MAYO CLINIC

Non-Hodgkin Lymphoma: Diagnosis and Treatment

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CME Activity

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Abstract

Non-Hodgkin lymphomas are lymphoid malignant neoplasms with diverse biological and clinical behavior. Patients typically present with persistent painless lymphadenopathy, but some patients may present with constitutional symptoms or with involvement of organs other than the lymphoid and hematopoietic system. An accurate diagnosis, careful staging of the disease, and identification of adverse prognostic factors form the basis of treatment selection. Patients commonly receive chemoimmunotherapy as initial treatment, and radiation therapy may be added if patients have early-stage disease. Most patients respond well to treatment, but relapses are frequent and additional therapies including stem cell transplant are often needed. Because many subtypes of lymphoma remain incurable with current management strategies, clinical trials are in progress to identify novel therapies with promising activity in this disease.

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Non-Hodgkin lymphomas are malignant neoplasms of B, T, and natural killer (NK) cells that typically infiltrate both lymphoid and hematopoietic tissues but can also extend to other organs. Although they include malignant neoplasms that arise from both mature and precursor cells (Table 1),[1] this review will focus on malignant neoplasms originating from mature cells. These entities constitute a diverse group of lymphoproliferative disorders that have distinct biological and clinical behavior but that typically respond to cytotoxic and biological therapies. Although generally responsive to therapy, their cure rates differ. In some cases, more than 50% of patients can be cured with current treatment; however, many subtypes of the disease remain incurable with current management strategies.

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In 2015, there will be an estimated 71,850 new cases of non-Hodgkin lymphoma in the United States.[2] This constitutes approximately 4% to 5% of all new cancers in males and females. The incidence of non-Hodgkin lymphoma steadily increases with age, and although the rate of increase has declined in recent years, the incidence of this disease continues to increase. There will be an estimated 19,790 deaths from non-Hodgkin lymphoma in 2015, and the overall 5-year survival rates are 73% for whites and 63% for African Americans.

The etiology of non-Hodgkin lymphoma has been the subject of ongoing investigation, and various genetic and infectious etiologies have been associated with different lymphoma subtypes.[3] Epstein-Barr virus is commonly associated with a number of B-cell lymphomas including Burkitt lymphoma, lymphomas arising in the setting of immunosuppression, or human immunodeficiency virus infection, as well as other lymphomas that occur in patients with seemingly normal immune systems.[4] These disorders include extranodal NK- and T-cell lymphomas involving the upper aerodigestive tract and a few other uncommon T-cell malignant neoplasms.[5] Other infectious agents that have been associated with lymphoma include human T-lymphotropic virus type 1, which has been associated with adult T-cell leukemia/lymphoma,[6] human herpesvirus 8, which has been associated with primary effusion lymphoma,[7] hepatitis B virus infection that has been associated with various subtypes of lymphoma,[8] *Helicobacter pylori* that has been associated with gastric mucosa—associated lymphoid tissue (MALT) lymphoma,[9] hepatitis C virus, which has been associated with splenic marginal zone lymphoma,[10] and *Chlamydia psittaci* and *Borrelia burgdorferi*, which have been associated with extranodal marginal zone lymphomas of the ocular adnexa or the skin.[11,12] A further risk factor for development of lymphoma is previous exposure to radiation or chemotherapy, particularly in patients with Hodgkin lymphoma who were previously treated with combination therapy.[13]

TABLE 1. Selected Entities From the World Health Organization Classification of Lymphoid Neoplasms 2008[1]

Precursor B- and T-cell neoplasms
Precursor B-cell lymphoblastic leukemia/lymphoma
Precursor T-cell lymphoblastic leukemia/lymphoma
Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Lymphoplasmacytic lymphoma
Plasma cell neoplasms
Splenic marginal zone lymphoma
Extranodal marginal zone lymphoma
Nodal marginal zone lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Primary mediastinal large B-cell lymphoma
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Hodgkin lymphoma
Mature T- and natural killer—cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Adult T-cell leukemia/lymphoma
Extranodal natural killer—/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitislike T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma, anaplastic lymphoma kinase—positive
Anaplastic large-cell lymphoma, anaplastic lymphoma kinase—negative
Immunodeficiency-associated lymphoproliferative disorders
Lymphoproliferative diseases associated with primary immune disorders
Lymphomas associated with human immunodeficiency virus infection
Posttransplant lymphoproliferative disorders

Data from *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*.[1]

GENERAL PRINCIPLES OF DIAGNOSIS AND STAGING

Most patients with non-Hodgkin lymphoma present with persistent painless lymphadenopathy, but some patients also present with constitutional symptoms, specifically drenching night sweats, persistent fevers, and unexplained weight loss. The diagnosis is established by tissue biopsy, and an adequate specimen should be obtained to ensure an accurate diagnosis. Currently, the pathologic diagnosis of lymphoma is based on the World Health Organization classification of lymphoid neoplasms (Table 1).[1] This classification separates lymphoid neoplasms into 4 main categories—precursor B- and T-cell neoplasms, mature B-cell neoplasms, mature T-/NK-cell neoplasms, and immunodeficiency-associated lymphoproliferative disorders. An accurate diagnosis of lymphoma is critical because the pathology result generally determines the management