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Expanding the bacterial origins of nodular lymphocyte predominant Hodgkin lymphoma
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In the current issue of Haematologica, Thurner et. al. provide further insights into the growing knowledge base for specific tumour cell reactivity in the unique disease of nodular lymphocyte predominant Hodgkin lymphoma ‘NLPHL’ (1). This Hodgkin lymphoma differs from classical variants by the fact 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 an association with EBV and is genetically distinct from classical HL(2). Clinically it has distinguishing features from classical Hodgkin lymphoma with a very strong male preponderance and a limited stage presentation in most cases. In recognition of the distinct pathologic, biologic, and clinical differences it is now renamed nodular lymphocyte predominant B cell lymphoma (NLPBL) in the 2022 International Consensus Classification of Mature Lymphoid Neoplasms (2022 ICC) (3). It should be noted that it retains its NLPHL nomenclature within the 2022 WHO classification(4). It is the most indolent of Hodgkin lymphomas with population-based studies indicating a low excess of lymphoma related death rate(5). Its relative rarity has hindered our understanding of the disease. The optimal treatment strategies are still unclear, but rituximab is generally added to systemic chemotherapy in advanced disease given the expression of CD20 on the malignant cells. Radiation therapy with or without chemotherapy is very effective for the more commonly occurring limited stage presentation(6).

Its distinct presentation and phenotype had led to a hypothesis that perhaps this lymphoma could be antigen driven. In additional, the very strong familial risk may indicate 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 NLPBL. Due to frequent presentation of NLPBL with cervical lymphadenopathy, the authors focussed 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 NLPBL cases, two antigens of R. mucilaginosa, a common oral commensal that commonly resides in cervical lymph node drainage areas were identified as targets of NLPBL BCRs 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, though at low concentration. Screening of patients with classical Hodgkin lymphoma and primary mediastinal B cell lymphoma (PMBCL), as well as 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 Bdh induced growth by activating
the BCR pathway. It should be noted that unlike Moraxella catarrhalis cases no HLA restriction was found in R. mucilaginosa cases and only one of the five cases showed IgD positivity. The authors additionally identified in newly presenting patients with NLPHL, three further cases showing reactivity to Moraxella spp. Thus 10/22 of analysed NLPHL to date have reactivity to this same bacterium which is confirmation of previous work(9).

As is the case for most NLPHL publications, this study is characterised by a relatively low number of cases but intriguingly 15 of 22 cases showed reactivity to bacterial species. It is possible that a wider screen of bacteria and even viruses may lead to additional cases that might be related to chronic antigenic stimulation. As the authors state, 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 warrant investigation of new therapy strategies that could include vaccination or antibiotic therapies. The rarity of the disease does make trials of such interventions 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 on the DEV cell line for functional work when it has lost expression of MHC II, which contrasts with the almost universal expression found in clinical cases. The emergence of greater understanding of the microbiome indicates that we may only be touching the surface of our understanding of how bacteria influence not only tumour 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 an international collaboration or consortium will be required to investigate these key questions with enough patients.

In summary, the authors should be commended for their work in 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 which provides a launching pad for not only exploration of further potential causative organisms but also encourages the development of novel agents and approaches for this unique disease.
References:


