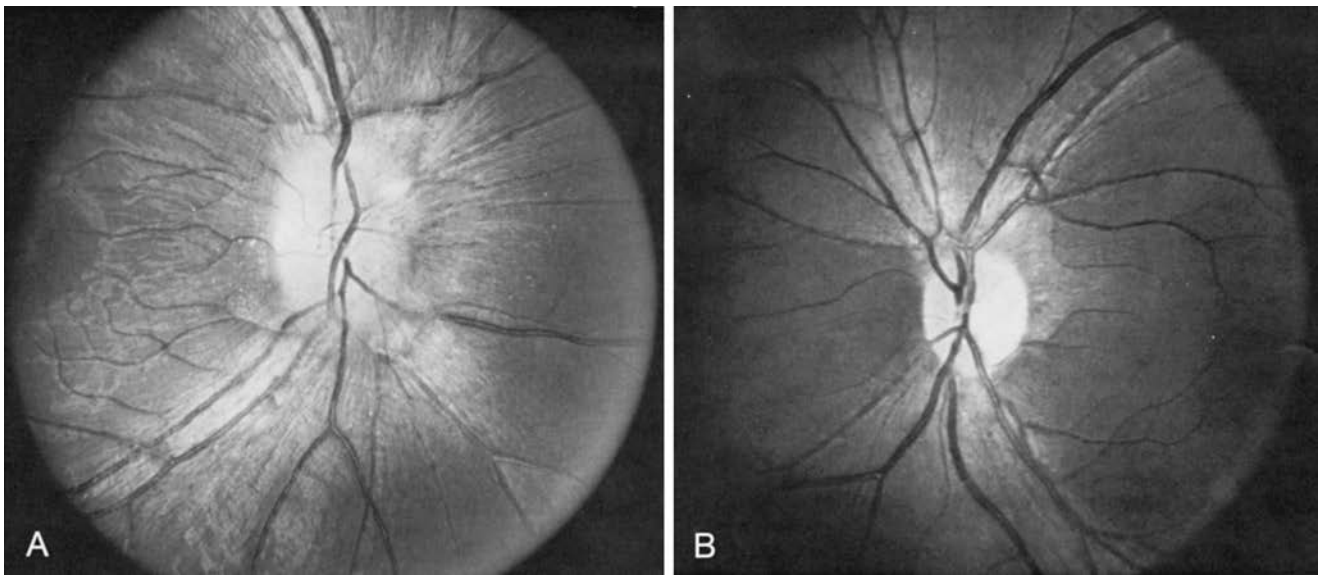



**Figure 34.23.** Unilateral anterior optic neuropathy unassociated with vitreous reaction in a 23-year-old woman who was eventually found to have the central nervous system form of diffuse large-cell lymphoma (reticulum cell sarcoma). The patient had a 3-week history of progressive visual loss in the right eye associated with occipital and vertex headache. She then developed nausea and vomiting. Visual acuity was no light perception in the right eye and 20/20 in the left eye. *A*, The right optic disc is swollen. *B*, The left optic disc is normal. A CT scan showed a large, enhancing mass in the left cerebellar hemisphere. Smaller masses were seen in the right cerebellar hemisphere and in the right parasellar region. The proximal portion of the right intraorbital optic nerve was enlarged. A biopsy of the large cerebellar mass established a diagnosis of diffuse large-cell lymphoma. The patient was given systemic corticosteroids and cranial irradiation. Following treatment, vision in the right eye improved to 20/30, and disc swelling resolved. (From Purvin V, van Dyk HJL. Primary reticulum cell sarcoma of the brain presenting as steroid-responsive optic neuropathy. J Clin Neuroophthalmol 1984;4:15–23.)

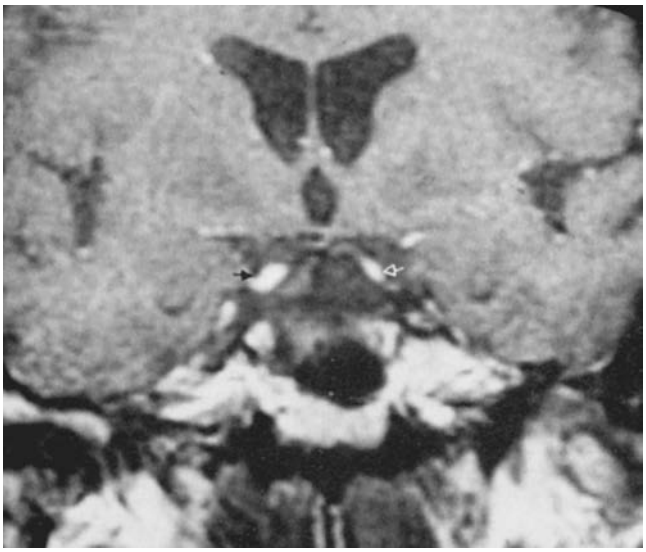


**Figure 34.24.** Neuroimaging appearance of primary leptomeningeal form of diffuse large-cell lymphoma in a patient with an acute right oculomotor nerve paresis. T1-weighted coronal magnetic resonance image after intravenous injection of gadolinium-DTPA shows enlargement and enhancement of the subarachnoid portion of the right oculomotor nerve (*solid black arrow*). The subarachnoid portion of the left oculomotor nerve also enhances but is not enlarged (*open white arrow*). (From Galetta SL, Sergott RC, Wells GB, et al. Spontaneous remission of a third-nerve palsy in meningeal lymphoma. Ann Neurol 1992;32:100–102.)

arachnoid portion of the right oculomotor nerve (Fig. 34.24). The left oculomotor nerve also enhanced but was not enlarged. An extensive evaluation was nondiagnostic. Over the next 2 months, the oculomotor nerve paresis completely resolved. One year later, the patient developed new neurological symptoms, and a repeat evaluation revealed evidence of a primary meningeal large-cell lymphoma.

Lee et al. (493) described a 44-year-old woman in whom the initial manifestation of a primary CNS large-cell lymphoma was an abducens nerve paresis associated with transient oculomotor nerve synkinesis and a trigeminal sensory neuropathy (Fig. 34.25). Neuroimaging revealed a lesion in the left cavernous sinus (Fig. 34.26). The patient's condition responded dramatically to chemotherapy, suggesting to the authors that the synkinesis was caused by a defect in ephaptic transmission in the oculomotor nerve nucleus rather than by primary aberrant regeneration of the oculomotor nerve itself.

According to Herrlinger, only ten patients have been reported with occult systemic lymphoma at the time of initial presentation of primary CNS lymphoma, and systemic lymphoma determined the course of the disease in none of them. Thus, initial staging procedures for patients with biopsy-confirmed primary CNS lymphoma can be restricted to regular blood tests, including HIV testing, and slit lamp examination of the eye (451), although some authors recommend an evaluation to include chest radiography, bone marrow examination, and liver/spleen scanning (494).

The primary CNS form of lymphoma occurs with increased frequency in patients with AIDS and other immunodeficiency states. Indeed, the highest incidence of primary CNS lymphoma, between 1.9–6%, occurs in patients with

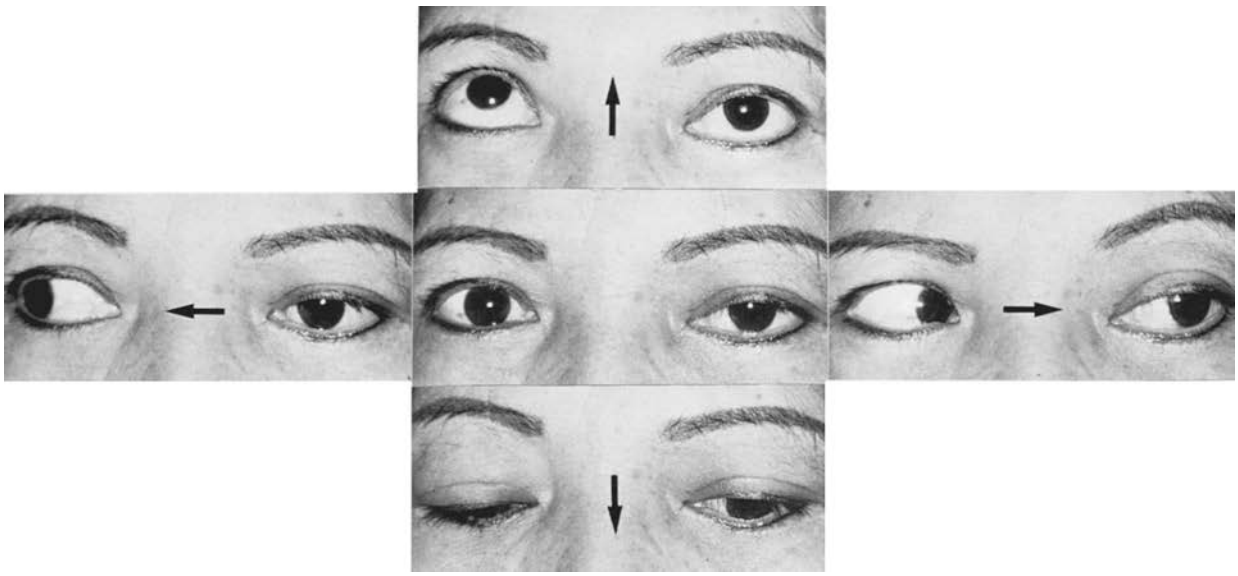


**Figure 34.25.** Primary oculomotor nerve synkinesis and left abducens nerve paresis in a 44-year-old woman with primary CNS large-cell lymphoma. *Arrows* indicate direction of attempted gaze. Note left ptosis in primary position, limitation of elevation, adduction, and abduction of the left eye, and elevation of left eyelid on attempted downgaze. (From Lee SH, Yeow YK, Ten CB, et al. Transient oculomotor nerve synkinesis in non-Hodgkin's lymphoma. J Clin Neuroophthalmol 1992; 12:203–206.)

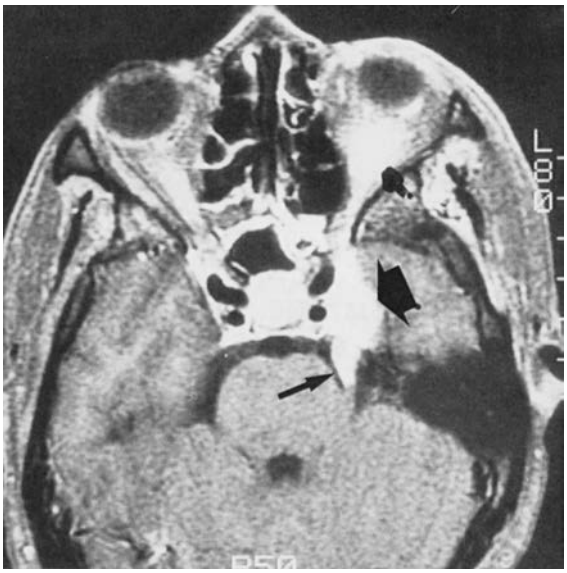


**Figure 34.26.** Magnetic resonance imaging in patient with primary CNS large-cell lymphoma whose external appearance is seen in Figure 34.49. T1-weighted axial image after intravenous injection of gadolinium-DTPA shows medial temporal mass abutting left cavernous sinus (*thick arrow*). Note thickened left trigeminal nerve (*thin arrow*). (From Lee SH, Yeow YK, Ten CB, et al. Transient oculomotor nerve synkinesis in non-Hodgkin's lymphoma. J Clin Neuroophthalmol 1992;12:203–206.)

AIDS (382,413,423). This is also true of its ocular and neuroophthalmologic manifestations (441,479,495,496). The diagnosis should therefore be considered in all patients with AIDS who develop evidence of neurological dysfunction, ocular dysfunction, or both. Neuroimaging studies often show a parenchymal lesion in such patients (497–499), but when these studies show no such lesion, the correct diagnosis may not be made until the abnormal cells are obtained by lumbar puncture or abnormal tissue is obtained by surgery (382,500,501). In other cases, a systemic evaluation may yield evidence of systemic lymphoma, but this is unusual (502).

The prognosis for patients with primary CNS lymphoma is extremely poor regardless of treatment. Most patients are treated with craniospinal irradiation (382,421,503,504). Patients may also be treated with systemic corticosteroids and may experience transient clinical and neuroimaging remission of their disease (382,505). Chemotherapy with various regimens is also used (149,382,415,421,506–508). Patients with primary CNS lymphoma who have intraocular involvement usually are treated with radiation (450). The high recurrence rate of CNS lymphoma treated with radiation alone has been reduced with the addition of chemotherapy, often administered as a combination of intravenous, intrathecal, and intravitreal therapy (447,448,509–511). Unfortunately, the beneficial effects of all forms of therapy are always transient, and most patients die of their disease within 1–2 years and occasionally within several months after symptoms begin, especially patients with AIDS (382,415,439). Furthermore, patients are at risk for a treatment-related neurotoxicity causing a progressive leukoencephalopathy (512). The treatment of primary CNS lymphoma continues to evolve with no clear consensus on the best option.

### Primary Intraocular Large-Cell Lymphoma

Rare patients have intraocular large-cell lymphoma with no clinical, neuroimaging, or laboratory evidence of systemic or CNS involvement (409,459,469,483,513,514). Most patients with primary intraocular lymphoma are initially diagnosed as having idiopathic uveitis or vitritis. Patients present with floaters and blurred vision, and on ophthalmologic examination, vitreous cells are present. Retinal involvement may consist of lymphomatous subretinal pigment epithelial infiltrates, vasculitis, and retinochoroiditis (515,516a).

The diagnosis of primary ocular lymphoma is suspected in idiopathic uveitis patients who become resistant to topical or systemic steroids (516b). Although both ocular inflammation and lymphoma may respond to steroids initially, steroids rarely result in a sustained remission of ocular lymphoma. In a series of 828 patients with idiopathic uveitis, 13 (1.6%) were diagnosed with ocular lymphoma (515). The diagnosis is established by vitrectomy or vitreous needle aspiration (517) with malignant lymphocytes identified on cytologic evaluation of the vitreous specimen. Because ocular lymphoma is frequently accompanied by a reactive lymphocytosis, the diagnosis may be challenging. If the vitreous specimen is obtained while the patient is being treated with steroids, the cytopathologic diagnosis may be inconclusive as corticosteroids may be cytotoxic to malignant lymphocytes. Molecular and cytokine analyses are useful adjuncts to cytology for the diagnosis of primary intraocular lymphoma (517–521). Most primary intraocular lymphomas are B-cell proliferations (522), where the reactive lymphocytes are T-cells, leading to the appearance of a mixed cell population.

Once a patient is diagnosed with ocular lymphoma, he or she should undergo an evaluation for CNS involvement with MR imaging of the brain and CSF analysis. It is not clear that patients with isolated ocular involvement need full-body CT scanning or bone marrow biopsy although a laboratory evaluation, including HIV testing, is recommended even if there are no signs of HIV infection. Nevertheless, some patients with primary intraocular lymphoma do have evidence of systemic involvement, leading one to consider whether a patient has primary ocular lymphoma with systemic involvement or systemic lymphoma with ocular involvement. In general, metastatic systemic lymphoma with ocular involvement, like other metastatic ocular tumors, is usually confined to the uvea, whereas primary ocular lymphoma, as noted above, affects multiple ocular structures. Compared with metastatic systemic lymphomas, primary ocular lymphoma have a much higher prevalence, worse prognosis, and are more likely to create a diagnostic dilemma (523).

Although the optimal treatment has not been established, standard therapy consists of ocular radiation to a level of 36 to 40 Gy. Typically, radiation is administered to both eyes. It is often effective in causing the vitreous cells to regress with improvement in vision. Complications such as radiation

optic neuropathy and retinopathy are considered to be unlikely. Most patients, however, develop cataracts. The limitation of ocular radiation alone is the subsequent incidence of CNS relapse in up to 80% of patients followed over several years. Unfortunately, the best approach to prevent subsequent CNS relapse is unknown. High-dose intravenous methotrexate may be beneficial in a subset of patients as a first-line therapy for primary ocular lymphoma (524).

Recurrent ocular lymphoma is challenging to treat as most patients will have been treated with ocular radiation and may have received systemic chemotherapy as well. Intravitreal chemotherapy with methotrexate and thiotepa has been advocated for such patients (525).

### Burkitt's Lymphoma

**Burkitt's lymphoma** is a remarkable tumor that differs from most other forms of cancer in several ways (526,527). The development of this disease is linked to exposure to a specific virus and, in some instances, to a heritable or familial predisposition that itself is associated with a relatively constant chromosome abnormality.

Burkitt's lymphoma is endemic to Papua, New Guinea and to tropical Africa, particularly the West Nile region of Uganda (528). It is infrequent in high-altitude regions and is most common in densely populated, rural areas of low socioeconomic status. In Uganda, the peak incidence is estimated to be 50–100 per million per year (529).

Sporadic cases of Burkitt's lymphoma occur in addition to endemic cases. In the United States, for example, an estimated 200–300 cases of this tumor occur yearly (530).

One of the factors that appears to contribute to the development of Burkitt's lymphoma, at least in its endemic form, is infection with EBV (18,531–535). Patients with endemic Burkitt's lymphoma always have serologic evidence of past infection with EBV, their titers of anti-EBV antibodies are generally higher than those in control groups, and the EBV genome is expressed from the DNA of Burkitt's cells in 97% of such patients (528,535). In nonendemic Burkitt's lymphoma, however, serologic evidence of previous infection with EBV is often lacking, and the genome EBV is found in the host DNA in 15% of such cases (535). It is clear from these data that EBV plays a role in the development of endemic Burkitt's lymphoma and in some cases of the nonendemic form of the tumor. It must be emphasized, however, that the great majority of persons infected with EBV **do not** develop Burkitt's lymphoma. In addition, the time course of serologic data suggests that when Burkitt's lymphoma does develop, it occurs many years after an initial infection with EBV.

AIDS had a dramatic impact on the incidence of nonendemic Burkitt's lymphoma as well as on other non-Hodgkin's lymphomas (534). Burkitt's lymphoma is 1,000 times more common among patients with AIDS in comparison with the immunocompetent population (536).

Genetic factors as well as viral infection play a role in the development of Burkitt's lymphoma. Specific chromosome abnormalities are present in patients with both the endemic and nonendemic forms of the disease, with translocations being present on chromosomes 2, 8, 14, and 22 in both forms (537). These translocations are observed in direct preparations of Burkitt's lymphoma cells and in cultured Burkitt's cell lines. Indeed, the translocation t(8:14) is present in over 90% of patients with endemic Burkitt's lymphoma (529).

Burkitt's lymphoma is a clearly defined histologic entity (538). Involved lymph nodes typically show a ''starry sky'' pattern that consists of occasional macrophages in a background of lymphoid tumor cells that are relatively uniform in size and shape (Fig. 34.27). The tumor is of B-cell origin. Endemic, sporadic, and AIDS-related Burkitt's lymphoma are histopathologically identical (538).

The clinical presentation of endemic Burkitt's lymphoma is different from that of the nonendemic form. **Endemic** Burkitt's lymphoma is essentially a pediatric disease, with the average age at diagnosis being about 8 years and the majority of patients being 6–9 years old. The disease may appear in even younger children, and rare cases (less than 5%) occur in adolescents and adults. Males predominate by

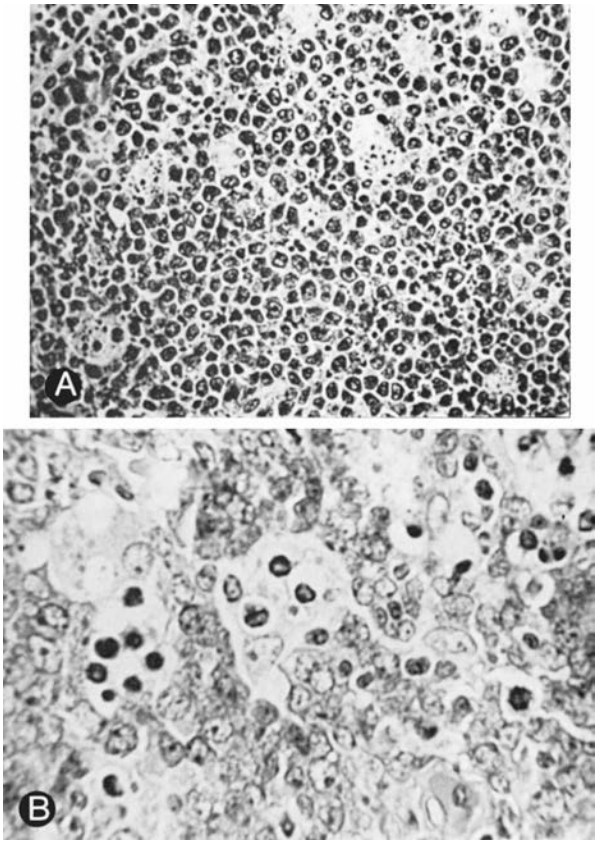



**Figure 34.27.** Histopathologic appearance of Burkitt's lymphoma. *A*, Regularly scattered among the neoplastic lymphocytes are large, pale staining histiocytes, conferring a ''starry sky'' appearance typical of Burkitt's lymphoma. *B*, The neoplastic lymphocytes of Burkitt's lymphoma have a blastic appearance and generally round nuclei. The pale-staining histiocytes are frequently related to pyknotic degenerating cells. (From Jakobiec FA, Font RL. Orbit. In Spencer WH, ed. Ophthalmic Pathology: An Atlas and Textbook. Philadelphia: WB Saunders, 1986:2459–2860.)

a 2:1–3:1 ratio in most series (528,539). The face, primarily the mandible, is the most common site of the disease and is affected in 55–75% of patients. The next most common area of involvement is the abdomen. Orbital and meningeal involvement is not unusual, occurring in about 10–20% of patients. Involvement of peripheral lymph nodes, the testicles, and the bone marrow may occur at some time during the course of the disease, but such involvement is not common in the initial stages. In addition to patients who present with involvement of isolated structures, many patients present with multiple sites of tumor. In fact, about 30–50% of patients with endemic Burkitt's lymphoma have advanced disease at the time of diagnosis (534).

The presentation of the **nonendemic** form of Burkitt's lymphoma that occurs in the United States is different from that of the endemic form. Patients are somewhat older, with a mean age at diagnosis of 12 years. About 25–33% of patients are older than 15 years of age. Although males predominate by a 3:1 ratio among patients younger than 13 years, the sex ratio is equal in older patients (534).

In nonendemic Burkitt's lymphoma, the most common site of involvement is not the mandible but the abdomen (534). Involvement of the head and neck occurs infrequently, as does initial involvement of the CNS. Involvement of bone marrow, pleura, or peripheral lymph nodes is rare. In the AIDS population however, extranodal involvement is common and the CNS is frequently involved (37,536).

