advanced age, HIV infection, and low socioeconomic status. The pathologic hallmarks of LD Hodgkin's lymphoma include a notable paucity of inflammatory cells and sheets of RS cells.

The NLP variant has emerged as a distinct entity that is more closely related to indolent NHL than to classic Hodgkin's lymphoma. The NLP form is characterized by a nodular growth pattern with variants of RS cells that have polylobated nuclei (i.e., popcorn cells); classic RS cells are usually absent. The immunophenotype of these variant cells is distinct from classic RS cells, with expression of B-cell antigens (CD19 and CD20) and CD45 and absence of CD15 and CD30. The existence of CD20 allows the therapeutic use of rituximab, an agent not typically employed in classic Hodgkin's lymphoma. The NLP variant accounts for 5% of Hodgkin's lymphoma cases, has a strong male preponderance, and tends to involve peripheral nodes but spare the mediastinum. The prognosis is excellent, although late relapses are more common than they are in classic Hodgkin's lymphoma.

Clinical Presentation

Hodgkin's lymphoma arises in lymph nodes, most commonly in the mediastinum or neck, and spreads to adjacent contiguous or noncontiguous nodal sites, including retroperitoneal nodes and the spleen. As the disease progresses, it spreads hematogenously to involve extranodal sites, including bone marrow, liver, and lung. Unlike NHL, Hodgkin's lymphoma rarely arises in extranodal sites, although it can involve extranodal sites by contiguous spread from an adjacent lymph node (e.g., vertebrae from retroperitoneal lymph nodes, pulmonary parenchyma from hilar nodes).

Hodgkin's lymphoma usually produces painless enlargement of lymph nodes, most often in the neck. Mediastinal adenopathy may be found incidentally in an asymptomatic patient on routine chest radiography. Massive mediastinal or hilar adenopathy, with or without adjacent pulmonary involvement, may cause respiratory symptoms such as cough, shortness of breath, wheezing, or stridor. At clinical presentation, about one third of patients have constitutional symptoms of fever, night sweats, or weight loss (i.e., B symptoms). Generalized pruritus is associated with the NS subtype, and patients may give a history of troubling pruritus for months to years before the diagnosis.

If left untreated, the natural history is one of inexorable, albeit often slow, progression to involve multiple nodal sites, followed by hematogenous spread to the bone marrow, liver, and other viscera. As the disease advances, patients experience B symptoms, malaise, cachexia, and infectious complications. Patients with progressive disease ultimately die of complications of bone marrow failure or infection.

Accurate staging of patients with newly diagnosed Hodgkin's lymphoma is important for treatment planning, prognosis, and assessing response to therapy. A modification of the Ann Arbor classification is used (see Table 49-4), and the suffix A or B is appended to denote the absence or presence, respectively, of B symptoms. The staging work-up of a newly diagnosed patient is similar to that for patients with NHL (see Table 49-3) and includes a history and physical examination; complete blood work, including erythrocyte sedimentation rate (ESR) and HIV serology; computed tomography (CT) scan of the chest, abdomen, and pelvis; positron emission tomography (PET) scan; and in selected cases, a bone marrow aspirate and biopsy. Additional radiographic tests (e.g., bone films, spinal magnetic resonance imaging [MRI]) should be obtained only if symptoms suggest involvement of these structures. Patients also require evaluation of cardiac and pulmonary function before administration of chemotherapy and testing for hepatitis B due to the risk of reactivation during chemotherapy. The information derived from this noninvasive work-up defines the clinical stage of a patient with Hodgkin's lymphoma.

Diagnosis and Differential Diagnosis

The diagnosis requires an adequate biopsy of the involved nodal tissue. Immunophenotyping is routinely performed to confirm the diagnosis made on routine light microscopy and to differentiate Hodgkin's lymphoma from morphologically similar NHLs (e.g., T-cell–rich large B-cell lymphoma, anaplastic large cell lymphoma).

Treatment

Hodgkin's lymphoma is highly curable; the cure rate exceeds 80% with the use of current treatment modalities. The optimal treatment, including the duration of chemotherapy and the use and dose of radiation therapy, is determined by the stage (i.e., early stage [I/II] vs. advanced stage [III/IV]), and additional prognostic features. Because most patients are young adults and experience long-term, disease-free survival, the emphasis during the past 3 decades has shifted to using therapies that minimize treatment-related morbidity and mortality without sacrificing curative potential. Primary radiation therapy is rarely used because of its delayed toxicities, which include a substantial risk of secondary solid tumors within the radiation field a decade or more after treatment, including a particularly high risk of breast cancer. Additional long-term sequelae of standard doses of chest irradiation include thyroid dysfunction (usually hypothyroidism) and accelerated coronary artery disease.

Most patients with early-stage (I/II) Hodgkin's lymphoma are treated with the ABVD chemotherapy regimen (i.e., doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) followed by a course of low-dose radiation (<30 Gy) to involved lymph node sites, which has not been associated with an increased risk of secondary solid tumors. The duration of chemotherapy and the dose of radiation depend on whether the patient has favorable or unfavorable early-stage disease. The definition of favorable disease usually incorporates the absence of a large mediastinal mass, a limited number of involved nodal sites, absence of B symptoms, younger age, and a low ESR. Patients with favorable early-stage disease typically receive two to four cycles (months) of ABVD followed by 20 Gy of radiation, whereas four to six cycles of ABVD and 30 Gy of radiation are required for patients with unfavorable disease (level I evidence).

Patients with advanced-stage (III/IV) Hodgkin's lymphoma are treated primarily with chemotherapy. The ABVD regimen is the most widely used initial treatment in the United States. ABVD is more effective and less toxic than the older MOPP regimen (i.e., nitrogen mustard, vincristine [Oncovin], procarbazine, and prednisone), and it does not cause the long-term sequelae of sterility, infertility, or treatment-induced leukemias