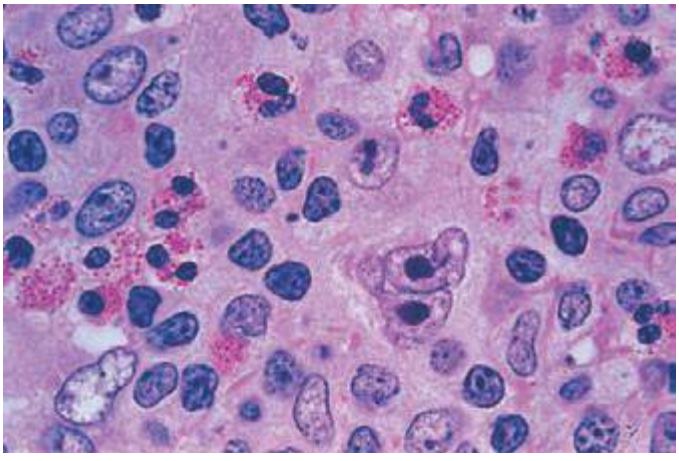

FIGURE 134-11 Mixed-cellularity Hodgkin's lymphoma. A Reed-Sternberg cell is present near the center of the field; a large cell with a bilobed nucleus and prominent nucleoli giving an "owl's eyes" appearance. The majority of the cells are normal lymphocytes, neutrophils, and eosinophils that form a pleomorphic cellular infiltrate.

The staging evaluation for a patient with Hodgkin's lymphoma would typically include a careful history and physical examination; complete blood count; erythrocyte sedimentation rate; serum chemistry studies including LDH; chest radiograph; CT scan of the chest, abdomen, and pelvis; and bone marrow biopsy. Many patients would also have a PET scan or a gallium scan. Although rarely used, a bipedal lymphangiogram can be helpful. PET and gallium scans are most useful to document remission. Staging laparotomies were once popular for most patients with Hodgkin's lymphoma but are now done rarely because of an increased reliance on systemic rather than local therapy.

TREATMENT CLASSICAL HODGKIN'S LYMPHOMA

Patients with localized Hodgkin's lymphoma are cured >90% of the time. In patients with good prognostic factors, extended-field radiotherapy has a high cure rate. Increasingly, patients with all stages of Hodgkin's lymphoma are treated initially with chemotherapy. Patients with localized or good-prognosis disease receive a brief course of chemotherapy followed by radiotherapy to sites of node involvement. Patients with more extensive disease or those with B symptoms receive a complete course of chemotherapy. The most popular chemotherapy regimen used in Hodgkin's lymphoma is a combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Today, most patients in the United States receive ABVD, but a weekly chemotherapy regimen administered for 12 weeks called *Stanford V* is becoming increasingly popular, but it includes radiation therapy, which has been associated with life-threatening late toxicities such as premature coronary artery disease and second solid tumors. In Europe, a high-dose regimen called *BEACOPP* incorporating alkylating agents has become popular and might have a better response rate in very-high-risk patients. Long-term disease-free survival in patients with advanced disease can be achieved in >75% of patients who lack systemic symptoms and in 60–70% of patients with systemic symptoms.

Patients who relapse after primary therapy of Hodgkin's lymphoma can frequently still be cured. Patients who relapse after initial treatment with only radiotherapy have an excellent outcome when treated with chemotherapy. Patients who relapse after an effective chemotherapy regimen are usually not curable with subsequent chemotherapy administered at standard doses. However, patients with a long initial remission can be an exception to this rule. Autologous bone marrow transplantation can cure half of patients in whom effective chemotherapy regimens fail to induce durable remissions. The immunotoxin, brentuximab vedotin, a CD30-directed chemotherapy that selectively targets cells expressing CD30, is active in the salvage setting and is being integrated into ABVD for initial treatment.

Because of the very high cure rate in patients with Hodgkin's lymphoma, long-term complications have become a major focus for clinical research. In fact, in some series of patients with early-stage disease, more patients died from late complications of therapy than from Hodgkin's lymphoma itself. This is particularly true in patients with localized disease. The most serious late side effects include second malignancies and cardiac injury. Patients are at risk for the development of acute leukemia in the first 10 years after treatment with combination chemotherapy regimens that contain alkylating agents plus radiation therapy. The risk for development of acute leukemia appears to be greater after MOPP-like (mechlorethamine, vincristine, procarbazine, prednisone) regimens than with ABVD. The risk of development of acute leukemia after treatment for Hodgkin's lymphoma is also related to the number of exposures to potentially leukemogenic agents (i.e., multiple treatments after relapse) and the age of the patient being treated, with those age >60 years at particularly high risk. The development of carcinomas as a complication of treatment for Hodgkin's lymphoma has become a major problem. These tumors usually occur ≥10 years after treatment and are associated with use of radiotherapy. For this reason, young women treated with thoracic radiotherapy for Hodgkin's lymphoma should institute screening mammograms 5–10 years after treatment, and all patients who receive thoracic radiotherapy for Hodgkin's lymphoma should be discouraged from smoking. Thoracic radiation also accelerates coronary artery disease, and patients should be encouraged to minimize risk factors for coronary artery disease such as smoking and elevated cholesterol levels. Cervical radiation therapy increases the risk of carotid atherosclerosis and stroke.

A number of other late side effects from the treatment of Hodgkin's lymphoma are well known. Patients who receive thoracic radiotherapy are at very high risk for the eventual development of hypothyroidism and should be observed for this complication; intermittent measurement of thyrotropin should be made to identify the condition before it becomes symptomatic. Lhermitte's syndrome occurs in ~15% of patients who receive thoracic radiotherapy. This syndrome is manifested by an "electric shock" sensation into the lower extremities on flexion of the neck. Infertility is a concern for all patients undergoing treatment for Hodgkin's lymphoma. In both women and men, the risk of permanent infertility is age-related, with younger patients more likely to recover fertility. In addition, treatment with ABVD increases the chances to retain fertility.

Nodular Lymphocyte-Predominant Hodgkin's Lymphoma Nodular lymphocyte-predominant Hodgkin's lymphoma is now recognized as an entity distinct from classical Hodgkin's lymphoma. Previous classification systems recognized that biopsies from a subset of patients diagnosed as having Hodgkin's lymphoma contained a predominance of small lymphocytes and rare Reed-Sternberg cells (Fig. 134-11). A subset of these patients have tumors with nodular growth pattern and a clinical course that varied from that of patients with classical Hodgkin's lymphoma. This is an unusual clinical entity and represents <5% of cases of Hodgkin's lymphoma.

Nodular lymphocyte-predominant Hodgkin's lymphoma has a number of characteristics that suggest its relationship to non-Hodgkin's lymphoma. These include a clonal proliferation of B cells and a distinctive immunophenotype; tumor cells express J chain and display CD45 and epithelial membrane antigen (EMA) and do not express two markers normally found on Reed-Sternberg cells, CD30 and CD15. This lymphoma tends to have a chronic, relapsing course and sometimes transforms to diffuse large B-cell lymphoma.

The treatment of patients with nodular lymphocyte-predominant Hodgkin's lymphoma is controversial. Some clinicians favor no treatment and merely close follow-up. In the United States, most physicians will treat localized disease with radiotherapy and disseminated disease with regimens used for patients with classical Hodgkin's lymphoma. Regardless of the therapy used, most series report a long-term survival of >80%.