Burkitt's lymphoma may damage vision by direct invasion of ocular structures or by its effects on the CNS. In Uganda, it is by far the most common of all orbital tumors, regardless of age (528,540). In such cases, acute or rapidly progressive proptosis is frequently the presenting symptom and the principal clinical feature (Fig. 34.28) (541,542). Other clinical manifestations are related to the infiltration of orbital soft tissue by the tumor and include swelling of the eyelids, conjunctival chemosis, tortuosity of retinal vessels, and corneal anesthesia with subsequent exposure keratitis, corneal ulceration, and panophthalmitis (543–548). In rare instances, the tumor invades the globe itself (543).

Burkitt's lymphoma may affect vision not only by involvement of the orbital and ocular structures but also by involvement of the CNS. As noted above, involvement of the CNS in nonimmunocompromised patients is uncommon, and usually occurs late in the course of the disease. Nevertheless, neurologic symptoms and signs may be the initial presentation of the tumor (549–551).

Newman (552) reported a 58-year-old-man who underwent liver transplantation. Shortly after liver transplantation, a small bowel perforation led to a surgical biopsy and diagnosis of extensive abdominal lymphoid proliferation that resolved with temporary cessation of immunosuppressive therapy. Four years later, while taking prednisone and cyclosporine, the patient complained of right chin pain, right hand weakness, and diplopia. An examination revealed a left trochlear nerve paresis and bilateral oculomotor and abducens nerve pareses. The patient also had a right mental neuropathy, right arm weakness, and absent deep-tendon reflexes. Neuroimaging, CSF analysis, total body CT scan-

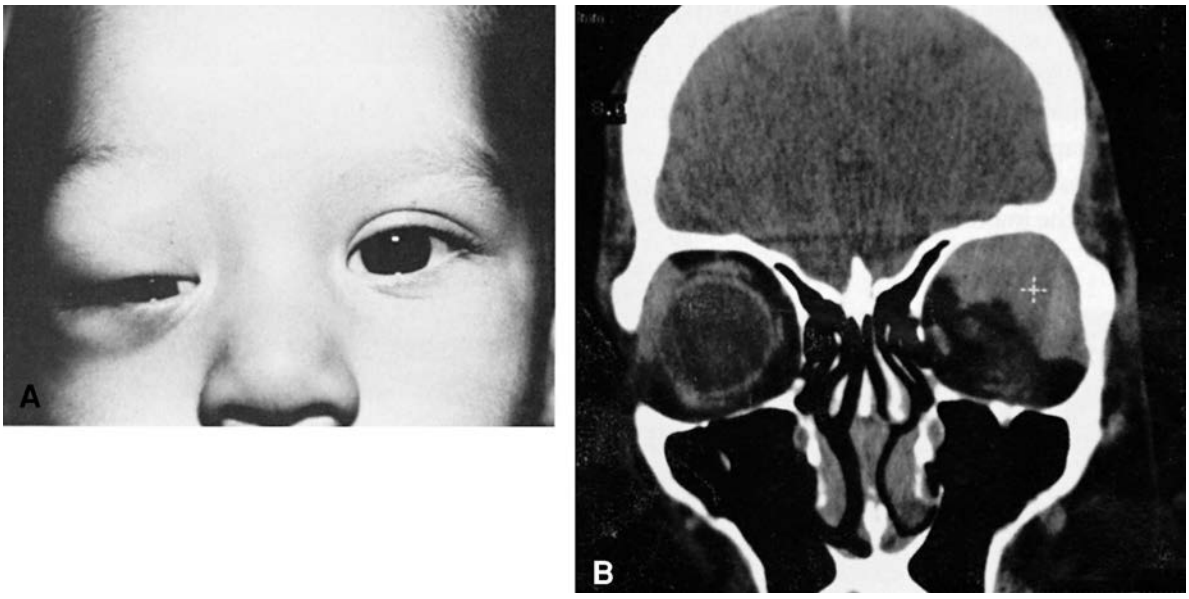



**Figure 34.28.** Clinical and neuroimaging appearance of orbital involvement in nonendemic Burkitt's lymphoma. *A*, Right proptosis with infiltration of the upper and lower eyelids in a patient with North American Burkitt's lymphoma. No associated bone defect was present. The absence of a bone defect is more common in North American Burkitt's lymphoma than in endemic Burkitt's lymphoma. *B*, Coronal computed tomographic scan in another patient with Burkitt's lymphoma shows a diffuse soft tissue mass (+) filling the superior and lateral aspects of the left orbit. Note lack of bony destruction. (*A,* From Jakobiec FA, Font RL. Orbit. In Spencer WH, ed. Ophthalmic Pathology: An Atlas and Textbook. Philadelphia, WB Saunders, 1986:2459–2860. *B,* From Au Eong KG, Choo CT. Burkitt lymphoma manifesting as acute proptosis. Am J Ophthalmol 1997;123:856–858.)

ning, and a paraesophageal biopsy revealed no abnormalities; however, sural nerve biopsy disclosed a lymphoid infiltration of the perivascular endoneurium, and evidence of Burkitt's lymphoma was eventually diagnosed by bone marrow biopsy. The condition responded to intravenous and intrathecal chemotherapy.

Chemotherapy is the primary mode of treatment for patients with Burkitt's lymphoma, regardless of the extent of the disease at the time of diagnosis (528,534,553), and cyclophosphamide is the most common agent used. This drug is given in high doses, either as a single agent or in combination with other drugs. Combination therapy appears to be superior, although the best regimen is not yet determined (554–556). In addition, surgery may play a role in the management of bulky abdominal tumors when at least 90% of the tumor can be removed. Radiation therapy is not of great efficacy as a primary mode of treatment, although patients with CNS involvement are often treated with craniospinal irradiation.

The majority of patients with Burkitt's lymphoma who are treated with chemotherapy, with or without surgery, experience an initial remission of their disease. Unfortunately, many subsequently relapse, usually 1–2 years after beginning therapy. The actual rate of relapse is related to the stage of the disease at diagnosis. The majority of patients in whom the tumor is confined to a single extra-abdominal site are cured, whereas a minority of patients with both intra- and extra-abdominal tumor achieve cure (534,557). The prognosis is extremely poor in patients with AIDS.

As noted above, Burkitt's lymphoma, at least the endemic variety, is one of the few tumors that appears to be directly related to infection with an exogenous agent—EBV. It is conceivable that if a vaccine could be developed against this virus and administered at an early age in endemic areas, the development of Burkitt's lymphoma might be prevented (528,533,534).

## Other Non-Hodgkin's Lymphomas

As noted in the beginning of this chapter, the classification of the lymphomas is complex and evolving. Diffuse large-cell lymphoma and Burkitt's lymphoma were discussed apart from other non-Hodgkin's lymphomas because of their particular affinity for the CNS and visual structures. The other non-Hodgkin's lymphomas and their impact on the nervous and visual systems are reviewed next.

### Etiology

The development of non-Hodgkin's lymphomas is a multi-step process influenced by viruses, genetic factors, immunodeficiency (and immunostimulation), drugs, and exposure to radiation. As discussed in the preceding section, the association of lymphoma and viruses is best studied in the relationship of Burrkitt's lymphoma to EBV. Evidence of EBV infection is also found in some patients with primary CNS non-Hodgkin's lymphoma, Hodgkin's disease, and in lymphomas associated with immunosuppression; i.e., AIDS, organ transplantation, the x-linked immunodeficiency syndrome, and several congenital immunodeficiency states (537,558). Nevertheless, the mechanism by which EBV predisposes patients to these lymphomas is unclear. In AIDS, HIV appears not to cause lymphoma but rather to provide the opportunity for the neoplasm to develop (559–561). Another virus, HTLV-I, can be isolated from patients with atypical cutaneous T-cell lymphoma (562) and also from patients with adult T-cell leukemia/lymphoma (537).

Chromosomal translocations in Burkitt's lymphoma are discussed above. Other chromosomal abnormalities occur in patients with other non-Hodgkin's lymphomas, including follicular (nodular) lymphoma, small lymphocytic lymphoma, and adult T-cell leukemia/lymphoma (419,537,563).

Additional factors that play a role in the pathogenesis of the non-Hodgkin's lymphomas include immunosuppressive agents such as azathioprine and cyclophosphamide, other drugs such as the hydantoins, and exposure to radiation (419,537,564,565).

### General Clinical Features

The non-Hodgkin's lymphomas may present as **nodal** or **extranodal** disease. Presenting symptoms and signs vary somewhat depending on subtype (556,566). In general, however, about 65% of patients present with involvement of the lymph nodes. The most common nodes affected are the cervical nodes (60%), followed in frequency by the inguinal nodes (20%), and the axillary nodes (14%) (398). About 8% of patients have involvement of multiple nodal sites when first examined.

Constitutional symptoms occur in about 20% of patients with the non-Hodgkin's lymphomas (419). These symptoms include malaise, fatigue, weight loss, fever, and sweating. It would appear that, like patients with Hodgkin's disease, patients with non-Hodgkin's lymphoma who experience weight loss, fever, and sweats have a poorer prognosis than do patients who present with asymptomatic involvement of their lymph nodes only (567,568).

Liver and spleen involvement is common in non-Hodgkin's lymphoma. Extranodal disease is more common in intermediate- to high-grade tumors. Sites include the stomach, small bowel, lung, skin, bone, prostate, and CNS. Other organs are less commonly involved, but none is uniformly spared (311,566,569–571).

### Ocular Adnexal Lymphomas

The orbit is an extranodal site for lymphoid tumors, and extranodal sites typically pose special difficulties in staging and pathologic diagnosis of these tumors (419,572). Part of the problem resides in the tendency of some clinicians and pathologists to combine lymphoid tumors—which typically present as slowly growing, insidious masses in older persons—with so-called ''inflammatory pseudotumors'' that are typically associated with moderate to severe pain, conjunctival hyperemia, and dysmotility of the involved eye in both children and adults (350,573). The other part of the problem resides in the cytomorphologic difficulties of cell classification and the limited ability to predict if a given lymphoid lesion will remain restricted to the orbit or

will eventually become part of a systemic disease (350, 574–578).

The most common types of ocular adnexal lymphomas are marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) and follicular lymphomas, occurring in an approximate ratio of 3:1 (579,580). The majority of these tumors represent B-cell proliferations (581). As noted, orbital involvement may occur in the systemic form of diffuse large-cell lymphoma and Burkitt's lymphoma, both of which are considered to be more aggressive tumors.

Non-Hodgkin's lymphomas are staged according to the extent and location of involvement in addition to the presence or absence of systemic symptoms (Table 34.4). Lymphomas that occur in the orbit may be associated with extraorbital lymphoma, or they may be primary tumors that arise in the eyelid, orbital fat, lacrimal gland, or extraocular muscles (350,576,577,582–586). Most ocular adnexal lymphomas are isolated to the orbit and are thus stage IE (579). Presentation with disseminated disease is more frequent with symptoms less than 1 year in duration and bilateral adnexal disease (587).

The clinical characteristics of patients with orbital lymphomas are the same whether the tumor is an extranodal metastasis or a primary growth. The lesion tends to grow slowly and to remain asymptomatic until it becomes manifest as a palpable mass or produces proptosis with or without diplopia and limitation of eye movement (Fig. 34.29*A* and *B*) (588). When the tumor arises in the posterior orbit, it can compress the optic nerve and produce slowly progressive loss of vision (Fig. 34.30) (589). There is rarely any associated pain or redness of the eye.

CT scanning and MR imaging may complement each other in the diagnosis of orbital lymphoma. CT typically demonstrates round, oval, or elongated lobular masses, commonly in the extraconal space, with intraconal extension in large tumors (590). Tumors adjacent to the globe wrap around the eye causing mass effect with displacement rather than indentation of the globe from the mass effect (591). Similar molding occurs along the orbital walls, especially laterally from extraconal lesions. Bone destruction or remodeling of bone is rarely seen in orbital lymphoma. No particular contrast enhancement pattern is diagnostic of lymphoma. The majority of lymphoid tumors are situated anteriorly and superiorly. On MR imaging, they appear as relatively hypointense images, particularly in T1-weighted MR scans (592).

Biospy is performed to establish the diagnosis of orbital lesions and distinguish lymphomas from chronic inflammation, reactive lymphoid hyperplasia, and atypical lymphoid infiltrates. The histologic diagnosis of ocular adnexal lymphoid lesions should be determined by an experienced pathologist who can interpret molecular studies in conjunction with clinical, histological, and immunophenotyping findings. In one study, molecular evidence of clonality was identified in 88% (15 of 17) of lymphomas, 39% (7 of 18) of chronic inflammations, and 50% (4 of 8) of reactive lymphoid hyperplasias and atypical lymphoid infiltrates (581).

When a patient has an orbital mass diagnosed as a lymphoma or lymphoid hyperplasia, the patient should be evaluated for systemic lymphoma. The evaluation should include physical examination, serum protein electrophoresis, antinuclear antibody level, rheumatoid factor, erythrocyte sedimentation rate, complete blood count, bone marrow aspiration, chest CT, abdominal CT, and on occasion, bone scan, and liver/spleen scan. If no evidence of systemic lymphoma is found, the patient's orbital tumor should be treated with radiation therapy. A relatively low dose of radiation (2000–3000 cGy) usually produces complete disappearance of the tumor and resolution of the symptoms and signs, including loss of vision (350,574,575,589,593–595), without significant ocular or orbital morbidity (Fig. 34.29*C* and 34.29*D*) (596). Specifically, the incidence of radiation-induced cataract is extremely low when the cornea and lens are shielded appropriately during treatment (594,597). It appears that a higher dose of radiation produces better local control in patients with MALT lymphomas compared with follicular lymphoma. Dose-response data suggest that the optimal radiation dose for MALT lymphoma of the ocular adnexa is 30.6–32.4 Gy in 1.8-Gy fractions whereas follicular lymphoma is adequately controlled with doses in the mid-20-Gy range (580).

The substantial risk of distant relapse, particularly in stage I ocular adnexal MALT lymphoma, underscores the importance of long-term follow-up for patients with this tumor. Unfortunately, patients whose tumors are thought to have arisen in the orbit and in whom no evidence of systemic lymphoma is found, as well as patients who appear to have polyclonal lymphoid lesions, may develop systemic lymphoma months to years after treatment of an apparently isolated orbital tumor (350,574–577). For stage I MALT lymphoma patients treated with radiation alone, the distant relapse-free survival rate was 75% at 5 years and 45% at 10 years in one study (580). Distant relapses were generally isolated and successfully salvaged by local therapy. The overall survival in this study was 81% at 10 years, with no deaths from lymphoma. In another study of stage I MALT

**Table 34.4**
**Staging of Lymphoma: Ann Arbor Classification***

| Stage | Description |
|---|---|
| I | Involvement of a single lymph node region (I) or of a single extra-lymphatic organ or site (IE) |
| II | Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extra-lymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE) |
| III | Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localized involvement of an extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE) |
| IV | Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement |

* Identification of the presence or absence of symptoms should be noted with each stage designation.
A = asymptomatic; B = fever, sweats, or weight loss greater than 10% of body weight.

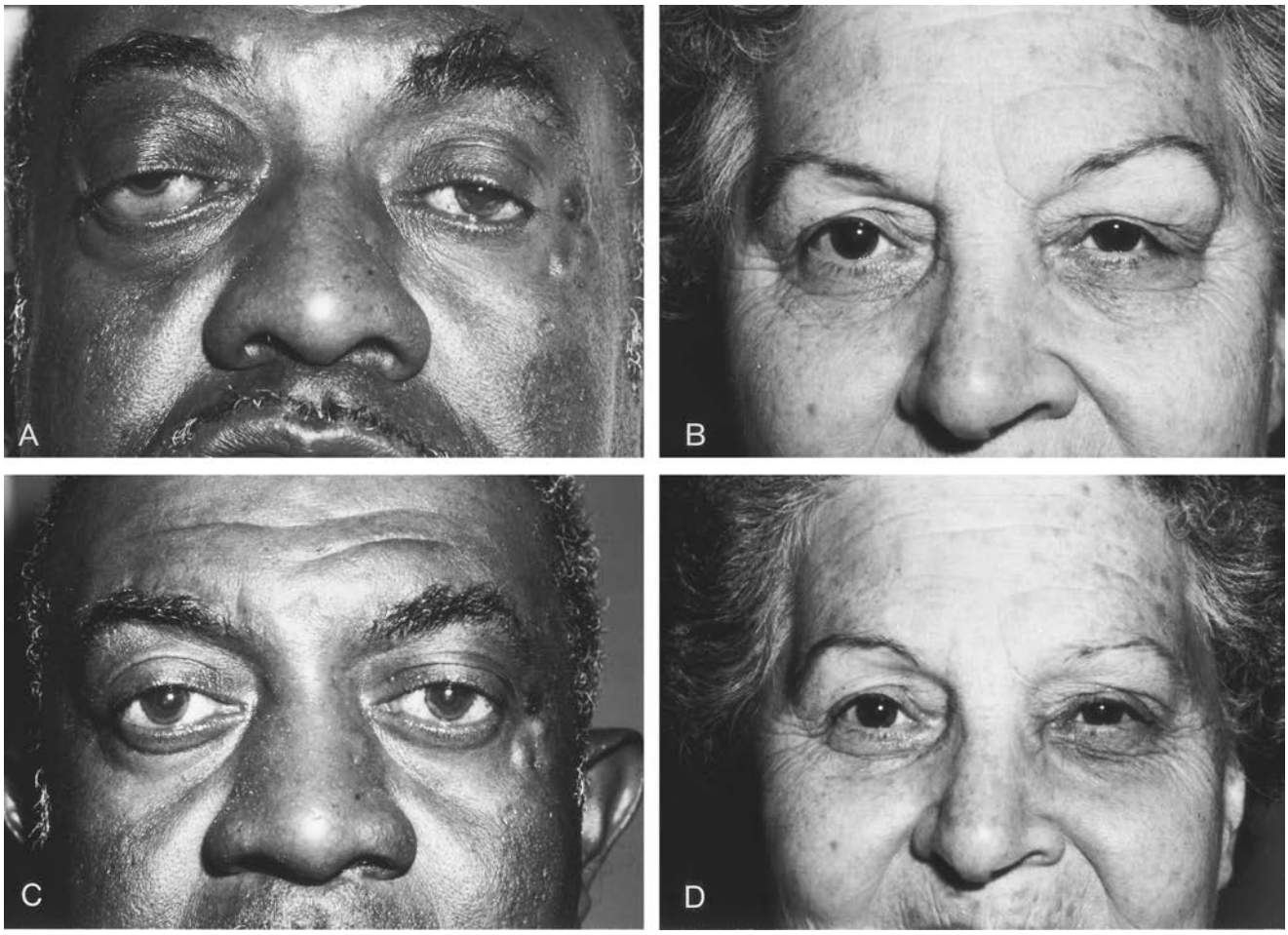



**Figure 34.29.** Primary orbital non-Hodgkin's lymphoma: *A*, In a 63-year-old man with painless proptosis of the right eye and diplopia. *B*, In a 71-year-old woman who noted a mass in the superior temporal region of the left orbit. In both cases, the mass was biopsied and found to represent a lymphoid tumor composed of monoclonal B lymphocytes. Neither patient had evidence of systemic lymphoma. Both patients were therefore given radiation in a dose of 2500 rads to the affected orbit. *C and D*, Appearance of the patients 3 months after finishing radiation therapy. The previously noted tumors are no longer present by either clinical examination or neuroimaging.

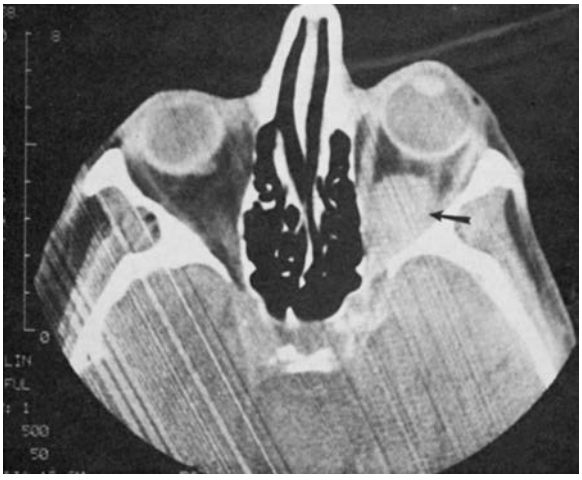


**Figure 34.30.** Neuroimaging appearance of non-Hodgkin's lymphoma of the orbit in an 84-year-old man with progressive left-sided proptosis and visual loss. Axial computed tomographic scan shows a large mass occupying the posterior half of the left orbit and displacing the left optic nerve laterally. (From Moshfeghi DM, Finger PT, Cohen RB, et al. Visual recovery after radiation therapy of orbital lymphoma. Am J Ophthalmol 1992;114:645–646.)

orbital tumors treated with local radiation, the 5-year overall survival rate was 91%, with one death occurring from lymphoma (598).

### Neurological Involvement

As is the case with the diffuse large-cell form of non-Hodgkin's lymphoma, involvement of the brain by other forms of non-Hodgkin's lymphoma may occur as either a secondary (metastatic, paraneoplastic) process or a primary process. Secondary involvement of the CNS occurs in about 10% of cases of systemic non-Hodgkin's lymphoma. It may be leptomeningeal or, less commonly, parenchymal (385,386,389,391,571,599–602). Compression of the spinal cord may also occur in such cases (386,392). Some cases of peripheral and cranial neuropathy appear to be paraneoplastic in origin rather than caused by metastatic tumor (601). Primary involvement of the CNS by non-Hodgkin's lymphoma other than diffuse large-cell and Burkitt's lymphoma occurs more commonly than does secondary involvement, particularly in patients with AIDS (380,428,438,559,603–609). The involvement may be parenchymal, in which case supratentorial tumors are more common than infratentorial ones (435); however, leptomeningeal involvement is not uncommon (434), and T-cell lymphomas usually begin in the leptomeninges (382,608,610–613). The lymphoma may occur as a discrete, well-circumscribed mass with multiple lesions, or as a diffusely infiltrative process (207,386). Most otherwise immunocompetent patients become symptomatic in the sixth and seventh decades of life, whereas patients in the AIDS population tend to be younger. Men are more frequently affected than women.

The neurological symptoms and signs that occur in patients with intracranial lymphomas are related to the location, size, and rate of growth of the tumor. Impairment of intellectual function and alteration of behavior are common, but focal deficits (including cranial neuropathies) also occur (382,437,559,611,614).

### Visual Involvement

Non-Hodgkin's lymphomas other than diffuse large-cell lymphoma and Burkitt's lymphoma may produce visual symptoms by infiltrating the eye or occluding its vessels (615–618) or by infiltrating or compressing the optic nerves, optic chiasm, optic tract, optic radiations, or striate cortex (Figs. 34.31 and 34.32) (609,613,619–623). Other visual symptoms such as diplopia and oscillopsia may result from damage to ocular motor structures in the cerebral hemispheres, brainstem, and cerebellum or from involvement of the ocular motor nerves themselves.

Whether visual symptoms result from involvement of the visual sensory system, the ocular motor system, or both, any

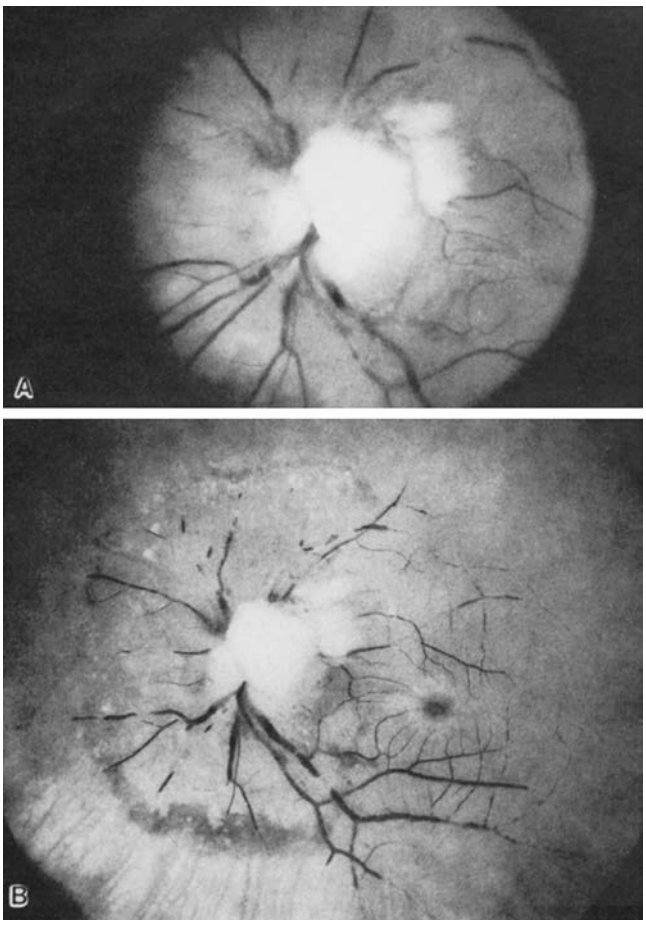



**Figure 34.31.** Anterior ischemic optic neuropathy and retinal vascular occlusions caused by metastasis of non-Hodgkin's lymphoma. Ophthalmoscopic (*A*) and fluorescein angiographic (*B*) appearance of left eye shows marked swelling of the optic disc with a large, yellow-white mass protruding internally, a cherry-red spot in the macula, and peripheral retinal nonperfusion. (From Guyer DR, Green WR, Schachat AP, et al. Bilateral ischemic optic neuropathy and retinal vascular occlusions associated with lymphoma and sepsis: Clinicopathologic correlation. Ophthalmology 1990;97: 882–888.)

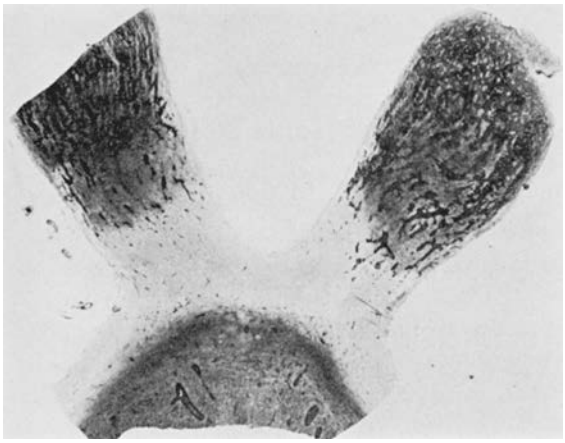


**Figure 34.32.** Infiltration of the optic chiasm and the intracranial portions of both nerves by non-Hodgkin's lymphoma. The patient was a 53-year-old man with systemic non-Hodgkin's lymphoma who lost vision in both eyes and developed bilateral optic atrophy two years before his death. (From Russell DS, Rubinstein LJ. Pathology of Tumors of the Nervous System, Baltimore: Williams & Wilkins, 1977.)

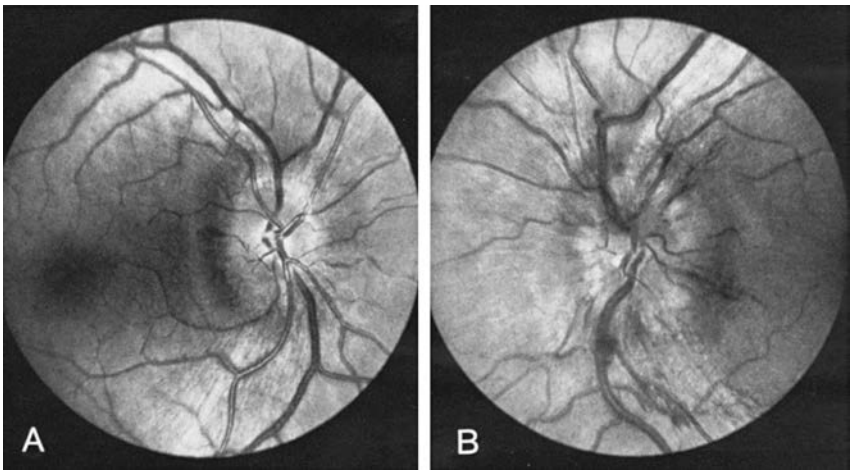



**Figure 34.33.** Bilateral optic neuropathy with optic disc swelling from lymphomatous infiltration of the optic nerves and chiasm in 24-year-old man with systemic non-Hodgkin's lymphoma. *A and B*, Both optic discs are swollen. Visual acuity is 20/20 in both eyes. (From Scarpatetti A, Schmid L, Zollinger U. Infiltrative Optikusneuropathic bei Non-Hodgkin-Lymphom. Klin Monatsbl Augenheilkd 1982;180:146–150.)

associated symptoms or signs are referrable to the site and extent of involvement. When the tumor infiltrates the orbit, for example, other symptoms and signs of orbital disease such as proptosis and chemosis are generally present (148,350). When involvement is intracranial, there may be no associated clinical manifestations, visual deficits related to involvement of adjacent structures, or symptoms and signs that are nonlocalizing or related to involvement of distant neural structures (624,625). Scarpatetti et al. (626) described a patient who was receiving chemotherapy for non-Hodgkin's lymphoma involving the stomach when he developed acute, bilateral loss of vision associated with bilateral optic disc swelling (Fig. 34.33). The patient eventually died from the effects of the disease and was found to have extensive meningeal involvement by the tumor, which also infiltrated both optic nerves, the optic chiasm, and both optic tracts (Fig. 34.34).

## Diagnosis

Non-Hodgkin's lymphoma should be considered in any immunocompromised patient who develops neurologic, ocular, or neuro-ophthalmologic symptoms and signs and in older patients whose neurologic and visual dysfunction is not clearly caused by another disorder. The differential diagnosis of patients with intracranial lymphoma includes a variety of tumors and inflammations. CT scanning, MR imaging, angiography, and examination of the CSF may be helpful in some cases (386,627), whereas in others, the appearance is so nonspecific that the correct diagnosis may not be made

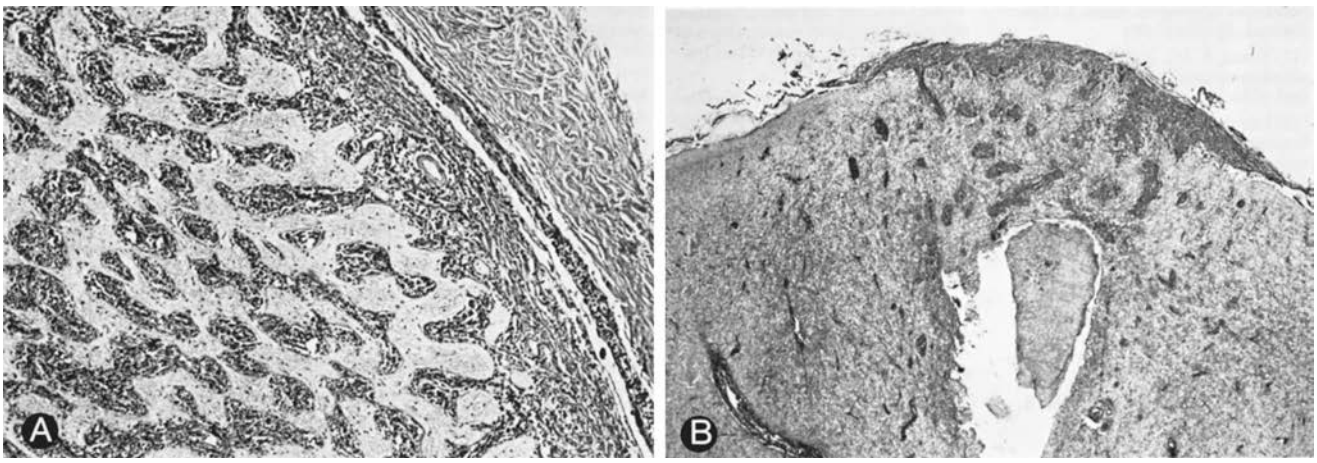



**Figure 34.34.** Infiltration of the anterior visual system by non-Hodgkin's lymphoma. *A*, Cross section of the right optic nerve within the orbit shows lymphoma in the subdural and subarachnoid spaces surrounding the nerve and extensively infiltrating the nerve itself. *B*, Section through the optic chiasm shows extensive lymphomatous meningitis as well as infiltration of the chiasm. (From Scarpatetti A, Schmid L, Zollinger U. Infiltrative Optikusneuropathie bei Non-Hodgkin-Lymphom. Klin Monatsbl Augenheilkd 1982;180:146–150.)

until abnormal tissue is obtained by open or stereotactic biopsy and is examined histopathologically (382,386,497,500, 501,559).

### Treatment and Prognosis

Most patients with non-Hodgkin's lymphoma are, as noted in previous sections of this chapter, treated with radiation therapy, often in combination with chemotherapy and, in some instances, surgery (628–631). As with other forms of lymphoma, however, therapy is rapidly changing as new information is learned about the immunobiology of these tumors and their response to various forms of treatment.

Prognosis in patients with non-Hodgkin's lymphoma is related to the extent and site of the disease, the histology of the tumor, and the age of the patient. Five-year survival rates for patients are quite variable, reflecting the extensive heterogeneity of the non-Hodgkin's lymphomas and their resultant clinical variability (613,631). In general, patients with primary lymphoma involving the CNS and patients with secondary lymphomatous meningitis or neural parenchymal disease have an extremely poor prognosis, as do patients with AIDS (382,390,391,504,508,630). Nevertheless, with improvements in therapy, we anticipate that survival rates will continue to improve for patients with all forms of lymphoma.

## MYCOSIS FUNGOIDES (CUTANEOUS T-CELL LYMPHOMA)

**Mycosis fungoides** is a malignant lymphoma that arises in the skin. It is derived from T-lymphocytes, in contrast to the vast majority of systemic lymphomas that are of B-cell origin (632–634). Three stages in the course of the disease can usually be distinguished: eczematous, infiltrative, and tumor. Although originally considered a malignancy of the skin, the late stages of the disease may affect the organs of the abdomen and chest, the CNS, and the eye (635).

The cause of mycosis fungoides is unknown. Genetic predisposition, environmental toxins, and infectious agents are all possible (636). An increased frequency of histocompatibility antigens is present in some patients with mycosis fungoides, suggesting a genetic predisposition (637,638). Toxic exposure was once considered a factor, but subsequent case-control studies did not support this hypothesis (636,639).

Mycosis fungoides is more common in men than in women. Most patients are between 45 and 70 years of age at diagnosis, but the disease may occur at any age, even in childhood.

Histopathologically, mycosis fungoides is characterized by three distinctive features. First, there is a band-like cellular infiltrate of atypical lymphoid cells that primarily involve the upper third of the dermis and are often in contact with the basement membrane of the epidermis (Fig. 34.35). These tumor cells may extend along blood vessels, nerves, and glands. Second, there are clusters of atypical lymphoid cells within the epidermis. These cellular clusters are often called **Pautrier's microabscesses**. Third, in addition to atypical lymphoid cells, lymphoid cells with large, irregular, and deeply indented nuclei are often present. These cells are called by a variety of names, including mycosis cells, cerebriform cells, and Sézary cells. In fact, they are helper T-cells that probably originate in the dermis or, in some cases, in the lymph nodes (633,638,640). Immunophenotypic studies may be performed when histopathology is not sufficient to establish the diagnosis (538).

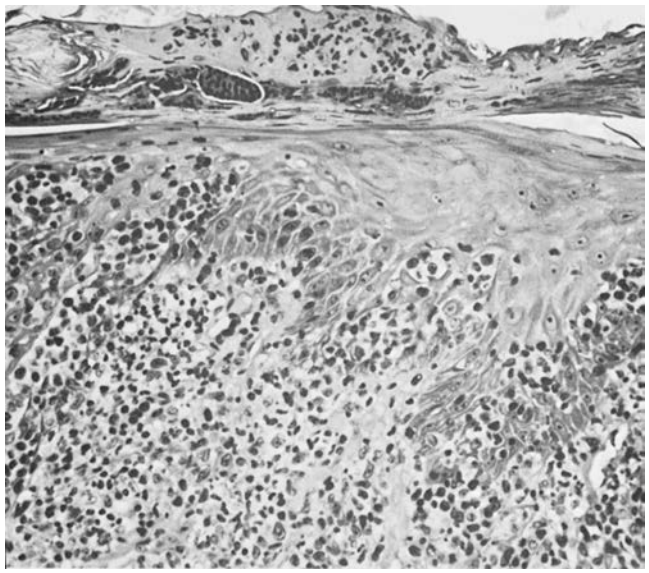


**Figure 34.35.** Mycosis fungoides of the eyelid. The upper dermis and epidermis are infiltrated by large, atypical mononuclear cells (''mycosis cells'') that exhibit hyperchromatic convoluted nuclei. Several Pautrier abscesses are present. (From Font RL. Eyelids and lacrimal drainage system. In Spencer WH, ed. Ophthalmic Pathology: An Atlas and Textbook. Philadelphia: WB Saunders, 1986;2141–2336.)

Mycosis fungoides produces a wide variety of dermatologic patterns (633). It may appear clinically as a persistent or intermittent, widespread, pruritic dermatitis that may be confused initially with psoriasis. In the late stages, extracutaneous dissemination may occur (638,641).

The CNS is affected in 11–14% of patients with mycosis fungoides (635,642,643). The meninges may be infiltrated, or there may be intraparenchymal extension from the perivascular spaces with formation of tumor nodules (644). In almost all cases, the diagnosis is known at the time neurologic symptoms and signs develop; however, the time from diagnosis to development of neurologic dysfunction varies greatly. Hallahan et al. (643) reviewed the records of nine patients with mycosis fungoides who developed evidence of damage to the CNS. The authors found that the interval from diagnosis of the condition to development of neurological symptoms and signs ranged from 6 months to 19 years, with an average of 5.3 years. Other investigators describe an interval of about 3 years from initial diagnosis to the onset of neurological dysfunction (635).

There is no characteristic pattern of neurological dysfunction. Both focal and nonlocalizing signs can develop, including signs of increased ICP. The presenting symptoms of the nine patients described by Hallahan and colleagues (643) included lethargy and somnolence, confusion, visual halluci-

nations, hoarseness, ataxia, diplopia, blurred vision, and leg weakness. Signs included lower cranial neuropathies, anisocoria, and oculomotor nerve paresis. Two patients eventually developed hemiparesis, one patient experienced seizures, and one patient became blind.

The diagnosis of mycosis fungoides affecting the CNS should be suspected when a patient with cutaneous manifestations of the disease develops neurological symptoms and signs. In most cases, neuroimaging studies are abnormal, and the CSF contains an elevated protein concentration and mycosis cells.

Mycosis fungoides may also involve every part of the eye and adnexa. The eyelid may be involved leading to ectropion (645). Orbital metastases may produce proptosis, diplopia, visual loss, or a combination of these manifestations (646). Clinical and histological involvement of the sclera, cornea, conjunctiva, anterior chamber, iris, ciliary body, choroid, retina, vitreous, and optic nerve have been reported (646–651). Optic disc swelling may thus result not only from CNS involvement and subsequent increased ICP but also from infiltration of the optic nerve by the tumor.

The therapy for mycosis fungoides depends on the extent of the disease, and, therefore, staging is important (632,638). For early mycosis fungoides, limited in surface area and without tumors, ulcers, or known extracutaneous disease, topical therapy is likely to provide long-term control of the disease. If topical treatment fails, and the disease is still solely cutaneous, electron-beam irradiation is appropriate and is associated with an extremely high complete response rate (638,652,653).

For mycosis fungoides extensive in surface area but without tumors, ulcers, or extracutaneous disease, total body electron-beam therapy is appropriate, with topical therapy added as needed for less responsive areas (638,652,653). Orthovoltage radiation may be given to specific problem areas where tumors are present.

Tumors, palpable lymphadenopathy, ulcers, visceral tumor involvement, or constitutional symptoms are associated with a poor prognosis and thus warrant consideration of systemic chemotherapy (638,652,653). As a general rule, chemotherapy using a single agent is given to patients who are elderly or very ill, whereas combination chemotherapy may be appropriate for patients in better general health. Agents including interferons, interleukin-2, monoclonal antibodies, and retinoids have also been employed with variable success (653).

Early aggressive therapy may improve the prognosis in this usually fatal disease. In a pivotal randomized controlled trial, patients with mycosis fungoides were randomly assigned to receive either combination therapy, consisting of 30 Gy of electron-beam radiation to the skin combined with parenteral chemotherapy with cyclophosphamide, doxorubicin, etoposide, and vincristine or sequential topical treatment (654). The complete response rate was higher in the chemotherapy group but morbidity was greater and, critically, there was no significant difference in disease-free or overall survival between the two groups. This study provides a rationale for the management of mycosis fungoides that is based on a skin-directed palliative approach that varies according to the stage of the disease. As in all cases of lymphoma, however, the specific therapy used to treat mycosis fungoides is constantly changing and should be based on the most currently available information.

## MULTIPLE MYELOMA, PLASMACYTOMAS, AND RELATED DISORDERS (MONOCLONAL GAMMOPATHIES)

Multiple myeloma and its variants, Waldenström's macroglobulinemia, the heavy chain diseases (HCDs), and the primary and myeloma/macroglobulinemia forms of generalized (systemic) amyloidosis, share two major features. The first is an uncontrolled proliferation of the B-lymphocyte/plasma cell series, and the second is the production of an excessive amount of homogenous immunoglobulin (Ig) or subunit by these cells. The type of protein produced serves as a convenient way to classify these disorders (e.g., IgG, IgA, IgD, IgE, or IgM myeloma) often are called **monoclonal gammopathies** (655).

### MULTIPLE MYELOMA AND PLASMACYTOMAS

As noted earlier, the predominant tumor cell in patients with **multiple myeloma** is a bone marrow-based, B-cell derived, plasma cell (656,657). Patients with multiple myeloma may develop symptoms and signs from the direct effects of the proliferation of these cells within the bone marrow, from the effects of substances secreted by these cells, from infiltration by these cells of soft tissues including the brain parenchyma (which, in turn, produces masses of tumor cells called **plasmacytomas**), and from secondary metabolic and immunologic effects of the disease.

#### General Considerations

Multiple myeloma accounts for 1% of malignant neoplasms in the United States (658). It is more common in men than in women, and its incidence increases with age (659,660). Peak rates are found in the 70- to 80-year-old group, with a mean age at diagnosis of 62 years (660,661). Multiple myeloma has a distinct racial distribution. It is the most common hematologic malignancy in African-Americans, occurring twice as frequently as in Caucasians (660,662).

#### Etiology

The three major causes that are usually implicated in the development of multiple myeloma are genetic factors, exposure to radiation, and antigenic stimulation.

Familial multiple myeloma is well documented. The majority of patients in the reported families are siblings, suggesting genetic rather than environmental factors (130,660). Genetic marker studies seem to support this view (663–665).

An excessive incidence of multiple myeloma occurs in persons exposed to ionizing radiation, including survivors of atomic bomb explosions and painters of radium dials

(666–669). In contrast to the experience with radiation-induced acute leukemia, in which an increased incidence occurs 2–15 years after exposure, the increase in the incidence of multiple myeloma occurs 10–30 years after exposure. The role of environmental toxins and occupational exposure is not established (660).

Multiple myeloma may be preceded by nonmalignant medical conditions. Research has focused on monoclonal gammopathy of undetermined significance (MGUS), a condition characterized by monoclonal (M) proteins without evidence of plasma cell malignancy (660,670,671). Malignant transformation of MGUS may be related to genetic mutations or to alterations of certain growth factors, including interleukin-6 (660,670,671). Another hypothesis suggests that chronic antigenic stimulation of the immune system, as occurs in chronic infections or autoimmune disorders, may lead to multiple myeloma. There is, however, insufficient evidence to support this theory (662).

### General Features

Patients with multiple myeloma usually present with weakness, bone pain, or symptoms of renal failure (657). Such patients usually have lytic lesions of bone, azotemia, and hypercalcemia (655,659,671). Other frequent abnormalities are hypoalbuminemia, a low anion gap, hyperuricemia, anemia, and osteoporosis.

The diagnosis of multiple myeloma depends on the demonstration of plasmacytosis in the bone marrow by electrophoretic techniques in over 99% of cases (659,670–672); 50% of patients with multiple myeloma have an M spike only in the serum, 30% have the spike in both serum and urine, and 20% have the M spike only in their urine (673).

At the time of diagnosis, 60% of patients with multiple myeloma have lytic bone lesions, and another 20% have osteoporosis, pathologic fractures, or both (671). Mundy and coworkers (674,675) showed that myeloma plasma cells produce an **osteoclast activating factor** (OAF) that stimulates osteoclastic bone resorption. Bone marrow biopsies show masses of osteoclasts adjacent to areas of heavy myelomatous infiltration.

Renal dysfunction complicates the course of multiple myeloma in about 50% of patients (676) and is the second most frequent cause of death (infection is the most common). Renal disease may become manifest as acute renal failure or as chronic progressive loss of renal function. Although many complications of multiple myeloma contribute to renal injury, including hypercalcemia, hyperuricemia, hyperviscosity, infection, and amyloidosis, the most important factor is free light chain (Bence Jones) proteinuria. Patients with Bence Jones proteinuria are much more likely to develop decreased creatinine clearance, and, in fact, there is an inverse correlation between the level of Bence Jones proteinuria and creatinine clearance (676).

