Review

Nodular Lymphocyte Predominant Hodgkin Lymphoma: Biology, Diagnosis and Treatment

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Abstract

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is an uncommon variant of classical Hodgkin lymphoma. It is characterized histologically by presence of lymphohistiocytic cells which have B-cell phenotype, are positive for CD19, CD20, CD45, CD79a, BOB.1, Oct.2, and negative for CD15 and CD30. Patients often present with early stage of disease and do not have classical B symptoms. The clinical behavior appears to mimic that of an indolent non-Hodgkin lymphoma more than that of classical Hodgkin disease. The purpose of the present report is to define the biology of NLPHL, review its clinical presentation, and summarize the available clinical data regarding treatment.

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Introduction

Hodgkin's lymphoma accounts for approximately 8% of lymphoid malignancies.[1] According to the World Health Organization (WHO) classification, Hodgkin lymphomas (HLs) are comprised of 2 disease entities based on the morphologic, genotypic, and phenotypic characteristics.[1] Classical HL (cHL), the more common of the 2 entities, can be subdivided into 4 subtypes (nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted) and most practicing oncologists are comfortable with the management of this entity. In addition, many large clinical trials have defined the management for cHL.

In contrast, the less common nodular lymphocyte predominant (LP) HL (NLPHL) comprises only 3% to 8% of all Hodgkin cases.[2,3] Because of the relative rarity of this entity, there are limited prospective clinical trial data to guide management and most of our knowledge has been acquired through retrospective data analyses. As such, many oncologists remain uncomfortable with treating this entity.

Epidemiology

Nodular LP HL is a predominantly male disease with a 3:1 male to female ratio in Caucasian and a 1.2:1 ratio in African American individuals. It exhibits bimodal age distribution curves—one peak in children and another in adults. In adults, the median age is similar to that of cHL, 30 to 35 years.[4]

Morphology and Immunophenotype

The characteristic cells of NLPHL are LP or popcorn cells (formerly lymphohistiocytic cells [L&H cells]). Histologically, NLPHL shows a nodular growth pattern in most cases. However, in some cases, nodular and diffuse architectures might coexist. The nodules are composed of small lymphocytes and histiocytes with scattered LP cells, few plasma cells, and eosinophils. The LP cells have vesicular polylobulated nuclei and distinct, but small, usually peripheral nucleoli, without perinucleolar halos that are typically surrounded by small lymphocytes (Figs. 1 and 2). In contrast, the key morphologic feature of cHL is the presence of Hodgkin cells (mononucleated giant cell) or Reed-Sternberg cells (multinucleated giant cell) (H-RS cells) in the background of acute and chronic inflammatory cells—plasma cells, eosinophils, histiocytes, and T cells.[5]

The immunophenotype of NLPHL is significantly different from that of cHL (Table 1).[6] LP cells of NLPHL characteristically express B cell-associated antigens—CD19, CD20, CD22, CD79a, and CD45 (Fig. 3). However, they lack CD15 and CD30 expression, a hallmark feature of cHL cells. NLPHL cells also express epithelial membrane antigen in 50% of cases, and transcription factors for B cell development, such as BOB.1 (Fig. 4), Oct.2, PAX5, BCL6, and germinal center marker, but are CD10-negative. The Reed-Sternberg cells of cHL typically express CD15 and CD30 and do not express CD45, J chain, B-cell antigens (CD20, CD79a, etc) or B-cell transcription factors (Oct.2, BOB.1) in most cases. H-RS cells are weakly positive for PAX5. The plasma

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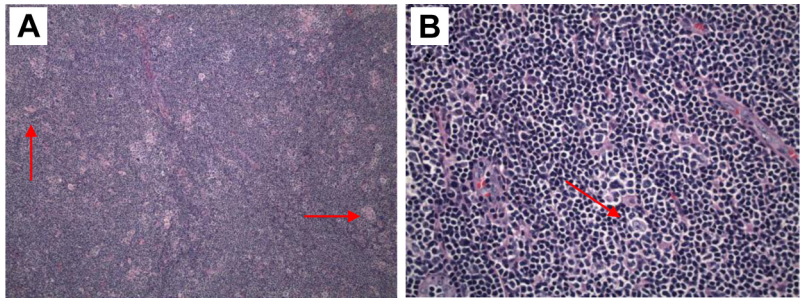
Figure 1 Lymphocyte Predominant (Popcorn) Cells. (A) Low Power and (B) High Power Lymph Node Biopsy Displaying Characteristic Large Multilobated LP Cells With Small Vesicular, Polylobulated Nuclei, and Distinct Peripheral Nucleoli, Without Perinucleolar Halos (Arrows). Hematoxylin and Eosin Stain



Abbreviation: LP = lymphocyte predominant.

