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Identifying racial differences in nodular lymphocyte predominant Hodgkin lymphoma

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Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is an uncommon, indolent lymphoma comprising less than 10% of all new diagnoses of Hodgkin lymphoma (HL). In “Race-specific features and outcomes of nodular lymphocyte-predominant Hodgkin lymphoma: analysis of the National Cancer Data Base”, Dr. Olszewski and colleagues present the first comprehensive analysis of racial disparities in NLPHL.¹ This entity is a predominantly male disease with a 3:1 male to female ratio and a 1.2:1 ratio in African Americans compared to Caucasians.² NLPHL displays a bimodal age distribution with peaks in childhood and early adulthood with a median age similar to classical HL of approximately 30 years, but bears more similarity clinically to many subtypes of non-Hodgkin lymphoma (NHL) than to classical HL.³ Because of the low frequency of this diagnosis there are few prospective clinical studies to guide clinical management producing controversies and conflicting data regarding the optimal management. This lack of consensus complicates our understanding of whether racial differences in patient management represent variations that may portend a worse outcome.

The indolent clinical course of NLPHL parallels indolent NHL, such as follicular lymphoma, similarly, malignant lymphocytic and histiocytic (L&H) cells are CD20 positive and lack the CD30 or CD15 expression seen in classical HL, however the pathogenesis of NLPHL may more closely parallel aggressive B-cell lymphoma.³ NLPHL is characterized by a diffuse malignant cell growth pattern notable for the prevalence of T cells and histiocytes, which makes immunohistochemistry staining essential for establishing a diagnosis and distinguishing NLPHL from other B-cell lymphomas such as T-cell-rich variant of diffuse large B-cell lymphoma (DLBCL).⁴ NLPHL has a propensity to transform to DLBCL and one study demonstrated a clonal relationship between LP cells and concurrent or eventual transformation to DLBCL, suggesting a common cell of origin.⁵ However, a large, retrospective study from the German Hodgkin Study Group with a median follow-up of 50 months demonstrated that freedom from treatment failure (88% versus 82%) and overall survival (OS; 96% versus 92%) were better for NLPHL than with classical HL.⁶

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Significant variability exists in the treatment strategies employed for NLPHL. As the authors note, “Treatment guidelines are largely based on extrapolation of data from classical HL or retrospective case series, with few prospective clinical trials dedicated specifically to NLPHL.” Approximately 80% of patients present with early-stage disease, and several strategies produce meaningful disease control and prolong OS. Although some centers advocate the use of combined chemotherapy and radiation therapy for patients with early stage NLPHL, experts and guideline consensus panels from the United States and Europe have recommended radiation alone particularly for patients with stage IA disease in part because single institution retrospective studies have failed to show improvement in survival with combined modality therapy compared with RT alone.⁴ In these studies more intensive initial therapy was associated with greater toxicity without a survival benefit. Surgical resection followed by observation has been commonly applied in pediatric patients who achieve complete remission after surgery with high early event-free survival and OS, and high salvage rates in patients who relapse.⁴ Because NLPHL demonstrates CD20 expression, rituximab has been explored as a single agent therapy with nearly 100% response rate, but with ¼ of patients experiencing relapse within four years.^{3, 4, 7} Most commonly, chemotherapy has been utilized for patients with advanced stage NLPHL employing regimens similar to those used in treating classical HL or DLBCL.^{4, 8} As noted above, this heterogeneity in treatment options and intermediate outcomes complicates the interpretation of racial differences in presentation and treatment for NLPHL. For an individual patient, selection of a particular treatment approach depend on patient characteristics, such as disease burden, performance status, and comorbid diseases.

While numerous studies have investigated socioeconomic and racial disparities in the patterns of presentation, treatment, and outcomes for other lymphoid malignancies,⁹⁻¹⁴ relatively little has been published on racial differences in these factors for NLPHL. The authors effectively compare and contrast the current findings to these prior studies. Olszewski and colleagues utilized the National Cancer DataBase (NCDB) to examine the largest cohort of African American patients with NLPHL ever assembled. This work adeptly utilizes appropriate analyses of one of the largest available clinical dataset of NLPHL patients to describe the patterns of presentation and outcome that occur by race, gender, and age. While the NCDB provides cancer registry information for more than 70% of the new cancer cases in the United States, NCDB is not a population-based registry, limiting the conclusions that can be draw from this dataset regarding incidence statistics, nor can these results be generalized to the entire population. Similar to previous findings from other investigators examining NHL subtypes, these authors found that black patients were on average younger than white patients and had unfavorable socioeconomic characteristics. They also found that black patients were more often female, and more likely to have axillary nodes as the primary site. While the authors propose hypotheses regarding how these features may portend differences in the etiology of NLPHL by race, at present these remain speculative.

Recent pooled case-control studies performed by the International Lymphoma Epidemiology Consortium (InterLymph) examining genome wide associations and epidemiological risk factors provide an enhanced understanding of lymphoma subtype-specific risk factors that include family history, genetics, medical history, lifestyle factors, and occupations for a

variety of lymphomas.¹⁵⁻¹⁷ This series of studies suggests a complex interaction between host genetics, environment, and epidemiological risk factors that contribute to lymphomagenesis in ways not fully understood. Large collaborative epidemiological studies for NLPHL similar to the recently completed InterLymph Subtype project for NHL are needed to delineate what the implications of racial difference in presentation may mean for etiology of NLPHL. In addition, similarities in the race-specific patterns of presentation for NLPHL and some NHL subtypes may have importance in understanding etiologic commonalities and heterogeneity that also was recently explored by InterLymph.¹⁸

However, patient cases and controls in the InterLymph studies and other similar analyses have been almost entirely comprised of individuals of European ancestry, and thus it is unclear whether the risk factors identified are generalizable to populations with a different racial/ethnic composition. In general, risk factors for lymphomas and NLPHL among racial and ethnic minorities are not well described. Future analyses would be necessary to determine the population genetics and epidemiological factors required for adequate lymphoma risk prediction in minority populations. Such approaches may also identify novel preventive and therapeutic targets for NLPHL. While population-based cancer registry data has been useful for describing epidemiology of lymphoma as a unified entity, identifying risk factors for individual NHL and HL subtypes has been challenging given the relatively low number of patients affected by each subtype. Large national and international collaborations are needed to adequately characterize the genetic and epidemiological factors associated with racial differences in NLPHL and other lymphomas. InterLymph and other large cohort studies involving consortia of lymphoma investigators are now underway to fill this void.

Also of interest is that despite the differences observed, the authors found no significant difference by race in stage distribution or in survival for NLPHL. This contrasts with the racial disparities identified for other lymphomas.⁹⁻¹⁴ Collectively, these studies indicate that for other B-cell malignancies African American patients more commonly present with advance stage disease, less commonly received chemoimmunotherapy, and experienced worse survival. For instance, despite the high cure rates for DLBCL, outcomes remain heterogeneous and are significantly worse for patients who are African American, uninsured, have activated B-cell-like biological subtype or a high international prognostic index score. Based on these and other publications, race/ethnicity, biological, and socioeconomic factors interact to influence lymphoma survival. However, at present there is no unifying, comprehensive model that incorporates these parameters to aid in assessing prognosis. For NLPHL, developing prognostic models that incorporate the differences in race described by Olszewski and colleagues is further complicated by the indolent nature of the disease and the heterogeneity of treatment strategies employed for patients with this lymphoma subtype. Despite these challenges, the authors provide the first insights into the nature of racial differences in NLPHL and provide useful inroads for future studies of epidemiology and outcomes research for this uncommon lymphoid malignancy.

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