Patients with multiple myeloma are particularly susceptible to infection (659,677). This susceptibility results from the many abnormalities in the normal host defense mechanism in these patients. Patients with multiple myeloma have decreased serum IgG and an impaired antibody response to many antigens. The granulocytopenic effects of chemotherapy and the immunosuppressive effects of systemic corticosteroids also contribute to the increased susceptibility to infection in these patients. Infectious complications are the major cause of death in patients with multiple myeloma (659,677,678).

### Neurological Complications

Neurological complications of multiple myeloma are common, occurring in about 40% of cases (37,679–684). In some cases, the patient is known to have multiple myeloma at the time that neurological symptoms develop. In other cases, however, these symptoms are the first manifestation of the disease or are the symptoms that eventually lead to its diagnosis. In addition, there are some patients in whom a solitary plasmacytoma occurs intracranially without any clinical, imaging, or laboratory evidence of multiple myeloma elsewhere in the body (685). It is unclear if such patients actually have multiple myeloma that simply is not extensive enough to be detected at the time the intracranial lesion becomes manifest or if the plasmacytoma is a truly isolated tumor unassociated with a systemic disorder as is the case with primary CNS Hodgkin's disease and non-Hodgkin's lymphoma (686).

Neurological dysfunction in patients with multiple myeloma may be caused by compression of neural tissue by single or multiple tumors or by displaced bone; meningeal dissemination with infiltration of neural tissue by tumor cells; systemic complications of the disease (e.g., metabolic or hematologic disturbances, infection); and complications of therapy for multiple myeloma rather than from the disease itself.

The neural structure most susceptible to compression is the spinal cord (678,679,687). Compression of the spinal cord may occur from an extradural plasmacytoma that originates within one or more of the vertebral bodies or in the epidural space. Compression may also occur from the effects of a plasmacytoma within the subdural or subarachnoid space. Neural structures other than the spinal cord may be compressed by myeloma cells or adjacent, diseased bone. These structures include the spinal nerve roots, the cranial nerves, and the brain parenchyma.

When spinal nerve roots are compressed, patients develop a radiculopathy that may be characterized by motor signs, sensory changes, and abolition of deep-tendon reflexes. Not all cases of polyneuropathy are associated with evidence of nerve root compression, however. Some appear to be paraneoplastic, i.e., related to a secondary or distant effect of the myeloma (688).

Cranial neuropathy occurs less frequently in patients with multiple myeloma than does spinal cord or nerve root compression. Nevertheless, almost any cranial nerve may be affected, either in isolation or in combination with other cranial nerves. In some cases, there is associated lethargy and a generalized decrease in the level of consciousness from diffuse meningeal involvement by myeloma cells (Fig. 34.36) (689).

Intracranial plasmacytomas, either in the setting of multi-

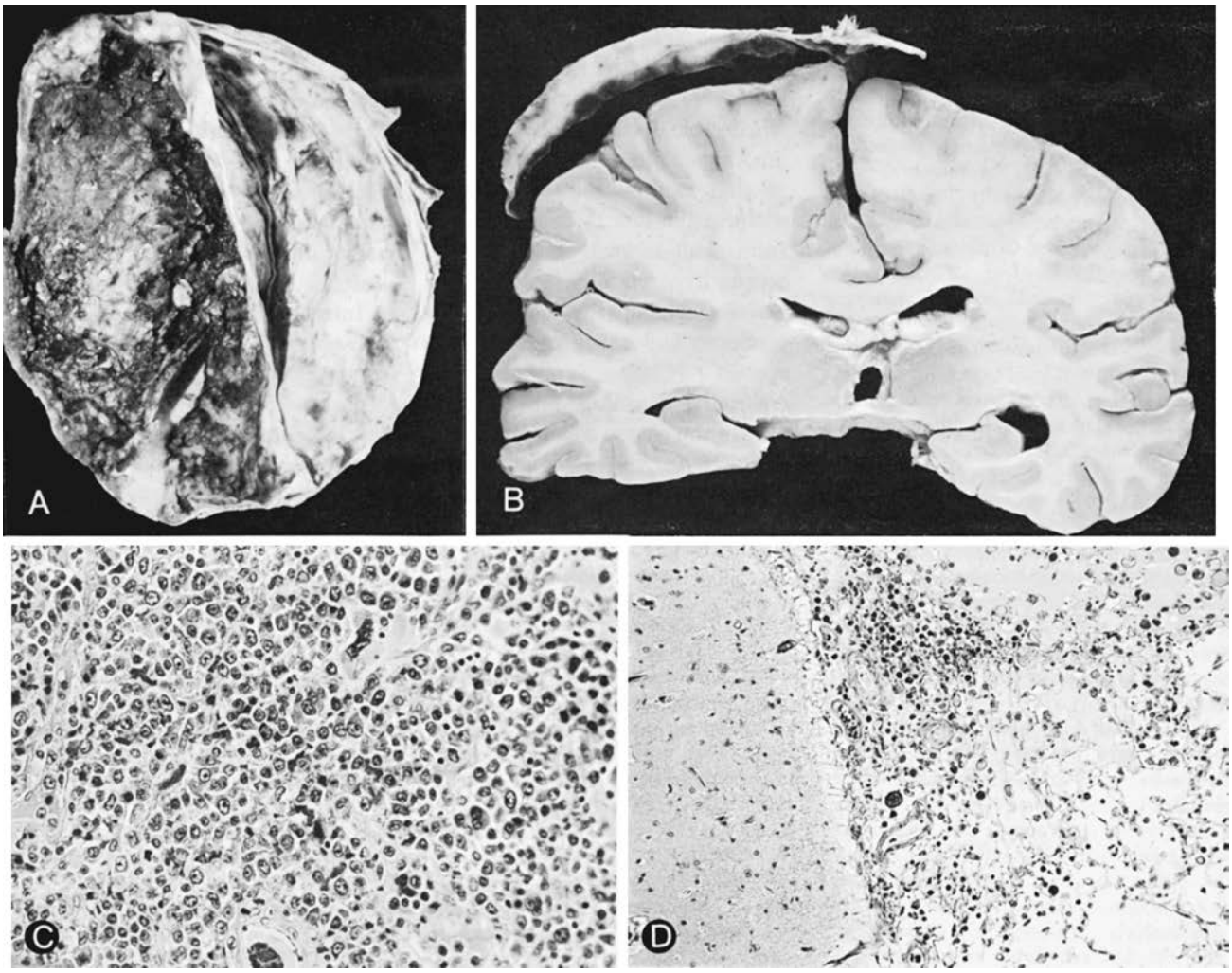



**Figure 34.36.** Meningeal involvement in multiple myeloma. A 40-year-old woman had been diagnosed as having multiple myeloma 5 months before becoming progressively lethargic. On examination, she was found to have bilateral papilledema. Despite treatment, she died 3 weeks after onset of neurologic symptoms. *A*, There is diffuse thickening of the cranial dura over the dorsal and lateral aspects of the left cerebral hemisphere produced by meningeal infiltration by myeloma cells which cover the entire left convexity. *B*, Cross section of cerebral hemispheres at the level of the posterior thalamus with piece of dura over left convexity. There is compression of the left cerebral hemisphere with edema of underlying white matter, compression of the left lateral ventricle, shift of midline structures to the right, subfalcine cingulate gyral herniation, and transtentorial herniation of the left uncus. *C*, Histopathologic appearance of dural infiltration shows numerous, pleomorphic myeloma cells. *D*, Subarachnoid space overlying left parietal cortex contains scattered myeloma cells, macrophages, and proteinaceous fluid. (From Maldonado JE, Kyle RA, Ludwig J, et al. Meningeal myeloma. Arch Intern Med 1970;126:660–663.)

ple myeloma or as isolated lesions in patients with no systemic evidence of multiple myeloma, may produce a variety of focal neurologic signs from compression of adjacent brain tissue (276,690), or they may cause increased ICP from a generalized mass effect or from obstruction of the dural venous sinuses (691–693). In most cases, the brain is involved by extension of the tumor from the calvarium, the dura overlying the cerebral and cerebellar hemispheres, or the falx cerebri; however, in rare instances, there are solitary or multiple plasmacytomas that have no osseous or dural component (207,686,694–696). It is in such cases that systemic evidence of multiple myeloma is least likely to be found, and treatment is usually directed toward surgical removal of the lesions followed by radiation therapy (693). Multiple myeloma may infiltrate neural tissue as well as compress it (37). This is particularly true with regard to cranial neuropathies (697); however, infiltration without evidence of a mass lesion may also occur in brain parenchyma (687).

The paraproteinemia that occurs in patients with multiple myeloma causes increased viscosity of the blood, uremia, hypercalcemia, and hemorrhage. Amyloidosis may also develop. These abnormalities in turn may produce neurological symptoms and signs (698). Camacho et al. (679) described acute organic mental changes in 6 of 110 patients with multi-

ple myeloma but without evidence of increased ICP or intracranial plasmacytoma. All six patients had serum calcium greater than 12 mg/dL, and in two patients, there was also hyperviscosity of the serum. All of these patients were treated with saline infusion, furosemide, and corticosteroids, and all experienced resolution of their mental difficulties.

Between 3–13% of patients with multiple myeloma develop a peripheral neuropathy which may be sensory, motor, or mixed sensorimotor type (37,679,699–701). When it is purely sensory, patients complain of numbness, pain, or both; when it is purely motor, it is characterized by slowly progressive, painless weakness of the extremities. Patients with the mixed sensorimotor type of peripheral neuropathy experience slowly progressive distal numbness, hypesthesia, and weakness, usually affecting the legs more than the arms. Nerve conduction studies are abnormal in all cases, regardless of the type of peripheral neuropathy. In some cases, the peripheral neuropathy is related to systemic amyloidosis or a ''sclerotic'' form of multiple myeloma (699); however, in most cases there is no evidence of either compression or infiltration of the involved neural tissue nor is there any evidence that the process is related to the metabolic or hematologic effects of the disease. It may be present before the diagnosis of multiple myeloma, and its course is usually independent of the course of the myeloma. The neuropathy thus bears close resemblance to the ''carcinomatous neuropathies'' that occur as paraneoplastic phenomena associated with certain types of systemic malignancies and are thought to be autoimmune in origin (688). Indeed, in about 40% of patients with peripheral neuropathy associated with multiple myeloma or one of the other monoclonal gammopathies, IgM reacts with myelin (686,702–705) or with the intermediate filament **vimentin** that is found in high concentrations in Schwann cells (702). Finally, the therapy of multiple myeloma may also produce neurologic dysfunction.

As noted above, infection is common in patients with multiple myeloma. It is usually a consequence of the hypogammaglobulinemia that occurs in association with the disease and the effects of immunosuppressive therapy (37, 706–708). Infections affecting the CNS are rare compared with pulmonary and urinary tract infections in patients with multiple myeloma. Nevertheless, bacterial meningitis caused by both Gram-positive and Gram-negative organisms (709), herpes zoster encephalitis (678,710), and cerebral toxoplasmosis (711) are all regularly described as infectious complications in patients with multiple myeloma.

## Visual Complications

Multiple myeloma and plasmacytomas may produce visual difficulties directly or indirectly through effects on the intracranial, intraorbital, and intraocular portions of the visual sensory and motor systems.

### Visual Sensory Dysfunction

Patients with multiple myeloma as well as those with a solitary plasmacytoma may experience visual sensory dysfunction from damage to the pre- or postgeniculate visual sensory pathways (712,713). The loss of vision is usually slowly progressive but may be sudden. In patients with multiple myeloma, the diagnosis may be known at the time visual loss occurs, or the visual loss may be the first sign of the disease. In patients with a solitary plasmacytoma compressing the optic nerve, the diagnosis usually is not made until the lesion is biopsied (Fig. 34.37). Not all patients who develop optic neuropathy in association with multiple myeloma do so from compression of the optic nerve. Gudas (697) described a 42-year-old man with multiple myeloma who experienced a progressive retrobulbar optic neuropathy and who eventually died of bronchopneumonia. At autopsy, the right optic nerve was found to be swollen from infiltration with myeloma cells (Fig. 34.38). There was no evidence of an extraneural plasmacytoma. Indirect demyelination of the optic nerve also occurs in patients with multiple myeloma. Cox and colleagues (714) reported a patient with IgA-lambda myeloma who developed painless progressive bilateral optic neuropathies over 1 year. Visual loss recovered spontaneously over 2 months. The authors suggested that the optic nerves were affected by the binding of IgA to myelin.

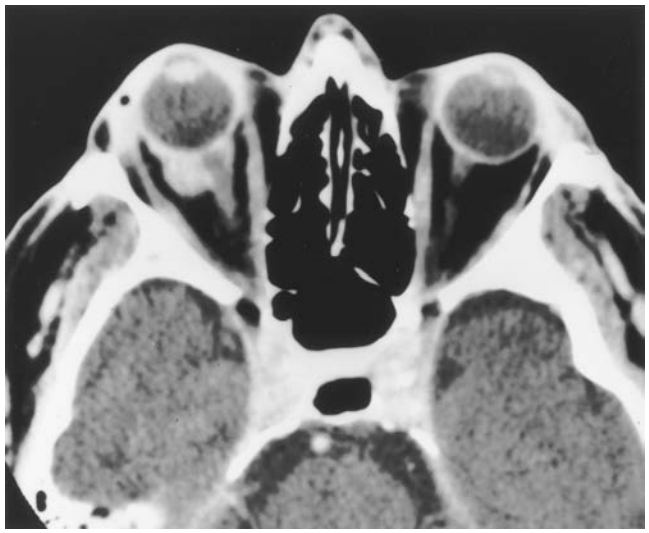


**Figure 34.37.** Computed tomographic scan, axial view, shows a soft tissue mass adherent to the right globe and surrounding the optic nerve in a 66-year-old man with a 4-year history of ocular ''inflammation'' and mild visual impairment. The lesion was biopsied and found to be a plasmacytoma. Systemic evaluation revealed no evidence of multiple myeloma.

An optic chiasmal syndrome may be produced by a plasmacytoma that mimics a pituitary adenoma. Homonymous field defects in patients with multiple myeloma may result from compression or infiltration of the postchiasmal visual sensory pathways by myeloma cells, from secondary effects of the disease (e.g., infarction of the occipital lobe), or from infectious complications of the disease, its therapy, or both (e.g., intracranial abscess formation).

### Ocular Motor Dysfunction

Because of its proximity to the base of the skull and its long extradural course, the abducens nerve is the cranial

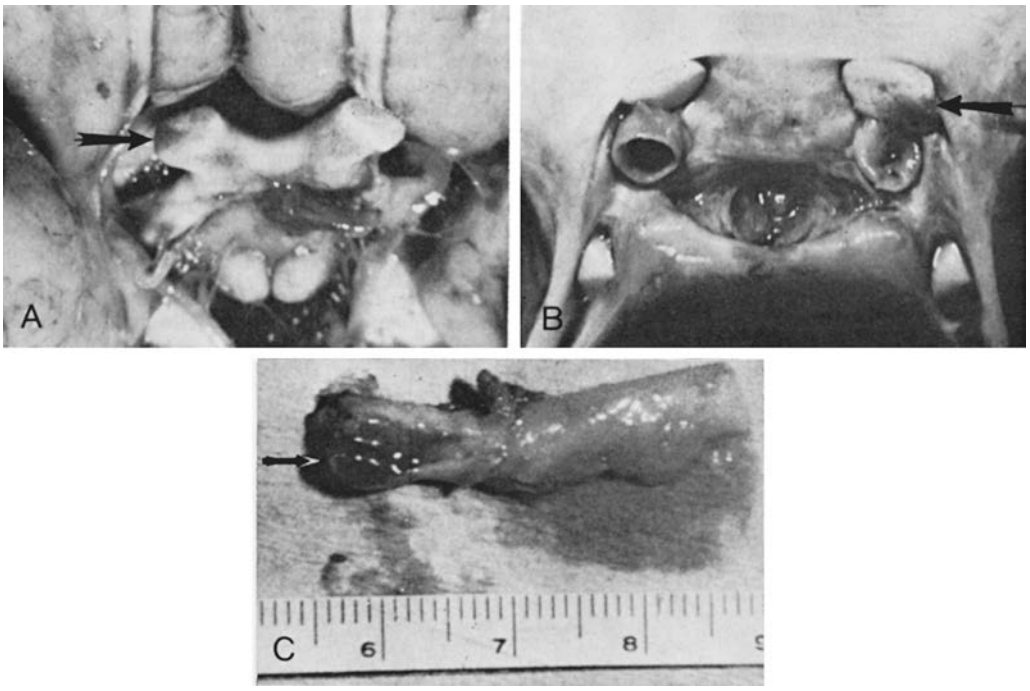



**Figure 34.38.** Infiltration of intracranial portion of the right optic nerve by multiple myeloma in a 42-year-old man who was not known to have the disease when he developed painful swelling under the right eye followed by blurred vision in the eye. The patient eventually lost all vision in the right eye and ultimately died from pneumonia. At autopsy, he had systemic involvement by multiple myeloma. *A*, View of base of the brain shows normal optic chiasm and sector infiltration of right optic nerve by myeloma cells (*arrow*). *B*, Appearance of base of skull shows normal left optic nerve. Right optic nerve shows sector infiltration by myeloma (*arrow*). *C*, Section of optic nerve between optic chiasm and globe shows extensive swelling from diffuse infiltration by myeloma cells. *Arrow* indicates intracranial end of cut nerve. (From Gudas PP Jr. Optic nerve myeloma. Am J Ophthalmol 1971;71:1085–1089.)

nerve most commonly affected by multiple myeloma, and it is also commonly involved by plasmacytomas located at the base of the skull. The dysfunction may be unilateral or bilateral (Fig. 34.39). It may be isolated (715–718), or it may occur in association with other cranial neuropathies (690,719–721), including optic neuropathy (712,714). Clarke found that in 25 cases of cranial neuropathy from multiple myeloma, the abducens nerve was affected in 15 (60%) (722). Cranial nerves other than the abducens nerve, including the vestibulocochlear and trigeminal nerves and the other ocular motor nerves, can be damaged by multiple myeloma and plasmacytomas. As with abducens nerve paresis, paresis of the oculomotor or trochlear nerves that occurs in these settings can be isolated or associated with other neurological abnormalities (334,679,690,716,723–726). The paresis may be the first sign of the disease, or it may occur late in the course of the disease. Rare cases of ocular motor nerve paresis are bilateral, thus mimicking an intrinsic brainstem process (727), but most are unilateral.

### Orbital Involvement

Patients with multiple myeloma may develop signs of an orbital process as the result of their myeloma. Such patients may present with proptosis, diplopia, visual loss, or a combination of these manifestations (728,729). Eye, brow, or orbit pain may be a prominent complaint, although this is by no means always the case. Some of these patients have multiple myeloma at the time their orbital symptoms and signs develop, but in most, the orbital process is the first sign of the disorder (196,730–735). In these patients, myeloma cells usually infiltrate orbital soft tissue. The infiltration is often diffuse, affecting all of the tissues in the orbit, including fat, extraocular muscles, and lacrimal gland (736), but it also may be limited, presenting as focal enlargement of the lacrimal gland (737) or as a well-defined mass (738). Orbital involvement is usually unilateral, but it may be bilateral (735,738,739). In rare cases, the orbital disease is not caused by infiltration by myeloma cells per se but by amyloidosis, which may occur in patients with multiple myeloma and is usually homologous with portions of the immunoglobulin light chains that are produced in abundance as a consequence of the disease (740–742).

As is the case with intracranial disease, some patients have a solitary plasmacytoma within the orbit unassociated with any systemic evidence of multiple myeloma (Fig. 34.37) (743–749). It is important to remember, however, that although such patients may have no evidence of systemic multiple myeloma at the time that the orbital lesion becomes apparent, only long-term observation can truly establish if the lesion is a benign, localized collection of

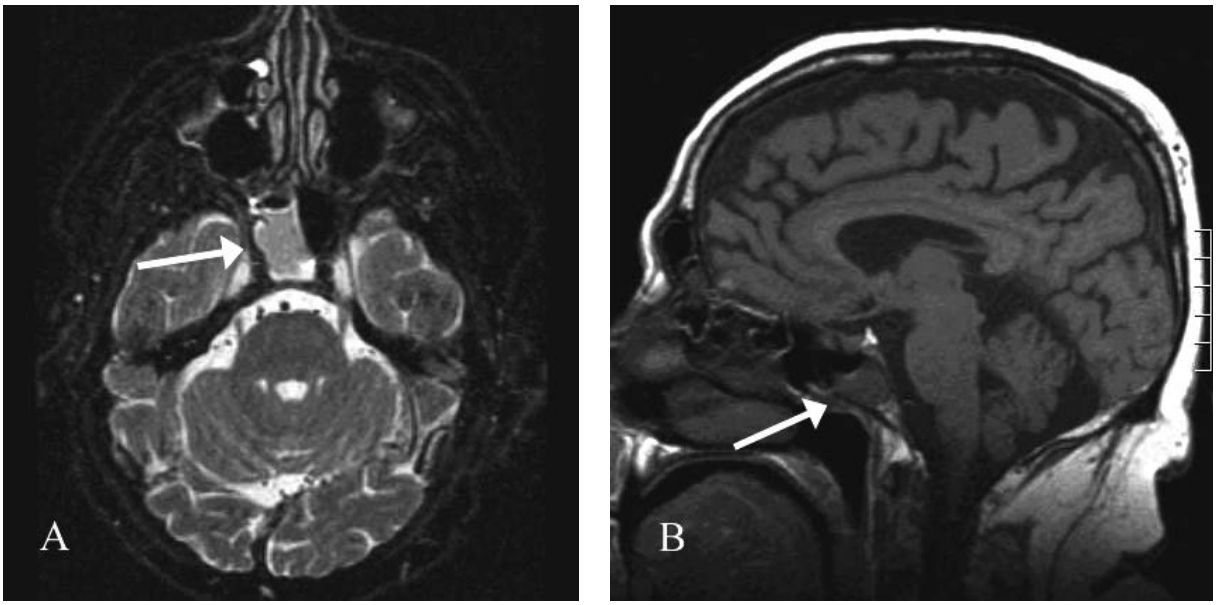



**Figure 34.39.** The clivus is infiltrated by a tumor in this 61-year-old man with multiple myeloma and a history of bacterial meningitis who presents with recurrent diplopia from a right 6th nerve palsy and decreased sensation of his right lower lip, gingiva, and chin from involvement of branches of the mandibular nerve. T2-weighted coronal (*A*) and T1-weighted sagittal (*B*) magnetic resonance images demonstrate tumor (*arrows*) involvement of the clivus and sphenoid. (Courtesy of Neil R. Miller and Kevin C. Lee.)

plasma cells or an early manifestation of systemic multiple myeloma (350).

### Ocular Involvement

The eye itself may be affected by multiple myeloma (750,751). Intraocular findings appear to result from direct invasion of ocular tissue by myeloma cells or from the effects of hyperviscosity (752,753). Infiltration of the eye by tumor cells is probably the less common mechanism (751,754,755).

Cysts of the ciliary body occur with increased frequency in patients with multiple myeloma (756–758). The cysts are said to occur in 33–50% of eyes studied histologically from patients with multiple myeloma (759). The cysts usually appear clear in vivo but become opaque after fixation in formaldehyde solution.

Aronson and Shaw described clusters of fine crystals in the conjunctiva and in the stroma of both corneas of a patient who subsequently was shown to have multiple myeloma (760). These authors suggested that the crystals were caused by deposition of myeloma protein in the corneas. Similar crystals were described by other authors in other patients with multiple myeloma (761–763). The development of the crystals can precede systemic evidence of multiple myeloma by several years (267).

Lewis et al. (764) reported the deposition of copper in both corneas at the level of Descemet's membrane in a patient with multiple myeloma and secondary hypercupremia. Copper was also deposited in the anterior and posterior capsule of the patient's lenses.

Patients with multiple myeloma often have retinal vascular abnormalities that appear to be related not to infiltration of the eye by myeloma cells but to the hyperviscosity that accompanies the systemic disease. The increased viscosity leads to reduction in blood flow in the retina and secondary ischemia. In the early stage of the disease, the main changes are in the veins, which become dilated and somewhat tortuous. As the process progresses, these vessels show segmentation with sausage-like dilations and constrictions. Progression produces intraretinal hemorrhage, exudation, and microinfarcts (cotton-wool spots). Eventually, the patient may suffer a branch retinal vein occlusion or a CRVO that may be unilateral or bilateral. Rarely, retinal findings presage the diagnosis of multiple myeloma (765,766). Histopathologic studies of patients with retinopathy in the setting of multiple myeloma demonstrate a variety of abnormalities, including dilation and occlusion of retinal veins, retinal hemorrhages, exudates, microaneurysms, microthrombi in small retinal vessels, serous detachment of the neurosensory retina, and detachment of the RPE (51,752,753,759). These changes are not specific for multiple myeloma; however, they also occur in patients with hyperviscosity syndromes from other causes (51).

Because patients with multiple myeloma have an increased risk of infection, it is not surprising that some patients with this disease lose vision from intraocular complications associated with infection by bacterial, viral, fungal, or other exogenous agents (764). Endophthalmitis, retinitis, and choroiditis may occur in isolation or in association with other evidence of systemic infection in these patients.

### Treatment and Prognosis

Left untreated, multiple myeloma is nearly always a fatal disease, with untreated patients having a median survival time of about 6 months (659,678). Patients with advanced disease causing anemia, renal insufficiency, and hypercalcemia have a particularly poor prognosis (678,767). Patients without these difficulties have a median survival of about 2 years (130,659). Patients with unequivocal multiple myeloma should therefore be treated as soon as the diagnosis is established. The treatment is directed both at the neoplastic process and at its secondary systemic effects. Most patients receive chemotherapy (659,768–771) combined with therapy for specific disease complications, including bone infiltration, hypercalcemia, renal insufficiency, and infection (657,659,675,677,771). Some patients are treated with bone marrow transplantation (772). Patients who experience objective improvement in their condition after any of the standard treatments often have extended survival and an improved quality of life (659,771,773,774).

## PLASMA-CELL GRANULOMAS

Plasma-cell granulomas are rare lesions characterized by plasma cells, histiocytes, and lymphocytes interspersed in a matrix of hyalinized fibrous tissue (775,776). They are distinct from plasmacytomas, which contain only plasma cells. Most plasma-cell granulomas occur in the lung or upper respiratory tract, but they may occur in almost every organ, and they occasionally involve the CNS (776). When they arise in the anterior cranial fossa, they may produce diplopia or loss of vision (777,778). MR imaging of these lesions reveals nonspecific features, including high signal intensity on T1-weighted images and low signal intensity on T2-weighted images. The lesions heterogeneously enhance after intravenous injection of gadolinium-DTPA or a similar paramagnetic substance (776). Diagnosis is almost always made by biopsy. Treatment is surgical resection followed by radiation therapy. The prognosis of these benign lesions is excellent.

## POEMS SYNDROME (CROW-FUKASE SYNDROME)

**POEMS syndrome** is an unusual multisystem disorder that is characterized by **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal gammopathy, and **S**kin changes (779–787). Polyneuropathy is frequently the initial and most disabling problem. It is usually associated with electrophysiologic and histologic evidence of mixed demyelination and axon degeneration (784,785,788). Enlarged organs include the liver, spleen, and kidneys (786,789). Endocrine abnormalities are diverse and include hypothyroidism, hypogonadism, hypocortisolism, and gynecomastia in men (781,783–785). Polycythemia is often present. Skin findings include diffuse hyperpigmentation in 93% of patients, edema of the legs in 91%, hypertrichosis in 80%, skin thickening similar to that observed in scleroderma in 77%, hyperhidrosis in 66%, and clubbing of the fingers (785,790–792). Rare patients have cutaneous angiomas (793,794). Additional systemic features include osteosclerotic bone lesions, lymphadenopathy, and peripheral edema. Neurologic manifestations in addition to polyneuropathy include increased ICP, papilledema, and pupillary light-near dissociation (779,784,788,795–798). In addition, optic disc drusen with peripapillary choroidal neovascularization has been associated with POEMS syndrome (799). Some patients develop an empty sella syndrome from chronically raised ICP (800).

Optic disc swelling may occur in patients with POEMS syndrome who have no evidence of increased ICP (797,798,801,802). For example, Bourdette and Rosenberg (796) described a patient with POEMS syndrome who developed bilateral orbital pain and was found to have bilateral optic disc swelling with normal visual acuity, color vision, and visual fields (except for enlargement of both blind spots). An orbital CT scan in this patient demonstrated diffuse swelling of the posterior orbital contents bilaterally. It was assumed that the patient had an infiltrative orbitopathy. She was treated with systemic corticosteroids with resolution of both orbital pain and optic disc swelling. In other patients, optic disc swelling unassociated with increased ICP may result from altered capillary permeability in the optic disc.

POEMS syndrome may be a variant of multiple myeloma, and the associated monoclonal immunoglobulin may mediate the multiple systemic manifestations (785,803). Although there is some direct evidence to substantiate this hypothesis (783), not all patients with POEMS syndrome have a demonstrable monoclonal protein or an intracranial plasmacytoma (779,788,804). There are no distinct findings on pathologic studies (785,805); however, edema, ascites, and pleural effusions are present in the absence of hypoalbuminemia or elevated venous pressure, suggesting a primary defect of vessel permeability (806,807).

Although the cause of the POEMS syndrome is unknown, radiation of localized sclerotic lesions combined with treatment with melphalan is effective in reversing the clinical syndrome in some patients (705,783,785,786,792,798,803). This suggests that a tumor product may be the cause of the condition.

## WALDENSTRÖM'S MACROGLOBULINEMIA

This disorder is characterized by a proliferation of B-cells that are morphologically intermediate between plasma cells and lymphocytes and that secrete a monoclonal IgM. Presenting symptoms are related to infiltration of lymphoid tissues, anemia, hyperviscosity, or a combination of these mechanisms. In many patients, the disease runs an indolent course.

The average age of patients with Waldenström's macroglobulinemia is 60 years, but there may be an asymptomatic period of many years before diagnosis. Many patients present with symptoms secondary to severe anemia that result from a combination of accelerated destruction of red cells, decreased erythropoiesis, and increased plasma volume. Other patients develop symptoms related to hyperviscosity. These symptoms, including those pertaining to vision, are described in the section on multiple myeloma. It is necessary only to emphasize that the ocular abnormalities referable to hyperviscosity in multiple myeloma also occur in patients

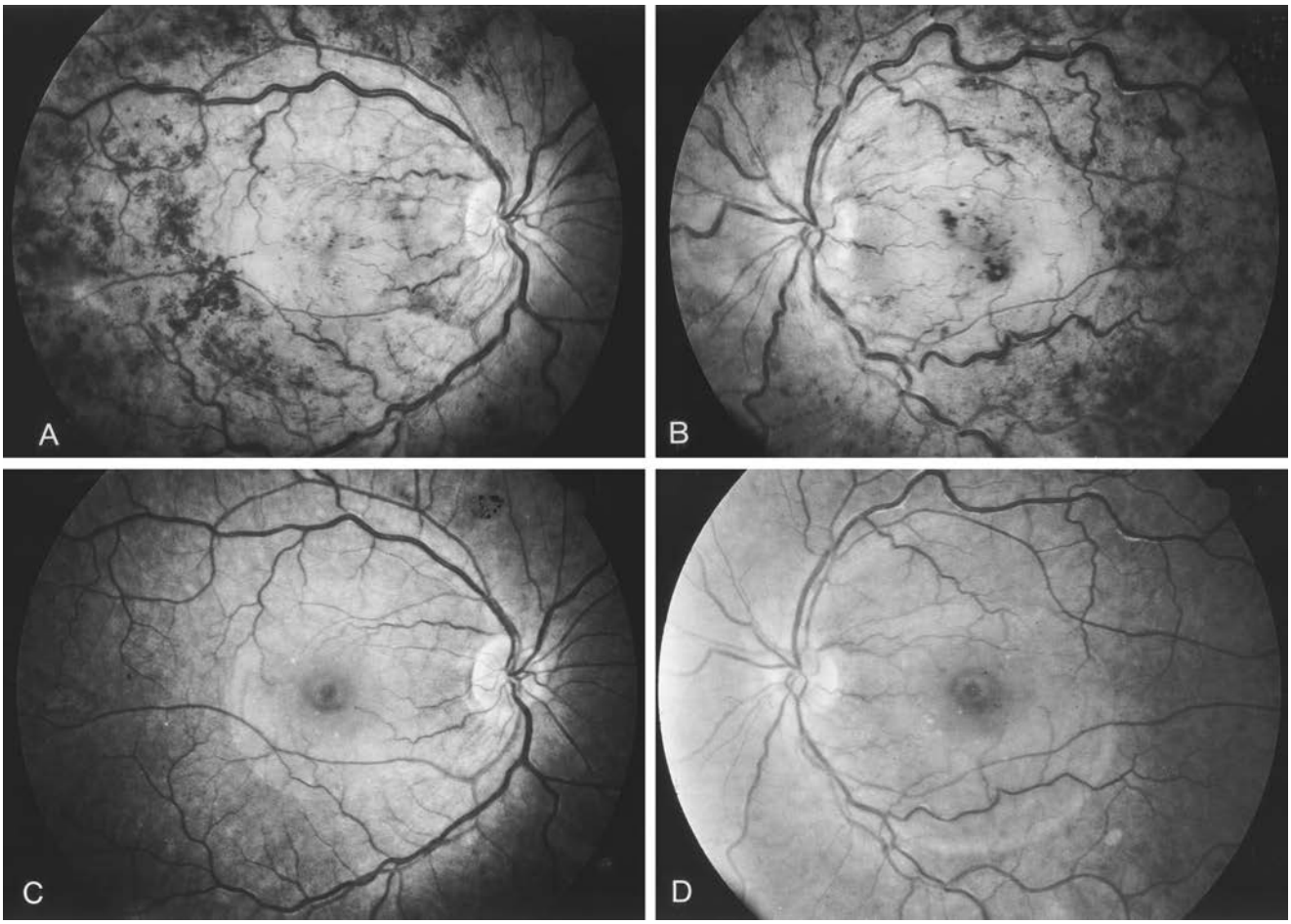



**Figure 34.40.** Retinal vascular disease in Waldenström's macroglobulinemia before and after plasmapheresis. *A and B*, Right and left fundi, respectively, of a patient with severe Waldenström's macroglobulinemia. Note mild dilation of retinal veins and numerous intraretinal hemorrhages. Appearance is that of central retinal vein occlusion. *C and D*, Appearance of right and left fundi after plasmapheresis. The previously noted hemorrhages have cleared almost completely, and the retinal vessels are no longer dilated. The patient had normal vision in both eyes. (Courtesy of Dr. Andrew Schachat.)

with Waldenström's macroglobulinemia (Fig. 34.40*A* and 34.40*B*) (51,808–811). Manor et al. (812) reported bilateral, nonsimultaneous AION in a 65-year-old woman with Waldenström's macroglobulinemia. At the time the second eye became involved, intraretinal hemorrhages were observed in the periphery of both ocular fundi. Because the patient had experienced a previous myocardial infarction, and because the retinal veins were not markedly dilated, tortuous, or sausage-shaped at the time either optic neuropathy occurred, it is not clear if the optic neuropathies were directly related to hyperviscosity or to atherosclerosis.

Lymphadenopathy, splenomegaly, and hepatomegaly develop in a variable percentage of patients with Waldenström's macroglobulinemia. In addition, neurological symptoms and signs occur in about 25% of patients. Such patients may develop focal and diffuse encephalopathy, intracranial hemorrhage, myelopathy, and radiculopathy. CNS involvement by neoplastic cells may occur in the absence of blood hyperviscosity (813). About 5% of patients develop a peripheral neuropathy that is similar to that which occurs in patients with multiple myeloma. In such patients, monoclonal IgM antibody frequently reacts with the myelin of peripheral nerves or with vimentin, which occurs in high concentrations in Schwann cells (702,703,705). The peripheral neuropathy that occurs in such patients (and by analogy in patients with other monoclonal gammopathies) thus appears to result from immunologically mediated demyelination.

The diagnosis of Waldenström's macroglobulinemia is based primarily on the coexistence of high serum concentrations of monoclonal IgM and abnormal accumulations of lymphocytoid cells in the bone marrow and other tissues (814). Waldenström's macroglobulinemia may remain asymptomatic for many years and once diagnosed, it may remain stable or be only slowly progressive; however, it eventually progresses and requires treatment. Plasma exchange can be useful to manage hyperviscosity but does not address the infiltrative process in the bone marrow, which requires cytoreductive therapy (Fig. 34.40*C* and 34.40*D*)

(809,814). Unfortunately, in most patients, the disease eventually becomes refractory to all forms of therapy. Once major abnormalities occur, the usual prognosis for life is similar to that of patients with multiple myeloma. As the disorder progresses, its cellular proliferative aspects may become more prominent. An occasional patient may thus show a good response to therapy and remain well controlled for several years, only to succumb to a disseminated proliferative phase indistinguishable from lymphocytic or diffuse large-cell lymphoma. In most cases, however, death is related to the effects of uncontrollable serum hyperviscosity, hemorrhage, or bacterial infection.

## HEAVY CHAIN DISEASES

The **heavy chain diseases** (HCD) are characterized by neoplastic proliferations of plasma cells that secrete heavy chains unattached to light chains. The five major immunoglobulin classes ($\alpha$, $\beta$, $\gamma$, $\delta$, and $\epsilon$) may be involved, with $\alpha$-HCD being the most frequent type of HCD (673,678). The clinical features of these entities overlap to some extent with those of other lymphoid neoplasms, but they have unique biochemical features that justify this separate classification.

No major descriptions of the neurological or visual abnormalities in this group of diseases have been written, but it may be safely assumed that the features are probably nonspecific and similar to those observed in other lymphoproliferative disorders. The reader interested in reviewing the features of the HCDs should consult the concise but comprehensive monograph by Kyle (678).

## PRIMARY AND MYELOMA-RELATED FORMS OF GENERALIZED (SYSTEMIC) AMYLOIDOSIS

Amyloidosis is a rare disorder that is characterized by the variable accumulation of an extracellular eosinophilic proteinaceous substance—amyloid—in nearly all the tissues of the body. Amyloid (from the Greek *amylon,* starch, and *eidos,* resemblance) is a complex protein mixture dominated by a fibrillar component that can be identified by electron microscopy (815).

With electron microscopy, amyloid fibers appear as rigid, linear, nonbranching strands measuring 0.7–10 $\mu$m in width but with an indefinite length. Amyloid occurs in patients with chronic inflammatory or infectious conditions. Familial varieties account for another subset within the systemic amyloidoses. The nonsystemic amyloidoses include those limited to a particular organ or organ system. The amyloid syndromes can be classified on the basis of the biochemical nature of these fibers (816,817), but the most commonly used clinical classification separates amyloidosis into three types: generalized (systemic), hereditary (familial), and localized (limited) (130,815). Systemic amyloidosis can be further separated into primary amyloidosis, in which there is no underlying or associated disease; secondary amyloidosis, in which there is preexisting or coexisting chronic inflammatory or suppurative disease (e.g., rheumatoid arthritis); and amyloidosis associated with multiple myeloma, Waldenström's macroglobulinemia, or the heavy chain diseases.

Clinical classifications notwithstanding, amino acid sequence studies of the fibrillar component of amyloid from patients with different clinical forms of amyloidosis have identified two distinct biochemical types of amyloid. In the primary and myeloma-associated forms of generalized amyloidosis, the fibrillar component is almost always a portion of variable length of light chain immunoglobulin or, in some cases, the entire light chain (678). Very rarely, the amyloid is an isolated heavy-chain fragment (818). Primary systemic amyloidosis and amyloidosis associated with multiple myeloma, Waldenström's macroglobulinemia, and the HCDs are therefore actually types of plasma cell dyscrasias. In contrast, in the secondary type of generalized amyloidosis and in some of the hereditary forms, the amyloid fibril is a substance that is the same in different patients and is not part of an immunoglobulin. Because the subject of this chapter is tumors involving hematopoietic cells and tissue, we have chosen to confine the discussion that follows to the primary and myeloma/macroglobulinemia forms of generalized amyloidosis.

In view of the demonstration of the immunoglobulin-like nature of the amyloid fibril, it is easy to understand why the symptoms and signs as well as the laboratory features of patients with primary amyloidosis resemble so closely those of patients with amyloidosis associated with multiple myeloma. In some cases, it is difficult to distinguish between these two possibilities, and the major criterion for diagnosis of multiple myeloma often is the involvement of bone.

### Primary Generalized (Systemic) Amyloidosis

Primary amyloidosis is rare before 40 years of age. Peak incidence occurs in the seventh decade of life, and men are more often affected than women. Symptoms are usually nonspecific and insidious in onset. Prominent symptoms include fatigue, weight loss, and paresthesias. In some cases, cardiac or renal insufficiency dominates the clinical syndrome. Carpal tunnel syndrome, nephrotic syndrome, and a sprue-like syndrome also occur. Hepatomegaly may be present, but splenomegaly and lymphadenopathy are uncommon. Macroglossia with indentations on the tongue margins caused by pressure of adjacent teeth is almost pathognomonic of the disease. Purpura is sometimes prominent, especially in areas subjected to trauma or increased hydrostatic pressure. Periorbital ecchymosis from coughing, vomiting, or being placed in the head-down position (e.g., during sigmoidoscopy) may be dramatic. The skin may be so fragile that it mimics epidermolysis bullosa, or it may be infiltrated with nodules or plaques resembling xanthelasma.

The PNS is primarily involved in some patients, resulting in motor, sensory, or autonomic dysfunction (772,819–823). Affected patients may complain of weakness, numbness, and paresthesias. They may have severe postural hypotension that may be difficult to control. Pupillary abnormalities are common in such patients, who may have anisocoria, nonreactive pupils, or tonic pupils with light-near dissociation

(823). Cranial neuropathies are rare but occasionally occur (824).

Patients with primary systemic amyloidosis may have a variety of laboratory abnormalities. These include proteinuria, Bence Jones protein, serum M proteins, anemia, bone marrow plasmacytosis, and evidence of renal failure.

Patients with primary systemic amyloidosis may develop a variety of ocular and neuro-ophthalmologic disturbances (823,825). Involvement of the eye may be manifest as diffuse vitreous opacities, most commonly seen in the hereditary amyloidoses, but also reported with CNS disease and in isolation (823,826–828). Such patients may have deposition of of amyloid in the adventitia and media of the ciliary, choroidal, episcleral, and conjunctival vessels. Amyloid also may be deposited beneath and within Bruch's membrane and in the substantia propria of the conjunctiva (829). Corneal deposits in primary systemic amyloidosis are, however, rare. Involvement of the orbital soft tissues may be asymptomatic or may be associated with proptosis, limitation of eye movements, and ptosis (Fig. 34.41) (826,829–833). Lacrimal gland involvement and the sicca syndrome may also occur (823,834,835). In addition, deposition of amyloid in the orbital and conjunctival vessels renders them fragile and thus predisposes to spontaneous subconjunctival, palpebral, or orbital hemorrhage. Involvement of the cervical lymph nodes may cause a Horner syndrome from compression of the oculosympathetic pathway. Other pupillary abnormalities that occur in patients in whom the condition primarily affects the peripheral nervous system are discussed earlier.

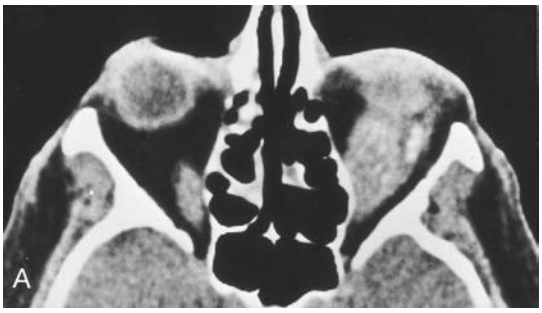
The diagnosis of primary amyloidosis is established by histologic examination. Biopsy material is easily obtained from the mucosa and submucosa of the rectum, gingiva, tongue, or a clinically affected area of skin. Amyloid may be identified using light microscopy, electron microscopy, or x-ray diffraction techniques. Amyloid has a fairly constant appearance when examined with various stains by light microscopy. When the hematoxylin and eosin stains are used, amyloid appears as an amorphous, acellular, eosinophilic material. It has a metachromatic reaction with crystal violet and fluoresces with thioflavin-S. The best stain with which to identify amyloid using light microscopy, however, is alkaline Congo red. Amyloid stained with Congo red has a pink color under white light and shows marked brilliant yellow to ''apple-green'' birefringence when examined under polarized light.

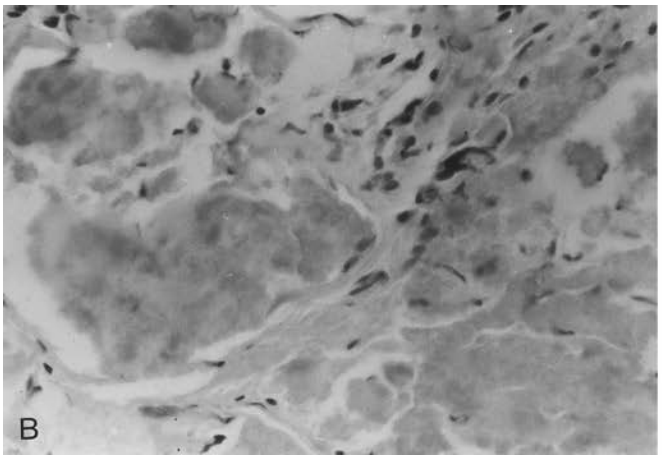
The results of treatment trials for primary amyloidosis are not encouraging (836). Prednisone, melphalan, and colchicine are used, but median survival is about 13 months, with most patients dying from cardiac or renal complications of their disease (678,836). High-dose chemotherapy followed by stem cell reconstitution seems to provide the highest reported response rates (837).

Patients with isolated advanced cardiac or hepatic amyloidosis should be considered for solid organ replacement prior to autologous hematopoietic transplantation (838).

### Myeloma/Macroglobulinemia-Associated Generalized (Systemic) Amyloidosis

Compared with patients with primary generalized amyloidosis, patients with amyloidosis associated with multiple



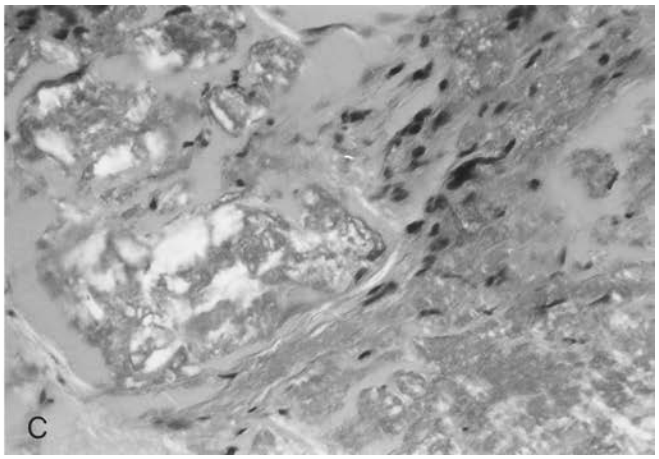




**Figure 34.41.** Primary systemic amyloidosis causing vertical diplopia from infiltration of the left inferior rectus muscle. *A*, CT scan shows marked enlargement of the left inferior rectus muscle in an elderly patient with no other complaints. *B*, Biopsy of this muscle shows extensive amorphous material that stains positively for amyloid. *C*, A phase-contrast photomicrograph of the field shown in *B* reveals that the amorphous material is birefringent, a characteristic of amyloid. (Courtesy of Dr. Thomas C. Spoor.)

myeloma and Waldenström's macroglobulinemia develop more severe skeletal destruction, more extensive plasma cell infiltration of the bone marrow, and more severe anemia and hypercalcemia. They may develop severe ptosis and ophthalmoplegia from orbital disease (742). They also have a greater incidence and amount of Bence Jones protein in the urine and M components in the serum. Such patients therefore suffer not only the relentless damage caused by deposition of amyloid in the body tissues, but in addition, they are subject to all the complications of progressive proliferation of plasma cells. The prognosis is accordingly less favorable than with either multiple myeloma/macroglobulinemia or primary generalized amyloidosis (836).

## DISEASES OF THE MONONUCLEAR-PHAGOCYTIC (RETICULOENDOTHELIAL) SYSTEM: HISTIOCYTOSES

### ORIGIN, COMPONENTS, AND FUNCTIONS OF THE CELLS OF THE MONONUCLEAR-PHAGOCYTIC SYSTEM

In this section, we consider disorders that are characterized by an abnormal accumulation or proliferation of the cells of the mononuclear-phagocyte system. Aschoff (839) originally described, under the designation of the ''reticuloendothelial system,'' a widely dispersed system of cells that isolated and destroyed foreign particles and that had an affinity for vital stains of high molecular weight. It was subsequently agreed that these cells, which are characterized by common phagocytic and defense functions, form a rather fixed and permanent network that exists in different forms in the liver, spleen, bone marrow, and lymph nodes.

This integrated concept initially met with great success because it was founded on a functional and physiological basis. Unfortunately, it led to the introduction of other terms and concepts of considerable vagueness, including ''reticular cell,'' a poorly defined cell that was thought to be either a stem cell or a ''connective tissue cell,'' and also ''reticuloendotheliosis,'' a term that combined systemic disorders characterized by the proliferation of fixed reticuloendoethelial cells, in contrast to the leukemias and lymphomas, considered to be disorders of the ''mobile'' cell lines.

The notion of a mononuclear-phagocyte system eventually replaced that of reticuloendothelial tissue because it became clear that **the cells of this system are not fixed**. They originate in the bone marrow, appear in the peripheral blood as monocytes, and eventually migrate to various tissues (Fig. 34.42) (7,8). The cells are called **histiocytes** when they are resting and **macrophages** when they are actively phagocytic. In the liver, the cells are called **Kupffer cells** and in the kidney, **mesangial cells**. In the spleen and lymph nodes, they are called **lining cells**. In the pleural, peritoneal, and pleural cavities, they are called **wandering macrophages**. In the bone, they are called **osteoclasts**. In the CNS, they are called **microglial cells** or, simply, microglia. The cells of the mononuclear-phagocyte system have three essential biologic functions: phagocytic activity, immunologic activity, and secretory activity.

The phagocytic activity allows capture, concentration, and destruction of a variety of microorganisms. The cells can also phagocytize solid particles and antigens.

Immunologically, the cells of the mononuclear-phagocyte system are able to concentrate and metabolize antigens and to respond to histocompatibility change. In addition, they are able to establish intimate physical contact with lymphocytes, foreign cells, and tumor cells through their membranes and receptors. Finally, by the secretion of monokines, they are essential agents in the proliferation and transformation of lymphocytes and are also able to react with lymphokines and antibodies produced by lymphocytes.

The cells of the mononuclear-phagocyte system have considerable and diverse secretory activity. They are rich in hydrolases and constantly secrete lysozyme. They are also involved in the activation of plasminogen in fibrinolysis, in the liberation of degradation products (which they phagocytize), and in the production of glycosidases and endogenous protease inhibitors (i.e., trypsin and chymotrypsin) (8).

Although cells of the mononuclear-phagocyte system all have similar origins and characteristics, several subpopulations of cells can be identified within this system using morphologic, cytoenzymatic, and immunocytologic criteria. Identification of these subpopulations is important, not only because it permits an understanding of their specific functions but also because, like the subpopulations of the lymphoid system, these cells give rise to diseases that are better understood when the precise cell of origin and its basic function are known.

The best defined of all the mononuclear-phagocyte system subpopulations is the **Langerhans cell histiocytic system** (Fig. 34.42) (840). This system contains several cells, the most differentiated of which is the **Langerhans cell**. This

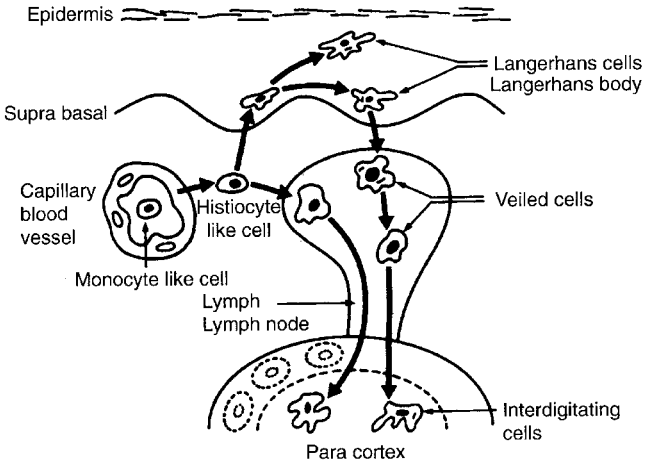



**Figure 34.42.** Langerhans cell histiocytic system. See text for details. (From Nezelof C, Barbey S. Histiocytosis: Nosology and pathobiology. Pediatr Pathol 1985;3:1–41.)

cell was originally thought to be a dendritic cell of epidermal origin; however, it clearly originates in the bone marrow and is part of the mononuclear-phagocyte system (8,841). It is identified by specific enzymatic, immunocytologic, and morphologic characteristics. Among its most important characteristics are that it stains positively for S-100 protein, and the monoclonal antibody OKT-6 stains its cell surface membrane receptors (8,842–846). Its outer cytoplasmic membrane has a high nonspecific esterase activity, and it possesses a peroxidase activity, the ultrastructural localization of which is similar to that demonstrated in so-called ''fixed'' macrophages (847). Finally, by electron microscopy, the Langerhans cell is characterized by a pentalaminar structure that grossly resembles a zipper and that is attached to the cell membrane (Fig. 34.43). This structure, originally described by Birbeck (848) is variously called ''racket body,'' ''Birbeck body,'' and ''Langerhans body'' (8,849–851).

In addition to the Langerhans cell, the Langerhans cell histiocytic system contains several other cells. **Intermediate dendritic cells**, like Langerhans cells, are found in the epidermis. **Interdigitating cells** are present in the thymus and spleen. **Veiled cells** are a mobile but differentiated form of Langerhans cells and are usually identified in efferent lymphatics of lymph nodes (852). All of the cells of the Langerhans cell histiocytic system have strong membrane activity that enables them to establish intimate contact with neighboring cells, particularly the T-lymphocytes of the thymus and of the lymph nodes. In this fashion, they function as part of the immune system (853). Langerhans cells express CD1 antigen and are HLA-DR positive.

## HISTIOCYTOSES

Diseases characterized by accumulation or proliferation of cells of the mononuclear-phagocyte system are generally called reticulohistiocytoses or, simply, **histiocytoses**. As is the case with the leukemias and the lymphomas, there are several classifications that separate the various types of histiocytosis. The traditional classification is: (*a*) secondary histiocytoses, which result from chronic infection or an immune disorder; (*b*) dystrophic or storage histiocytoses, characterized by the systemic or localized storage of either an exogenous or endogenous material; and (*c*) proliferative histiocytoses, characterized by the uncontrolled proliferation of various cells of the mononuclear-phagocyte system (854–856). However, in 1997, The Writing Group of the Histiocytosis Society divided the histiocytic syndromes into three groups: Langerhans cell histiocytoses, benign non-Langerhans cell histiocytoses, and malignant histiocytoses. In this chapter, we use the latter classification and discuss histiocytoses that are neoplastic or have a neoplastic quality.

### Langerhans Cell Histiocytosis (Histiocytosis X, Eosinophilic Granuloma, Hand-Schüller-Christian Disease, Letterer-Siwe Disease)

The term **eosinophilic granuloma** was first used by Lichtenstein and Jaffe (857) to describe a single histiocytic lesion

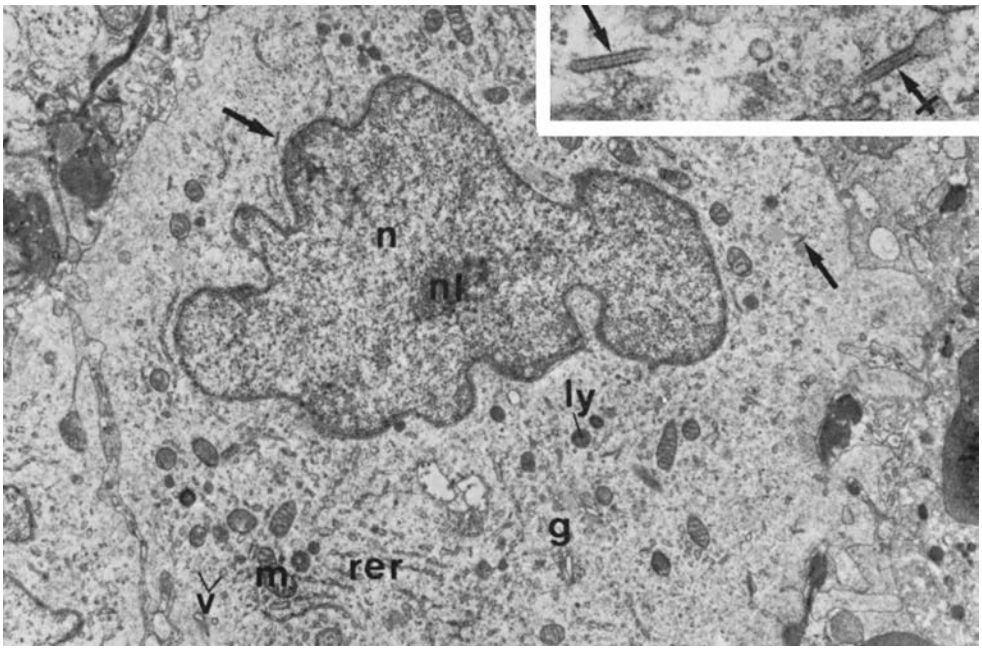



**Figure 34.43.** Electron micrograph showing ultrastructure of Langerhans cell. The *arrows* indicate cytoplasmic Langerhans granules, better shown in the *inset.* These granules have a central striated line. The granule on the right, indicated by the *crossed arrow,* has an open vesicular end. This appearance explains why such granules are often called ''racquet bodies.'' Other cytoplasmic structures are lysosomes (ly), short profiles of rough endoplasmic reticulum (rer), scattered mitochondria (m), and smooth vesicular reticulum (v). g, Golgi apparatus; n, nucleus; nl, nucleolus. (From Jakobiec FA, Font RL. Orbit. In Spencer WH, ed. Ophthalmic Pathology: An Atlas and Textbook. Philadelphia: WB Saunders, 1986;2459–2860.)

in bone and later to describe a condition in which there were multiple histiocytic lesions, all of which were confined to bone (858). Subsequently, it was noted that as a rule, the younger a patient with ''eosinophilic granuloma'' the greater the propensity for multifocal disease. Patients younger than 2 years of age were noted to display multisystem disease, including cutaneous, visceral, lymph node, and, rarely, ocular and orbital manifestations. This was called **Letterer-Siwe disease** (859,860). In somewhat older children, multifocal lesions at the base of the skull would occasionally produce the triad of lytic defects in the skull, proptosis, and diabetes insipidus. This triad was called **Hand-Schüller-Christian disease**. In 1953, Lichtenstein proposed the term **histiocytosis X** to include these three related disorders, which he believed were simply different clinical expressions of a single nosologic entity. This universal concept was difficult to accept because of the extremely different clinical presentations and evolutions of the disorders. Subsequently, however, it became clear that all of these entities result from a clonal proliferation of cells of the Langerhans cell histiocytic system (855,856,861). It is therefore appropriate that all of these entities be combined under the heading **Langerhans cell histiocytes** (840,852).

The basic feature of Langerhans cell histiocytosis is a granuloma that contains numerous large cells with the characteristics of Langerhans cells, a few plasma cells, and a variable proportion of neutrophils, eosinophils, and lymphocytes (129,861–863). The mononuclear cells at first are numerous. With time, however, there is necrosis, and later, xanthomatous changes and fibrosis. Although the origin of Langerhans cell histiocytosis is clear, the stimulus that produces the proliferation of Langerhans cells is unknown. A true neoplastic process appears unlikely because of the polymorphic infiltrates and the spontaneous regression observed

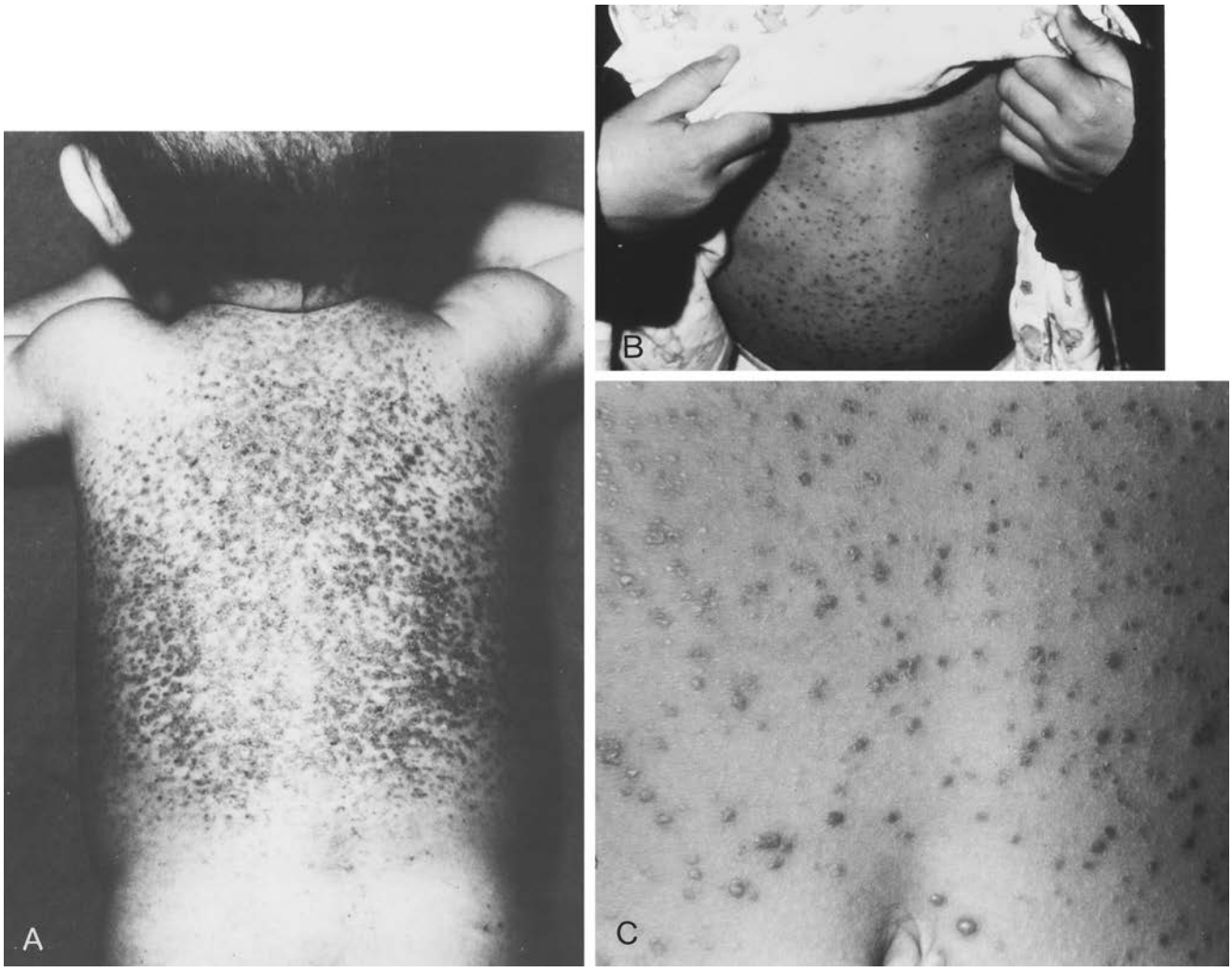



**Figure 34.44.** Disseminated Langerhans cell histiocytosis. Maculopapular rash is present in two patients with this condition. *A*, In a 6-month-old child, there is an extensive rash across the entire back. Note lack of rash on arms. *B*, In a 4-year-old child, the rash is present on the abdomen. *C*, A magnified view of the abdominal rash seen in *B* shows its maculopapular characteristics. (*A,* From Nezelof C, Barbey S. Nosology and pathobiology. Pediatr Pathol 1985;3:141.)

in many patients (864). The role of lymphokines and proinflammatory cytokines (865) is being assessed.

Langerhans cell histiocytosis most frequently affects the bones, particularly bones with hematopoietic activity. It also affects, in decreasing frequency, the lungs, skin, lymph nodes, spleen, and liver. The distribution of the lesions varies with age. In children, the skeleton and the skin are most frequently involved, whereas in adults, the lung is most often affected. Most patients with intracranial disease are older children or adults who also have other sites of involvement (866–870). Males and females are equally affected. It is usually possible to separate **localized** from **disseminated** forms of Langerhans cell histiocytosis, and each of these may be further separated into **acute** and **chronic** forms.

The **acute disseminated** form of Langerhans cell histiocytosis corresponds to what was once called Letterer-Siwe disease. It is almost always observed in newborns, occurs only occasionally in middle age, and is extremely rare in the elderly. The main clinical manifestation is a maculopapular rash that primarily affects the areas of the skin in proximity to the skeleton (Fig. 34.44). The scalp and the thoracic skin are thus the most frequently involved, but the skin of the eyelids may also be affected (Fig. 34.45). Other clinical manifestations include hepatosplenomegaly, that may be very severe, and pulmonary infiltrates. This form of Langerhans cell histiocytosis is often fatal (840,871), with death frequently being preceded by a syndrome of activation of the cells of the mononuclear-phagocyte system that is characterized by the rapid development of hypersplenism, anemia, thrombocytopenia, fibrinogenopenia, and hemorrhagic diathesis.

In some patients, the **disseminated** form becomes **chronic**. Newton and Hamoudi (872) distinguished two histologic types of chronic disseminated Langerhans cell histiocytosis: type I, which is always lethal and is characterized by the proliferation of undifferentiated cells that do not express specific markers, and type II, which has a more favorable outcome and is characterized by infiltrates composed of rather well-differentiated cells containing many Langerhans bodies.

Although the chronic disseminated form of Langerhans cell histiocytosis may present acutely, it most often occurs as a primary chronic disorder characterized by multiple skeletal lesions, infiltrates in the skin and mucosa, and occasional involvement of the viscera, particularly the liver.

One form of **chronic disseminated Langerhans cell histiocytosis** is characterized by the triad of proptosis that is frequently bilateral and asymmetric, pitressin-sensitive diabetes insipidus, and ''punched-out'' lesions in the bone of the skull (Fig. 34.46). This form was once called Hand-Schüller-Christian disease (873–875). The punched-out lesions are, of course, granulomas involving the bone of the skull, and the proptosis results from similar lesions in the bone (and occasionally in the soft tissue) of the orbits. In chronic forms of Langerhans cell histiocytosis, lesions in the maxilla, palate, mandible, and mastoid are frequent. These lesions often produce local sequelae such as deafness and edentation. The diabetes insipidus in patients with this form of chronic disseminated Langerhans cell histiocytosis results from infiltration of the hypothalamus by Langerhans cells (Gagel's granuloma—discussion following), with or without associated infiltration or fibrosis of the posterior pituitary gland (876–879). Dunger (880) found the risk of diabetes insipidus in the setting of Langerhans cell histiocytosis to be 42%. The polyuria and polydipsia may occur before, concurrently with, or subsequent to the development of lesions in the bones and extraneural soft tissues (867,881). Patients with this form of Langerhans cell histiocytosis also have

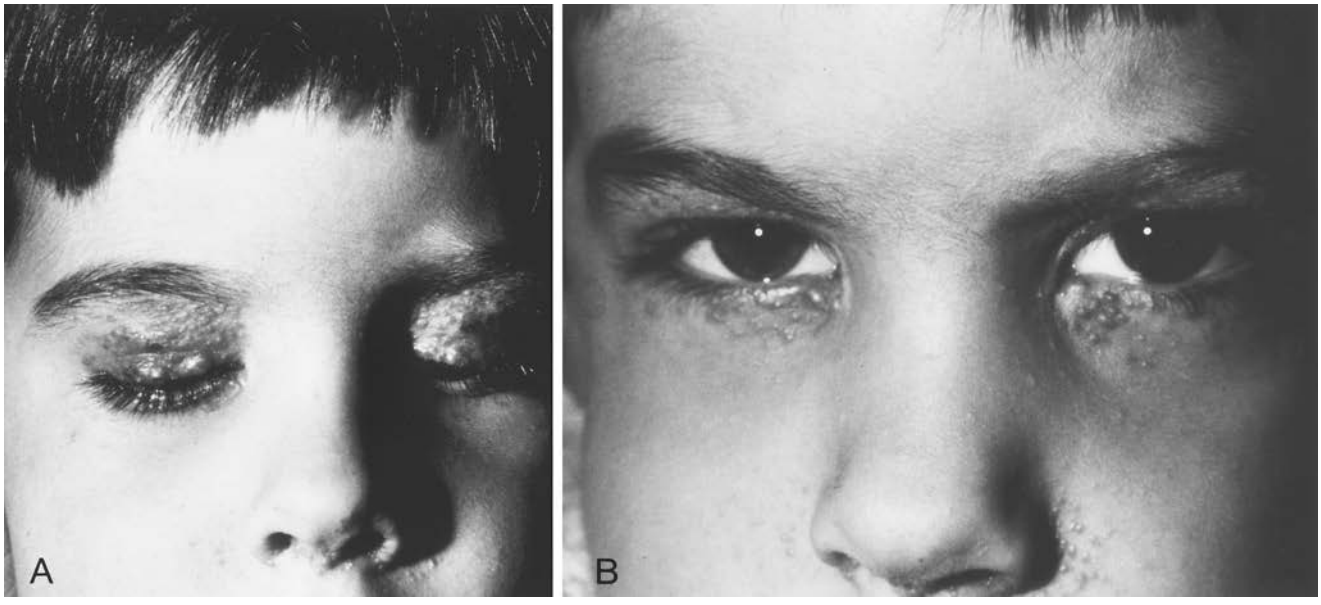



**Figure 34.45.** Eyelid involvement in Langerhans cell histiocytosis. Note maculopapular rash affecting the upper (*A*) and lower (*B*) eyelids of a 4-year-old boy with the chronic disseminated form of the disease.

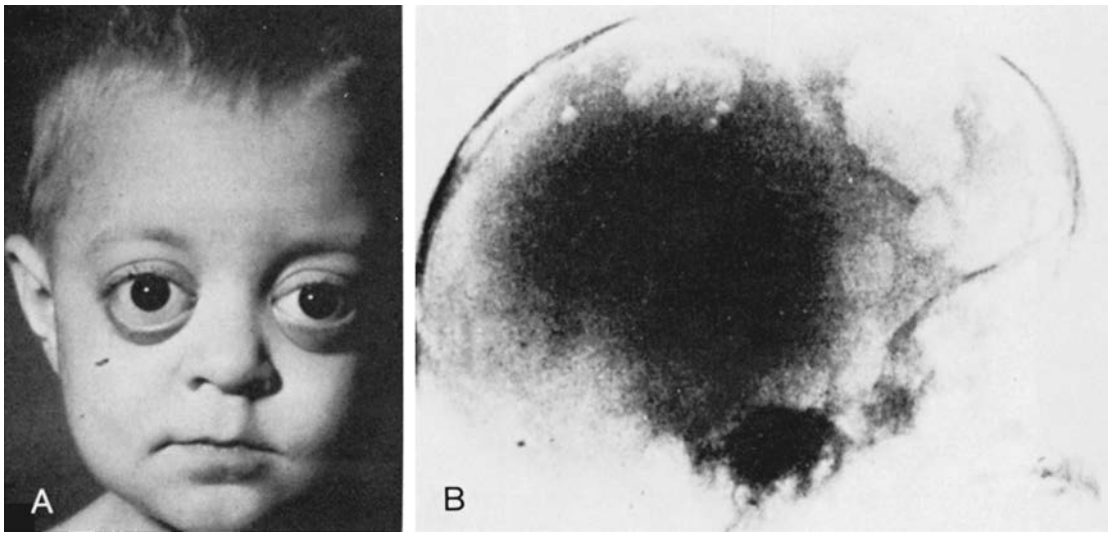



**Figure 34.46.** Langerhans cell histiocytosis of the orbit (formerly called Hand-Schüller-Christian disease). *A*, The patient has bilateral proptosis from involvement of the bones of the orbit. *B*, Skull radiograph shows multiple punched-out lesions of the calvarium typical of this condition. Such patients may also have diabetes insipidus from involvement of the hypothalamic-pituitary axis. (From Jakobiec FA, Font RL. Orbit. In Spencer WH, ed. Ophthalmic Pathology: An Atlas and Textbook. Philadelphia: WB Saunders, 1986:2459–2860.)

short stature, thought to be related to an associated deficiency of growth hormone (882–885). In general, however, children with Langerhans histiocytosis do not experience growth retardation (886). Other endocrine manifestations in these patients include hypothalamic hyperprolactinemia (887), hypogonadism, hypothyroidism, panhypopituitarism, and hyperosmolar syndrome (129,876). These manifestations are quite rare, however.

Patients with the Hand-Schüller-Christian variant of Langerhans cell histiocytosis may lose vision from infiltration of the optic chiasm by Langerhans cells (888–892). Patients may develop unilateral or bilateral loss of visual acuity, bitemporal visual field defects, or even homonymous field defects in this setting. As noted above, although most of these patients have other evidence of Langerhans cell histiocytosis (487), in some cases, the lesion affecting the hypothalamus, anterior visual sensory system, and base of the skull near the sella turcica is the **only** intracranial lesion detectable. It may therefore be misdiagnosed as one of the more common lesions that occur in this region, such as a pituitary adenoma, craniopharyngioma, glioma, or germinoma (890,893–895).

In most patients with **localized Langerhans cell histocytosis**, the disease evolves chronically, lasting many years. It sometimes relapses after a symptom-free interval of several years. Localized Langerhans cell histiocytosis has a predilection for bones and lungs. This disorder, which was once called **eosinophilic granuloma**, usually affects the proximal end of long bones. When the disorder affects the lungs, it produces a characteristic bullous lesion (896). In this form, recurrent pneumothorax is common not only at the onset of symptoms but also throughout the course of the disease. The diagnosis is usually made by demonstration of Langerhans cells in bronchial washings.

In extremely rare instances, acute localized Langerhans cell histiocytosis is restricted to the CNS. The most common site for such isolated lesions is the hypothalamus (Fig. 34.47) (879,891,893,897–899). Foci of Langerhans cell histiocytosis in the hypothalamus were previously called **Gagel's granuloma** (878,891,900). Focal lesions can also occur in the spinal cord (901,902) and in the cerebral hemispheres (903–911). In such patients, the outcome may be fatal.

Damage to **intracranial** structures in patients with acute localized Langerhans cell histiocytosis may also produce visual difficulties. Patients with lesions that involve the base of the skull may develop various cranial neuropathies (912,913). Diplopia may result from involvement of the ocular motor nerves. Gross et al. (914) described a patient who developed a sphenocavernous syndrome characterized by left-sided ophthalmoplegia associated with pain and loss of sensation on the ipsilateral side of the face and a left optic neuropathy. Neuroimaging revealed a soft-tissue mass in the left cavernous sinus, biopsy of which revealed Langerhans cell histiocytosis. Hardenack et al. (915) described a patient who developed a right oculomotor nerve paresis with involvement of the pupil. MR imaging revealed an enhancing lesion located between the right cerebral peduncle and the dorsum sellae in the region of the subarachnoid portion of the right oculomotor nerve. Craniotomy revealed a focal enlargement of the nerve. The area was resected and found to be Langerhans cell histiocytosis.

There may be facial paralysis from damage to the facial nerve and facial dysesthesia or hypesthesia from trigeminal neuropathy. Deafness may occur from damage to the vestib-

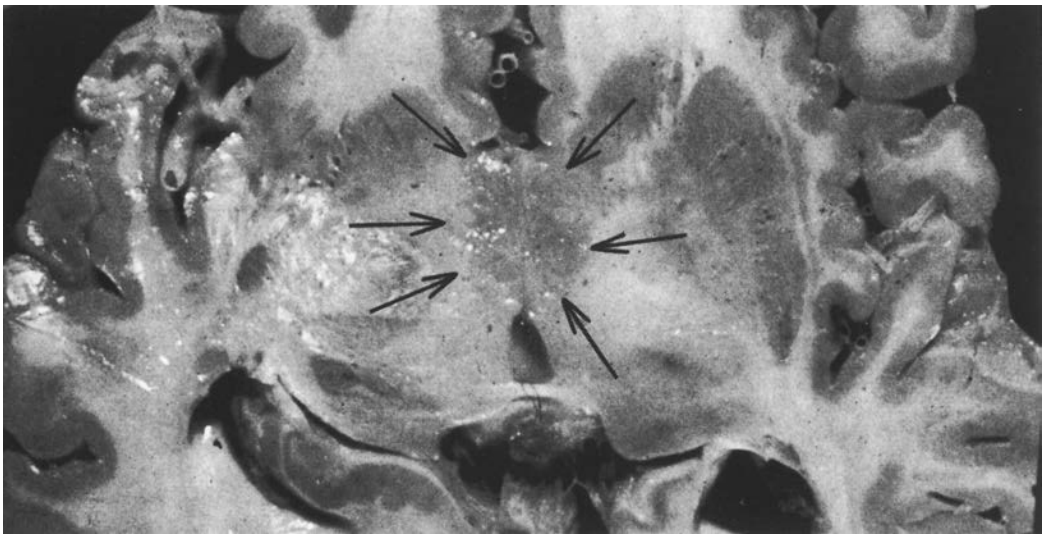


**Figure 34.47.** Langerhans cell histiocytosis of the hypothalamus (Gagel's granuloma) (*arrows*). The anterior portion of the 3rd ventricle is compressed by the lesion. Patients with such lesions have diabetes insipidus and other disorders related to hypothalamic dysfunction. (From Kepes JJ, Kepes M. Predominantly cerebral forms of histocytosis X: A reappraisal of ''Gagel's hypothalamic granuloma,'' ''granuloma infiltrans of the hypothalamus'' and ''Ayala's disease'' with a report of four cases. Acta Neuropathol 1969;14:77–97.)

ulocochlear nerve, and taste may be impaired from dysfunction of the facial nerve, glossopharyngeal nerve, or both. Cranial neuropathy may result from compression or infiltration of neural tissue (892). Nystagmus may develop from compression of the brainstem or cerebellum by predominantly bony lesions or from infiltration of these structures by Langerhans cells with resultant formation of intraparenchymal granulomas. Intracranial tumors may become sufficiently large to produce increased ICP, papilledema, and secondary optic atrophy (916).

Localized Langerhans cell histiocytosis may also present as unilateral or bilateral visual loss from direct involvement of the optic nerve. One of the patients described by Kepes and Kepes (891) was a 20-year-old man with a 3-year history of diabetes insipidus, visual loss, and nausea. He was eventually found to have Langerhans cell histiocytosis of the left optic nerve and hypothalamus. Stromberg et al. (917) described a 16-year-old boy who developed progressive loss of vision in the left eye associated with a soft-tissue mass in the sphenoid sinus with osteolytic bone destruction of the left lateral wall of the sinus. Transsphenoidal biopsy revealed histologic features consistent with Langerhans cell histiocytosis. The patient was treated with radiation therapy and experienced marked improvement in vision.

A rare and poorly understood syndrome of progressive cerebellar ataxia occasionally occurs in patients with Langerhans cell histiocytosis. Dubowy and colleagues (918) described two patients with this condition. Both patients had bone involvement of the skull and orbit. About 3–4 years after initial diagnosis, both patients developed progressive cerebellar ataxia, corticospinal tract abnormalities, and weakness of the extremities. CT scans in both patients showed symmetric hypodense areas in the cerebellar hemispheres, involving the dentate nuclei. The vermis as well as the cerebellar and perimesencephalic cisterns were normal in appearance. One of the patients underwent a biopsy of the cerebellum. The histologic findings of the specimen included a marked decrease in Purkinje and granular cells with gliosis of the white matter and of the Purkinje and granular layers. The white matter also showed marked loss of both myelin and axons. Rare, large mononuclear cells were present at the junction of the white matter and granular cell layer. In view of these findings, it is unclear if this syndrome is caused by direct involvement of the cerebellum and brainstem by the disease, is related to the effects of its therapy, or is a paraneoplastic condition. In fact, the condition may be caused by more than one mechanism.

The **orbit** is affected in about 20% of patients, usually those with the chronic form of the disease (919–925). Orbital involvement is usually characterized by solitary or multiple lytic lesions of the bones of the orbit, with some patients also having granulomas involving the soft tissue of the orbit. Isolated involvement of orbital soft tissues without that of adjacent bone may occur but is extremely rare (921). Although patients with isolated lesions of the orbital bones may not have any symptoms or signs suggesting orbital disease (926–929), most patients have clinical evidence of orbital disease, including proptosis, chemosis, and limitation of eye movements. Miller et al. (930) described a patient with diffuse Langerhans cell histiocytosis, in whom swelling of the eyelid occurred, and Beller and Kornbleuth described a 14-year-old boy with Langerhans cell histiocytosis involving the orbit who developed an orbital apex syndrome characterized by complete ophthalmoplegia and optic neuropathy (931). Spontaneous regression of orbital histiocytosis has been observed (864).

**Ocular** lesions in patients with Langerhans cell histiocytosis are rare. They usually occur in infants with the subacute disseminated form of the disease and are characterized by infiltration of intraocular structures, particularly the uveal tract, with Langerhans cells (932–936). Epibulbar lesions have also been observed (937). In some cases, intraocular disease is not suspected during life and is identified only at autopsy; however, some patients develop intraocular manifestations during the acute illness (932,933). Secondary open-angle glaucoma (936), bilateral perforating corneal ulcers (934), infiltration of the cornea with pannus formation (938,939), and posterior scleritis can also occur in patients with Langerhans cell histiocytosis. Localized histiocytosis may involve the eye, presenting as a tumor of the choroid (940).

The diagnosis of Langerhans cell histiocytosis should be suspected in patients with neurological dysfunction who are found to have cutaneous lesions, lytic lesions of bone, or both. Such patients often have multiple, intracranial, parenchymal lesions detected by CT scanning or MR imaging (866,917,941,942) that may be mistaken for the lesions of multiple sclerosis unless the bony lesions of the skull are appreciated (943).

The therapy of Langerhans cell histiocytosis must be adapted to each variant of the disease. Infrequently, there is spontaneous remission. For patients with localized disease, options include intralesional injection of corticosteroids, curettage, low-dose radiation therapy, or combinations of these procedures (120,912,914,917,944–946). The disseminated forms require more aggressive therapy, particularly if they are progressive. Systemic corticosteroids have a generally favorable effect on the skin lesions but are less effective for those of the lungs, liver, and spleen. The use of combination chemotherapy lowers the mortality in all age groups (840,947); however, the risk of sepsis and myelosuppression with the use of chemotherapy, particularly in infants, is substantial (840). Chemotherapy includes vinblastine, 6-mercaptopurine, methotrexate, and etoposide (VP-16). Radiation therapy is successful in some patients with disseminated systemic or purely intracranial lesions (867,948), and patients with chemotherapy-resistant disease may benefit from an allogeneic bone marrow transplant (840,949).

The prognosis for patients with Langerhans cell histiocytosis depends on the extent of the disease. The localized forms always have a good prognosis, particularly in children, whereas the visceral forms have a rather poor outcome. Hepatic and splenic involvement is associated with a particularly poor prognosis (871,942,950). Although some investigators emphasize the importance of age in the prognosis of patients with Langerhans cell histiocytosis (951), it is really the tendency for the lesions to be disseminated in infants and the elderly that adversely affects these patients rather than age per se (855,942). In addition, Lahey (944) emphasized that the number of organ systems involved may not be as important prognostically as the dysfunction of those organs, particularly the liver, lungs, and hematopoietic system. In a large series of 348 patients, the French Langerhans' Cell Histiocytosis Study Group (952) found a 91.7% overall survival rate after 3 years from diagnosis. Early response to treatment was the most important parameter related to survival. Patients who had a poor initial response to therapy tended to have a poor overall prognosis.

### Non-Langerhans Cell Histiocytoses

This group of disorders also originates from cells belonging to the mononuclear-phagocyte system, but these cells do not have characteristics of Langerhans cells. The non-Langerhans cell histiocytoses can be divided further into two groups based on pathophysiology: reactive disorders and neoplastic disorders.

#### Reactive Non-Langerhans Cell Histiocytoses

These disorders are secondary histiocytoses that are usually associated with a chronic infection, an underlying immunologic defect (often familial), or both (863).

Chronic infection with an obligate intracellular microorganism is by far the most common cause of reactive, non-Langerhans cell histiocytosis. These agents include leishmania, hematozoa, mycobacteria, chlamydia, rickettsia, salmonella, and brucella. These reactive histiocytoses are usually disseminated, but some, such as Whipple's disease and rhinoscleroma, are localized. The reactive forms of non-Langerhans cell histiocytosis that are caused by an infectious agent are often very difficult to diagnose because the agent is usually extremely small and dispersed in a cytoplasm where the stored lipids and pigments preclude easy identification.

Immune deficiencies are the second leading cause of reactive, non-Langerhans cell histiocytosis. In this group of disorders, hyperplasia of the macrophagic system is secondary to cellular or humoral immune deficiency. In some cases, the histiocytosis is only relative. In these cases, the mesenchyme and the absolute population of histiocytes and macrophages are normal but appear abnormally abundant because of the depletion of lymphocytes in the various lymphoid tissues of the body (953). In other cases, however, true histiocytosis is caused by either a graft-versus-host reaction or by a chronic infection. The reactive, non-Langerhans cell histiocytoses that result from immunodeficiency include a number of familial disorders, including familial reticuloendotheliosis with eosinophilia, familial lipochromic histiocytosis, familial granulomatosis, familial hemophagocytic reticulosis, and familial lymphohistiocytosis. Of these disorders, familial lymphohistiocytosis is most likely to be associated with neurological and ocular dysfunction (863, 954,955). Petersen and Kuwabara (956) described the autopsy findings in a 16-month-old male infant with this condition. There was infiltration of the choroid, retina, and vitreous with lymphocytes and large erythrophagocytic histiocytes. Both optic discs were swollen. The patient also had histiocytic infiltration of the liver, spleen, lymph nodes, thymus, meninges, and lungs. The specific disease entities in this group were described in detail by Stephan (863).

#### Neoplastic Non-Langerhans Cell Histiocytoses

The disorders in this group include malignant histiocytosis and true histiocytic sarcoma. **Malignant histiocytosis** is a

systemic progressive invasive proliferation of morphologically atypical histiocytes (957,958). The term replaces several older designations, including histiocytic medullary reticulosis, leukemic reticulosis, malignant leukemic reticulohistiocytosis, and histiocytic leukemia. Malignant histiocytosis should not be confused with the tumor that was once called histiocytic lymphoma and reticulum cell sarcoma. This lesion is derived not from histiocytes but from lymphocytes and hence is called ''diffuse large-cell lymphoma'' (discussed earlier).

Malignant histiocytosis is characterized by fever, anemia (often hemolytic), thrombocytopenia, and fibrinogenopenia, often leading to a hemorrhagic diathesis. The liver and spleen are enlarged. The peripheral lymph nodes also become enlarged and are often painful. Bone lesions may develop, and there may be involvement of the intestines (959). Skin lesions are common especially in children (634). Malignant histiocytosis is a major cause—if not the major cause—of the midline granuloma syndrome (960,961). Although the CNS is rarely involved at the time of diagnosis, overt neurological disease may develop during therapy (962) and is commonly found at autopsy. Ocular involvement is also extremely rare; however, Cogan (963) observed infiltration of the choroid by normal-appearing histiocytes in two patients who had this disease, and we assume that any layer of the eye can be involved.

Many cases previously diagnosed as malignant histiocytosis have been reclassified, falling into the newer categories of the anaplastic lymphomas and the reactive hemophagocytic syndrome (964–967). The pathologic diagnosis of malignant histiocytosis may be extremely difficult in the early stages. The histologic pattern is often pleomorphic and sometimes appears as a granulomatous infiltrate in which the atypical histiocytes are difficult to identify (966). In fact, the infiltrate is composed of lymphocytes, leukocytes (particularly eosinophils), macrophages, a few giant cells, and sometimes cells very similar to Reed-Sternberg cells (Fig. 34.48) (964–966,968,969). A precise diagnosis requires analysis of the tumor cells using cytoenzymatic and immunocytologic techniques and identification of features that implicate a histiocytic origin (960,964,965,967). The reclassification of many patients previously thought to have malignant

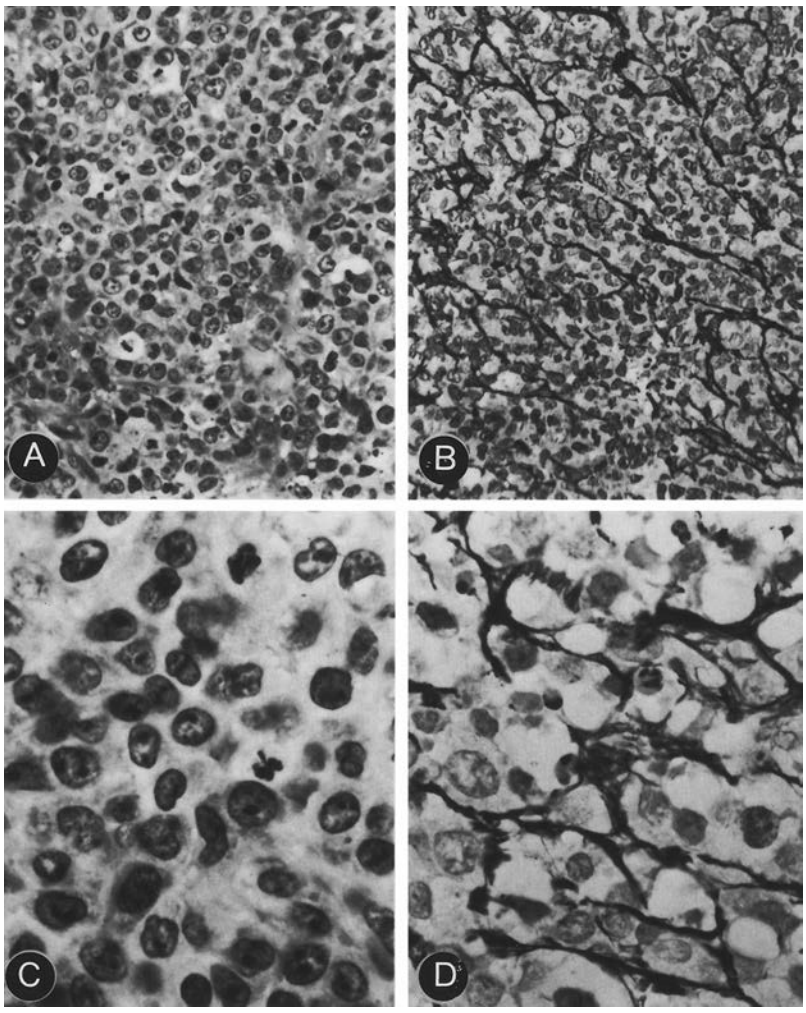



**Figure 34.48.** Histopathologic appearance of malignant histiocytosis. *A*, Low-power, hematoxylin and eosin stain. *B*, Low-power, silver stain. *C*, High-power, hematoxylin and eosin stain. *D*, High-power, silver stain. (From Laeng H, Gerber H, Mueller J. Malignant histiocytosis [histiocytic sarcoma]. Acta Otolaryngol 1986;101:135–145.)

histiocytosis into new categories of nonhistiocytic malignancy makes it difficult to draw accurate conclusions with regard to prognosis and therapy (966).

