Expanding the bacterial origins of nodular lymphocyte-predominant Hodgkin lymphoma

Maher K. Gandhi[1,2] and Colm Keane[2,3]

[1]Mater Research, University of Queensland; [2]Princess Alexandra Hospital and [3]Frazer Institute, University of Queensland, Brisbane, Queensland, Australia

Correspondence: C. Keane
c.keane@uq.edu.au

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In the current issue of *Haematologica*, Thurner *et al.* provide further insights into the growing knowledge base on specific tumor cell reactivity in the unique disease of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).[1] This HL differs from classical variants by the fact that the malignant cell clearly retains its B-cell identity. It expresses functional B-cell receptors (BCR), is surrounded by rosettes of T-follicular helper cells, retains CD20 expression, and has no CD30 expression. It is not believed to have any association with Epstein-Barr virus and is genetically distinct from classical HL.[2] Clinically, it has distinguishing features from classical HL with a very strong male preponderance and, in most cases, a limited stage presentation. In recognition of the distinct pathologic, biologic, and clinical differences, in the 2022 International Consensus Classification of Mature Lymphoid Neoplasms (2022 ICC) it has now been renamed nodular lymphocyte predominant B-cell lymphoma (NLPBL).[3] (It should be noted that it retains its NLPHL nomenclature within the 2022 WHO classification.[4]) It is the most indolent of HL, with population-based studies indicating only a slightly higher lymphoma-related death rate compared to death from other causes.[5] Its relative rarity has hindered our understanding of the disease. The optimal treatment strategies are still unclear, but in advanced disease rituximab is generally added to systemic chemotherapy given the expression of CD20 on the malignant cells. Radiation therapy with or without chemotherapy is very effective for the more common limited-stage presentation.[6]

Its distinct presentation and phenotype had led to some suggesting that perhaps this lymphoma could be antigen-driven. In addition, the very strong familial risk may indicate that specific environmental factors could be responsible.[7] Previous work has demonstrated antigen specificity for *Moraxella catarrhalis* with specific IGVH genotypes and associated HLA class II haplotypes.[8,9] These HLA associations showed specific T-follicular helper cell reactivity and direct immune synapses between these supporting T cells and the malignant B cells, further enhancing the hypothesis that antigenic stimulation supports malignant B-cell propagation. The current study expands on this work to identify additional antigens that are associated with NLPHL.[1] Due to frequent presentation of NLPHL with cervical lymphadenopathy, the authors focused on several bacteria commonly found in the oral cavity, upper respiratory tract, and gut, such as *Rothia spp*, *Enterococcus spp*, and *Lactobacillus spp*. With this expanded bacterial screening of NLPHL cases, two antigens of *R. mucilaginosa* (a common oral commensal that commonly resides in cervical lymph node drainage areas) were identified as targets of NLPHL BCR, and, like *M. Catarrhalis* RpoC, light chain-restricted antibodies to *R. mucilaginosa* Gltf and 2,3-BDH were found in the sera of patients with the disease, although at low concentration. Screening of patients with classical HL and primary mediastinal B-cell lymphoma (PMBCL), and T-cell/histiocyte-rich large B-cell lymphoma found no similar antibodies in the sera of any of these patients. The authors also confirmed that *R. mucilaginosa* Gltf and 2,3-BDH induced growth by activating the BCR pathway. It should be noted that, unlike *M. catarrhalis* cases, no HLA restriction was found in cases of *R. mucilaginosa*, and only one of the 5 cases showed IgD positivity. In newly presenting patients with NLPHL, the authors also identified 3 further cases showing reactivity to *Moraxella* spp. Thus, 10 out of 22 of analyzed NLPHL to date have reactivity to this same bacterium, which confirms the findings of a previous work.[9]

As is the case for most publications on NLPHL, the study by Thurner *et al.* is characterized by a relatively low number of cases but, intriguingly, 15 of 22 cases showed reactivity to bacterial species.[1] It is possible that a wider screen of bacteria, and even viruses, may lead to the identification of additional cases that might be related to chronic antigenic stimulation.

As stated by Thurner *et al.*, screening of other lymphomas such as marginal zone lymphoma or duodenal follicular

lymphoma could lead to the identification of other causative or supportive organisms. The description of antigenic stimulation and the indolent and sometimes waxing/waning course of NLPHL does, indeed, warrant investigation of new theraputic strategies that could include vaccination or treatment with antibiotics. The rarity of the disease makes trials of such approaches difficult, but perhaps the indolent nature of the disease could allow novel interventions to be tested. A priority for this disease is the development of better pre-clinical models and cell lines that more accurately mimic the disease, given the current dependence for functional work on the DEV cell line when it has lost expression of MHC II, which contrasts with the almost universal expression found in clinical cases. Better understanding of the microbiome indicates that we may only be touching the surface of understanding how bacteria influence, not only tumor development, but also response to therapy. Future work on the microbiome and gut microflora may provide further insights into rare lymphoma subtypes and their response to therapy. It is likely that an international collaboration or consortium will be required to investigate these key questions in sufficient numbers of patients.

In summary, Thurner *et al*. should be commended for their work on this rare lymphoma and for the fascinating description of a second bacterium that is likely a key factor in the disease pathogenesis. Almost 70% of tested cases demonstrated bacterial reactivity,[1] which provides a launching pad not only for exploration of further potential causative organisms, but that also encourages the development of novel agents and approaches for this unique disease.

Disclosures

CK has sat on advisory boards, and received consulting/speaker fees for Roche, Janssen, Astra Zeneca, MSD Takeda and Beigene. MKG has received supplies of study drugs for investigator-led clinical trials from Beigene and Janssen.

Contributions

MKG and CK both wrote the manuscript.

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