Hodgkin Lymphoma: Diagnosis and Treatment

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CME Activity

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Abstract

Hodgkin lymphoma is a rare B-cell malignant neoplasm affecting approximately 9000 new patients annually. This disease represents approximately 11% of all lymphomas seen in the United States and comprises 2 discrete disease entities—classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma. Within the subcategorization of classical Hodgkin lymphoma are defined subgroups: nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich Hodgkin lymphoma. Staging of this disease is essential for the choice of optimal therapy. Prognostic models to identify patients at high or low risk for recurrence have been developed, and these models, along with positron emission tomography, are used to provide optimal therapy. The initial treatment for patients with Hodgkin lymphoma is based on the histologic characteristics of the disease, the stage at presentation, and the presence or absence of prognostic factors associated with poor outcome. Patients with early-stage Hodgkin lymphoma commonly receive combined-modality therapies that include abbreviated courses of chemotherapy followed by involved-field radiation treatment. In contrast, patients with advanced-stage Hodgkin lymphoma commonly receive a more prolonged course of combination chemotherapy, with radiation therapy used only in selected cases. For patients with relapse or refractory disease, salvage chemotherapy followed by high-dose treatment and an autologous stem cell transplant is the standard of care. For patients who are ineligible for this therapy or those in whom high-dose therapy and autologous stem cell transplant have failed, treatment with brentuximab vedotin is a standard approach. Additional options include palliative chemotherapy, immune checkpoint inhibitors, nonmyeloablative allogeneic stem cell transplant, or participation in a clinical trial testing novel agents.

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In 2015, approximately 9050 new cases of Hodgkin lymphoma will be diagnosed in the United States.[1] Hodgkin lymphoma has a bimodal disease distribution, with an increased incidence in patients in their teenage years or early 20s and a similar increased incidence in patients older than 55 years.[2] The exact cause of Hodgkin lymphoma remains unknown, but factors associated with an increased risk for Hodgkin lymphoma include exposure to viral infections, familial factors, and immunosuppression. Siblings of patients with Hodgkin lymphoma have an increased risk for this disease,[3,4] and a twin of a patient with Hodgkin lymphoma is also at substantially increased risk.[5,6]

Although familial factors may suggest a genetic cause for Hodgkin lymphoma, multiple studies have also suggested that an abnormal immune response to infection may play a role in the pathogenesis of Hodgkin lymphoma. Epstein-Barr virus has been implicated in the etiology of Hodgkin lymphoma in multiple epidemiological and serologic studies, and the Epstein-Barr virus genome has been detected in tumor specimens in certain trials.[7] Furthermore, patients with human immunodeficiency virus infection are at considerably increased risk of Hodgkin lymphoma compared with the general population.[8] Patients with immunosuppression associated with human immunodeficiency virus commonly present with more advanced stage of the disease in unusual sites and have a poorer prognosis after initial treatment.[9,10] In contrast, studies have found that infections such as chickenpox, measles, mumps, rubella, and pertussis in childhood are in fact inversely associated with the risk of Hodgkin lymphoma and may be protective.[11]

Advances in therapy have substantially increased the likelihood of cure for patients with Hodgkin lymphoma. Currently, more than 80% of patients with newly diagnosed Hodgkin lymphoma are likely to be cured of their disease. Some subsets of patients still have a poorer prognosis, however, particularly patients who are elderly when they present with Hodgkin lymphoma. Although many patients have a good outcome, approximately 1150 deaths from Hodgkin lymphoma occur annually in the United States.[12]

DIAGNOSIS OF HODGKIN LYMPHOMA

Most patients with Hodgkin lymphoma present with supradiaphragmatic lymphadenopathy. Retroperitoneal and inguinal lymphadenopathy occur less frequently. Approximately one-third of patients present with constitutional symptoms. These symptoms include high fevers, drenching night sweats, and profound weight loss. Patients may also present with chronic pruritus. Although it is more common for the disease to involve regional lymph nodes, Hodgkin lymphoma may also involve extranodal sites either by direct invasion or hematogenously. Common sites that may be involved include the spleen, liver, lungs, and bone marrow.

In patients with Hodgkin lymphoma, a definitive diagnosis is critical and requires that the treating physician provide the pathologist with an adequate pathologic specimen. Fine-needle aspiration or core-needle biopsy specimens are commonly inadequate because they do not represent the architecture of the lymph node and therefore preclude an accurate diagnosis. Hodgkin lymphoma has the unique characteristic of malignant cells constituting only a minority of the intratumoral cell population, and therefore, a small biopsy specimen may not include sufficient malignant cells.[13] To establish a definitive diagnosis, it is necessary to identify Reed-Sternberg cells within the biopsy specimen. These cells are commonly seen within a rich cellular environment composed of reactive lymphocytes, eosinophils, and histiocytes. Two distinct disease entities have been defined in Hodgkin lymphoma, the commonly diagnosed classical Hodgkin lymphoma and the uncommon nodular lymphocyte-predominant Hodgkin lymphoma.[14] Within the category of classical Hodgkin lymphoma, 4 subgroups have been identified: nodular sclerosis Hodgkin lymphoma, mixed cellularity Hodgkin lymphoma, lymphocyte depletion Hodgkin lymphoma, and lymphocyte-rich Hodgkin lymphoma.

The pathologic hallmark of classical Hodgkin lymphoma is the presence of large malignant multinucleated Reed-Sternberg cells, which are present within a characteristic reactive cellular background. Each subtype of Hodgkin lymphoma has distinct clinical features. Nodular sclerosis subtype tends to affect adolescents and young adults. Most commonly, this subtype presents with localized disease often involving the mediastinum and supraclavicular or cervical lymph nodes. In contrast, mixed cellularity Hodgkin lymphoma is more prevalent either in children or elderly persons, commonly presents