### Other Non-Langerhans Cell Histiocytoses

Several other histiocytoses that do not involve Langerhans cells have yet to be classified. Two of these disorders are of particular interest to the neurologist and the ophthalmologist.

#### Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease)

**Rosai-Dorfman disease** is a nonneoplastic disorder characterized by massive painless cervical lymphadenopathy, fever, and weight loss (970–976). Although involvement of the cervical chain is most frequent, any of the lymph nodes may be involved. Extranodal involvement is frequent and may be the presenting feature of the disease. The tissues of the orbit may be involved in such cases (977–979). For example, some patients develop bilateral or unilateral proptosis from large collections of histiocytes mixed with lymphocytes in the soft tissues of the orbit (Fig. 34.49). In addition, Stopak et al. (975) described a patient in whom the condition presented as an epibulbar mass, and Dolman et al. (980) described a patient who developed epiphora and paranasal swelling from involvement of the lacrimal sac and duct. Loss of vision associated with optic disc swelling may occur from compression or infiltration of one or both optic nerves, and diplopia may result from compression or infiltration of the extraocular muscles (Fig. 34.50).

Neurological dysfunction from involvement of the brain, spinal cord, or both may occur in patients with Rosai-Dorfman disease (981,982). The clinical manifestations in these patients depend on the size and location of the lesions. Some patients have multiple dural-based lesions, the appearance of which suggest single or multiple meningiomas (983).

In some cases, intracranial involvement by Rosai-Dorfman disease causes visual manifestations. Bhattacharjee and colleagues (984) described a 78-year-old man with Rosai-Dorfman disease who developed blurred vision and headaches from an isolated lesion in the suprasellar cistern, and Shaver et al. (985) reported a 5-year-old boy who presented with signs of a cavernous sinus syndrome and was found to have a similar lesion confined to the temporal bone. Kitai described occipital lobe involvement with this disease (986).

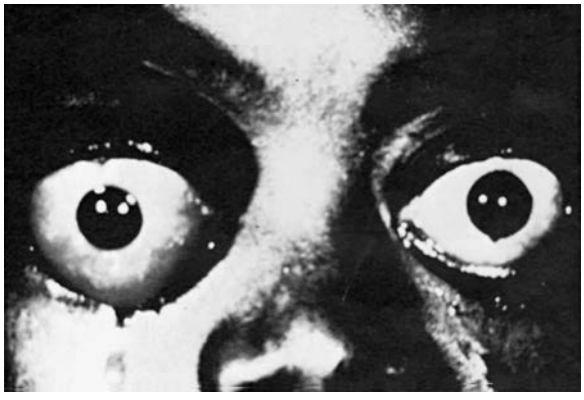


**Figure 34.49.** Bilateral proptosis in an African child with sinus histiocytosis and massive lymphadenopathy (Rosai-Dorfman disease). (From Jakobiec FA, Font RL. Orbit. In Spencer WH, ed. Ophthalmic Pathology: An Atlas and Textbook. Philadelphia: WB Saunders, 1986:2459–2860.)

The histologic appearance of the lesion in Rosai-Dorfman disease is distinctive. Sheets of histiocytes that have none of the enzymatic, immunocytologic, or morphologic characteristics of Langerhans cells are present (976,987,988). These histiocytes often contain engulfed erythrocytes or lymphocytes. Scattered among the sheets of histiocytes are mature lymphocytes. In some lesions, there is a follicular pattern. The cause of the disorder is not known, although there appears to be an association with autoimmune disorders (976).

Rosai-Dorfman disease is generally self-limited, although the course of the illness may be long. Because it is not associated with involvement of the viscera, the prognosis is quite good. Patients with intracranial involvement may be successfully managed by microsurgical resection followed by stereotactic radiation for residual tumor in cases where complete resection carries a risk for potential excess morbidity (989).

#### Juvenile Xanthogranuloma and Eruptive Histiocytoma

**Juvenile xanthogranuloma** is an uncommon disorder, characterized by a proliferation of non-Langerhans cells, that is neither clearly reactive nor neoplastic. The condition is termed ''juvenile,'' because it always affects infants and young children. It is characterized by multiple small nodules that are initially pink and tense and later yellow and wrinkled. These lesions affect the face, trunk, and, occasionally, ocular and orbital structures (Fig. 34.51). They usually regress spontaneously without scarring.

Two forms of this disorder are described. A **micronodular form** is characterized by lesions that are 2–5 mm in diameter and is sometimes associated with neurofibromatosis type 1 (NF1). A **macronodular form** is characterized by lesions that are 10–20 mm in diameter and is sometimes associated with systemic lesions in the skeleton, lungs, gonads, kidneys, and pericardium.

Ophthalmologically, juvenile xanthogranuloma is best known for iris lesions that may bleed spontaneously, causing a hyphema (990–992). An extremely unusual case of optic nerve, retinal, and choroidal involvement was reported by Wertz et al. (993). The patient was a 20-month-old girl who had become irritable and was noted to have darkening of the iris. She had neither skin lesions nor any evidence of a systemic disease. The ocular lesion was accompanied by hemorrhagic infarction of the retina and neovascularization of the iris, apparently related to occlusion of the central retinal vein. The eye became blind, glaucomatous, and painful. It was enucleated 3 weeks after the onset of symptoms. Histologically, the optic disc, retrobulbar portion of the optic nerve, juxtapapillary retina, and choroid all contained large numbers of histiocytes and Touton giant cells (Fig. 34.52). Foci of lymphocytes, plasma cells, and eosinophils were also

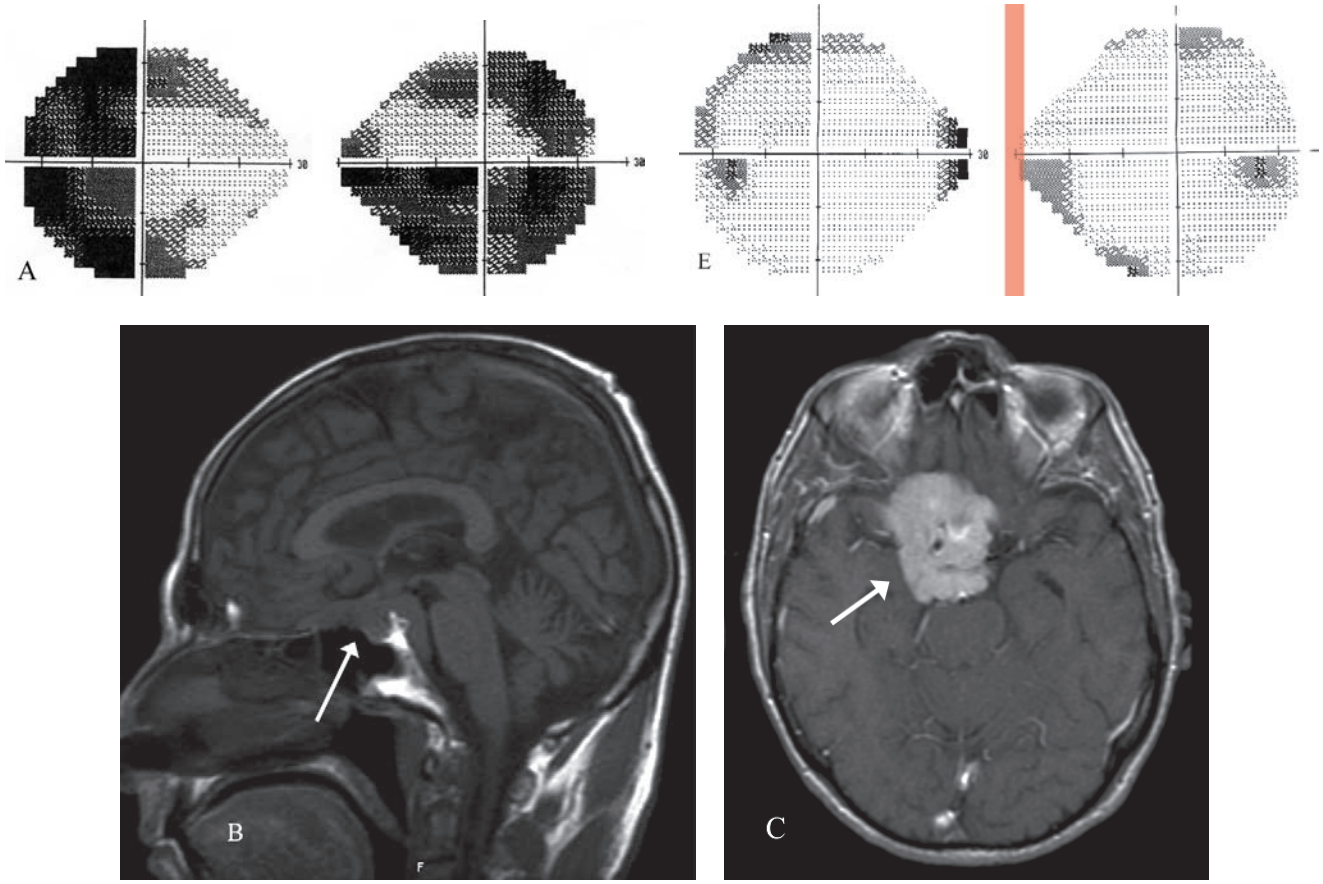



**Figure 34.50.** A 68-year-old physician presented with a 7-month history of visual loss in his left eye. Visual acuity was 20/25 in the right eye and 20/400 in the left eye. *A*, Visual field testing revealed a bitemporal defect plus an inferior nasal defect in the right eye. There was a mild left relative afferent pupillary defect, and the optic discs appeared normal. *B*, T1-weighted, sagittal precontrast magnetic resonance image demonstrates a tumor in the sellar and suprasellar region that is isointense with brain (*arrow*). *C,* T1-weighted, axial magnetic resonance image after intravenous injection of gadolinium-DTPA demonstrates enhancement of the lesion. *D,* The patient underwent biopsy and decompression of the chiasmal region. Pathology showed aggregates of histiocytes with eosinophilic cytoplasm with engulfment of viable lymphocytes and plasma cells by histiocytes (emperipolesis) consistent with a Rosai-Dorfman disease. *E,* At five weeks postoperatively, the visual acuity was unchanged, but visual fields showed significant improvement. (Courtesy of Neil R. Miller.)

present. The patient described by Borne et al. also had involvement of the retina, choroid, and iris (992). This patient also had no cutaneous lesions. The correct diagnosis was made by excisional biopsy of the iris.

Eyelid and other cutaneous lesions occur in some patients with juvenile xanthogranuloma (Fig. 34.51). These lesions have a typical yellow, waxy, nodular appearance that is caused by infiltration of the dermis by histiocytes. As noted above, viscera are occasionally affected in the macronodular form of this condition, and orbital involvement with destruction of bone may occur (922,994–996).

The CNS may also be involved with this condition. Botella et al. (997) reported an 18-year-old man who developed the characteristic dermatologic papules of juvenile xanthogranuloma, which were confirmed by histopathology. He subsequently developed memory loss. A CT scan showed several cerebral and cerebellar lesions, although these were not confirmed histologically.

Juvenile xanthogranuloma can occur in association with juvenile chronic myelogenous leukemia and juvenile NF1. Zvulunov et al. (998) found a family history in 47% of patients with juvenile xanthogranuloma and NF1. These authors concluded that children manifesting the two conditions are at substantial risk for developing juvenile chronic myelogenous leukemia.

The cell that characterizes juvenile xanthogranuloma is

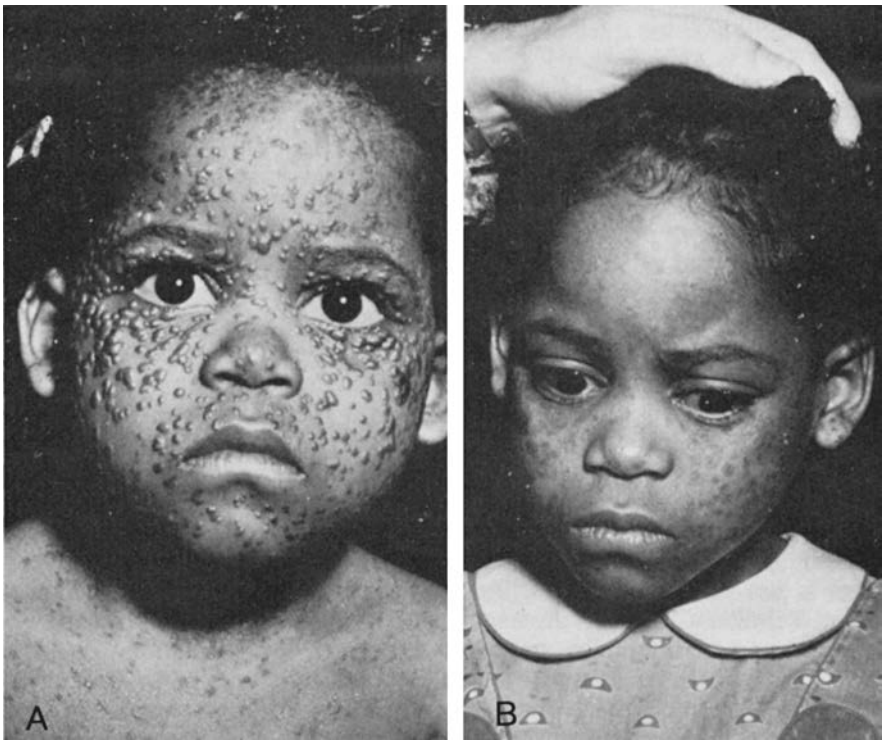



**Figure 34.51.** Juvenile xanthogranulomas of face and thorax. *A*, Extensive involvement of face and thorax in a 2½-year-old girl. Note that these lesions are larger than those of Langerhans cell histiocytosis and preferentially involve the face rather than just the scalp and trunk. *B*, Spontaneous regression of lesions began when the patient was 4 years old and was complete by the time she was 5½. This photograph was taken when the patient was 6 years old. (From Zimmerman LE. Ocular lesions of the juvenile xanthogranuloma: Nevoxanthoendothelioma. Trans Am Acad Ophthalmol Otolaryngol 1965; 69:412–439.)

the multinucleated **Touton giant cell**. This cell is characterized by multiple nuclei arranged in a circle in the middle of the cell and enclosing a central, intensely eosinophilic cytoplasm. The outer cytoplasm between the nuclei and the cell membrane is more frothy and vacuolated. Surrounding the Touton giant cells are lymphocytes, plasma cells, occasional eosinophils, and mononucleated polygonal and spindled non-Langerhans histiocytes. Immunohistochemical analysis demonstrates the histiocytes to be of monophage-phagocyte and, therefore, plasma cell origin (999).

The adult counterpart of juvenile xanthogranuloma is the disorder called **eruptive histiocytoma** (855,1000). This con-

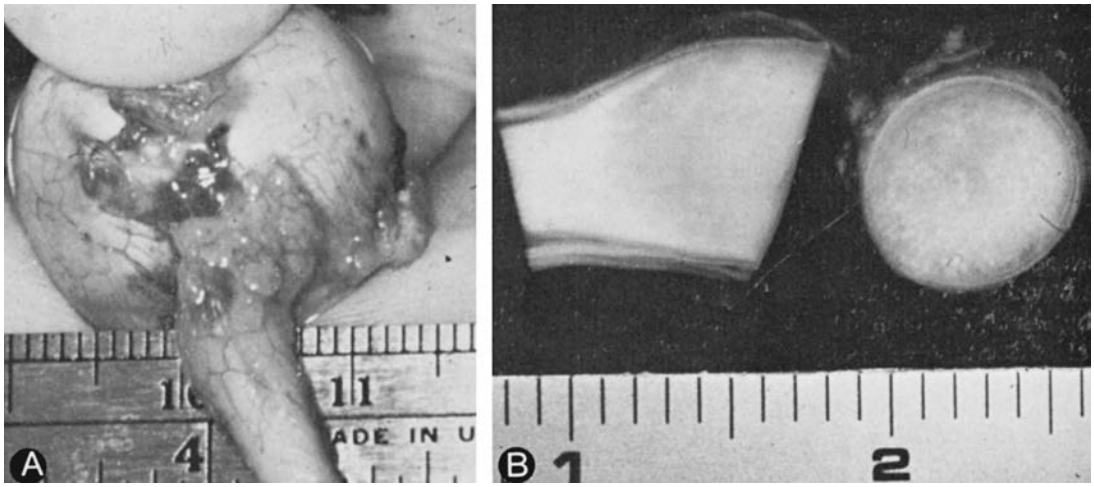



**Figure 34.52.** Juvenile xanthogranuloma of the optic nerve. The patient was a 20-month-old girl who had become irritable and was noted to have darkening of the iris. She had neither skin lesions nor any evidence of a systemic disease. The ocular lesion was accompanied by hemorrhagic infarction of the retina and neovascularization of the iris, apparently related to occlusion of the central retinal vein. The eye became blind, glaucomatous, and painful. It was enucleated 3 weeks after the onset of symptoms. *A*, Enucleated eye and attached portion of optic nerve demonstrates fusiform thickening of retrobulbar optic nerve. *B*, Longitudinal and cross-sectional view of thickened portion of optic nerve. *(Figure continues.)*

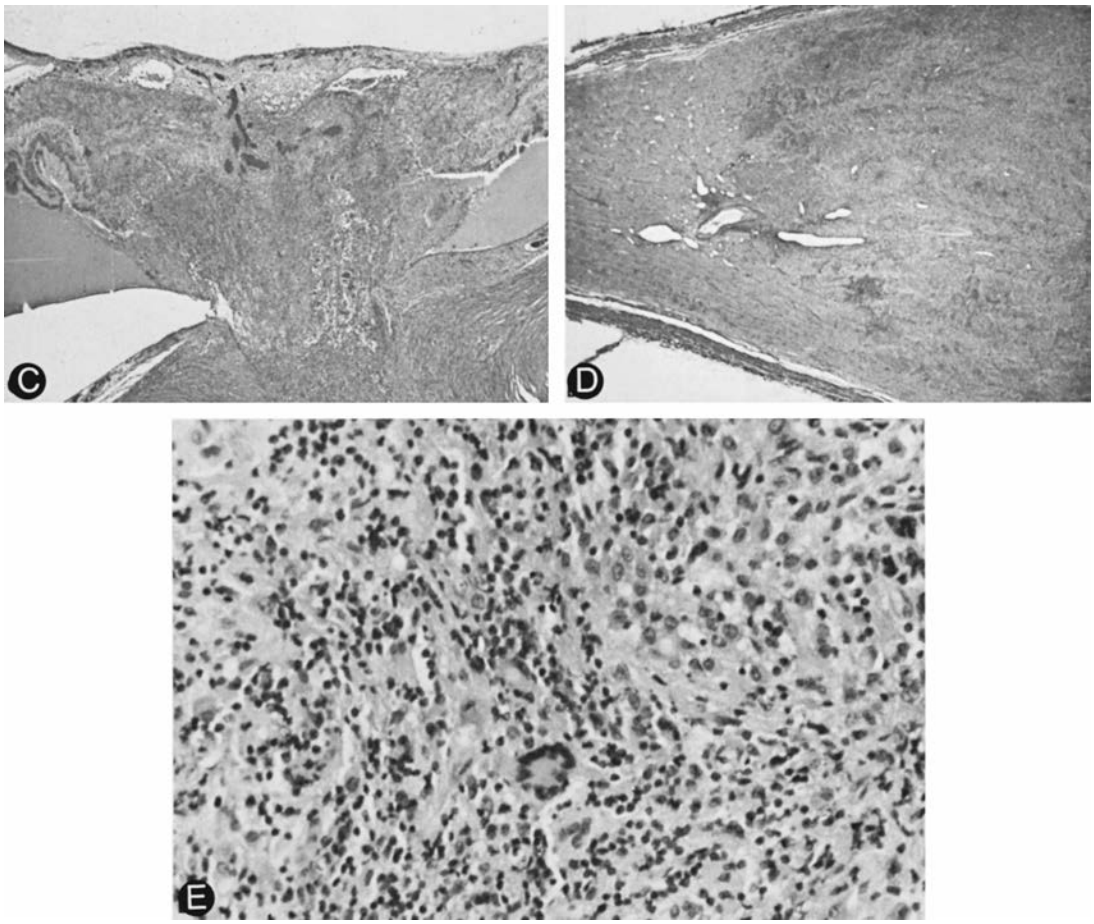



**Figure 34.52.** Continued. *C*, Histopathologic section through optic disc shows marked infiltration and thickening of the optic nerve by histiocytic cells. A similar histiocytic infiltrate is present in the choroid immediately to the right of the optic disc. There is a serous detachment of the peripapillary retina. *D*, Longitudinal section through the optic nerve corresponding to the gross longitudinal section through the nerve seen in *B*. The thickened portion of the nerve is replaced by histiocytic cells. *E*, High-power view of infiltrated optic nerve shows a prominent Touton giant cell and many eosinophils among the predominating histiocytes. (From Wertz FD, Zimmerman LE, McKeown CA, et al. Juvenile xanthogranuloma of the optic nerve disc, retina, and choroid. Ophthalmology 1982;89:1331–1335.)

dition is characterized by lesions on the face, trunk, and sometimes the mucosa. The lesions have the same clinical evolution and the same histologic picture as do the lesions of juvenile xanthogranuloma.

Both juvenile xanthogranuloma and eruptive histiocytoma are benign, self-limited disorders that tend to recur over months to years. The lesions usually respond well to systemic corticosteroids or to low doses of radiation therapy.

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