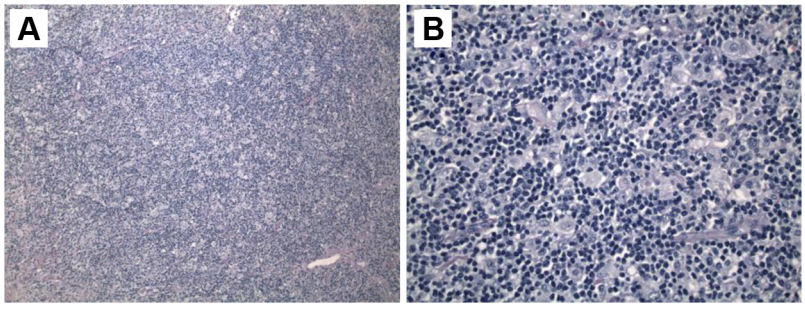
cell-specific transcription factor MUM1 is inconsistently expressed in LP cells, whereas in cHL MUM1 is consistently positive in H-RS cells with high staining intensity. LP cells are negative for Epstein Barr virus, however positivity can be seen in up to 40% of cHL cases.

The background of NLPHL demonstrates an expanded meshwork of follicular dendritic cells, which could be highlighted by CD21 immunostains (Fig. 5). The background cells are composed of small lymphocytes and histiocytes. The lymphocytes are germinal center T-lymphocytes (CD4-positive [$CD4^+$]/$CD57^+$) and polyclonal small B lymphocytes with a mantle zone phenotype (immunoglobulin [Ig]M^+IgD^+) (Fig. 6).[7]

The lymphocyte-rich variant of cHL (LRCHL) has some morphological similarities with NLPHL and often has a similar clinical presentation and disease course. LRCHL commonly demonstrates a nodular pattern; the nodules are composed of expanded mantle zone B cells (IgM^+IgD^+) with eccentric regressed germinal centers without eosinophils, plasma cells, or neutrophils. The H-RS cells can be seen in the nodules or between the nodules. Immunophenotyping is needed to differentiate LRCHL from NLPHL; the H-RS cells in the LRCHL are positive for CD15 and CD30, and negative for CD20 and CD45.

It also is important to distinguish T-cell/histiocyte rich B-cell lymphoma (T/HRBCL), a variant of diffuse large B-cell lymphoma (DLBCL), from NLPHL because they both share similar morphology and immunophenotype. In NLPHL, tumor cells are characteristically LP cells, in a background meshwork of follicular dendritic cells, abundant small B cells, and mainly $CD4^+$/$CD57^+$ follicular T cells forming rosettes. In T/HRBCL, most tumor cells resemble centroblasts and immunoblasts, with only some LP-like cells and only scarce RS-like cells in the background of absent follicular dendritic cells (FDC), rare small B lymphocytes, T cells (which are mainly $CD8^+$ cytotoxic T cells), and histiocytes with rare formation of T-cell rosettes. NLPHL and T/HRBCL share many immunophenotypic features, with the exception that CD79a and BCL2 are more frequently expressed in T/HRBCL. Moreover, the transcription factor PU.1, which is necessary in early B cell differentiation, is reduced or absent in T/HRBCL, but variably expressed in NLPHL. In NLPHL, neoplastic cells inside FDC networks appear to have an increased expression of J chain and

Figure 2 Lymph Node Biopsy (A) Low Power and (B) High Power Lymph Node Biopsy Displaying Characteristic LP Cells in a Background of Small Lymphocytes and Follicular Dendritic Cells. Classic Rosette Formation Around the LP Cells can be Seen. Hematoxylin and Eosin Stain



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