



Understanding Non-Hodgkin's Lymphomas

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The non-Hodgkin's lymphomas (NHLs) have the second fastest rising incidence of cancer in the United States (Cure for Lymphoma Foundation, 1999), and since the 1970s, the number of new cases per year has nearly doubled (National Cancer Institute, 2000) as a result of improved detection and diagnostic methods, as well as an actual increase in the number of new cases. The incidence of NHL increases with age, and more than 50% of patients are older than 60 years of age at the time of diagnosis. In 2002, 53,900 new cases of NHL were diagnosed and 24,400 individuals died of the disease (Jemal, Thomas, Murray, & Thun, 2002).

NHLs are a diverse group of malignancies that originate in the lymphoid system. This system includes the lymph nodes as well as extranodal sites, such as bone marrow, the spleen, the tonsils and adenoids, the thymus gland, and Peyer's patches in the small intestine. The lymphocyte lineage provides immunity against infection. B cells are responsible for antibody-mediated immunity (humoral immunity), and T cells are responsible for cell-mediated immunity. B cell lymphomas comprise the majority of the lymphomas and generally are not as aggressive as T cell lymphomas (Yarbro, 2000).

As they develop, normal lymphocytes go through many stages from small, resting, inexperienced cells to larger, functioning cells. Malignant lymphocytes resemble the normal tissue from which they are derived. Hereditary, acquired (e.g., infection, autoimmune disorders, certain drugs), or environmental (e.g., toxins) factors stimulate this change, and lymphoid malignancies can originate from cells arrested at any of these stages. Lymphomas derived from naive cells that have not been exposed to one or more of these factors usually are clinically indolent and histologically low grade, whereas naive cells that have been exposed to one or more of these factors and have undergone blast transformation usually become proliferating large cell lymphomas.

NHLs can present in a variety of ways; therefore, an extensive workup is required to make a definitive diagnosis. This begins with a thorough history and physical examination to assess the progress of the disease and presence of B symptoms and to identify any palpable lymphadenopathy. Next, a tissue biopsy by excision of a lymph node, computerized tomography (CT), or open surgical biopsy is performed to identify the histology of the tissue, conduct cytogenetic and molecular biologic studies of the tumor, and test immunohistochemistry stains to determine surface markers. Cell surface markers are clusters of differentiation used to identify groups of antigens on the cell surface. Initial blood studies include a complete blood count, routine kidney and liver function panels, lactate dehydrogenase, and serum B₂-microglobulin. A bone marrow biopsy and CT scan of the chest, abdomen, and pelvis are performed to complete the staging. For patients with aggressive lymphomas, a pretreatment gallium scan may be performed as a baseline to evaluate response to therapy. Positron emission tomographic (PET) scanning has shown the same specificity and sensitivity as gallium scans in staging patients with lymphoma (Armitage, Mauch, Harris, & Berman, 2001). In addition, Schoder et al. (2001) found that PET imaging had a major impact on the management of patients with lymphoma, contributing to changes in the clinical stage in 44% (21% were upstaged, and 23% were downstaged) and in treatment in more than 69% of cases.

Over the years, several different classification systems have been used to identify the various lymphomas. In the United States, the Rappaport Classification (Rappaport, Winter, & Hicks, 1956) was used until the 1970s. This classification distinguished lymphomas based on the morphologic features of the pattern of growth (i.e., nodular or diffuse) and degree of cytologic differentiation of the predominant malignant cell (i.e., well differentiated, poorly differentiated, and undifferentiated). In 1982,

a study funded by the National Cancer Institute proposed the working formulation based on morphologic features that classified the lymphomas into low grade, intermediate grade, and high grade ("National Cancer Institute Sponsored Study," 1982).

In 1993, the International Lymphoma Study Group developed the Revised European American Lymphoma (REAL) classification (see Table 1), which categorizes all lymphoid neoplasms, lymphomas, and leukemias as B cells or T cells according to the clinical features of their morphology, immunophenotype, and genetic features. In most typical cases of lymphoma, the morphology of the cell is sufficient for diagnosis and classification because the REAL classification system is based on the location within the structure of the lymphocyte as well as the point in cell maturation from which tumor growth is initiated. In cases that are not clearly identified by morphologic features, immunophenotyping and cytogenetics are necessary to differentiate benign tissue from malignant tissue and clearly define the neoplasm. Thus, this classification system considers B cell small lymphocytic lymphoma and B cell chronic lymphocytic leukemia as different manifestations of the same cell type and the acute lymphocytic leukemias and lymphoblastic lymphomas as different manifestations of the same cell type (Armitage & Weisenburger, 1998). In the late 1990s, the World Health Organization (WHO) modified the REAL classification system by incorporating all lymphoid neoplasms in a single classification. As a result, the REAL/WHO

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