Progress in understanding the biology of nodular lymphocyte predominant Hodgkin lymphoma

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It has been 77 years since Hodgkin’s paragranuloma, now known as nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), was described as a clinicopathologic entity by Jackson and Parker. They noted that “Hodgkin’s paragranuloma bears little or no resemblance to a true tumor, either in its histologic picture or its clinical course.” They suggested that it may be an infectious rather than a neoplastic process. They noted that it may be a precursor of the more aggressive Hodgkin’s granuloma, but that “patients with Hodgkin’s paragranuloma may live unembarrassed by their disease - if the pathologic picture does not change - for many years. One patient (L.C. S36-1256) is living and active thirty-eight years after the first proved lymph-node involvement, although the condition as shown by multiple biopsies, is still present.” The observation that this entity usually has an indolent course regardless of treatment approach, and that a subset of patients does well with active surveillance, has been recently reaffirmed. NLPHL is rare and comprised about 6% of Hodgkin lymphomas. Approximately 1% of patients per year transform to diffuse large B-cell lymphoma that is associated with a shorter survival and is the major indication for treatment. The tumor lymphocyte predominant cells, initially termed L&H cells (for morphologic resemblance to lymphocytes and histiocytes), are morphologically distinct from the Reed Sternberg cells of classical Hodgkin lymphoma with multilobulated nuclei and indistinct nucleoli, and have a germinal center B-cell phenotype and genotype.

Progress has been made in understanding of molecular determinants of transformation of NLPHL to DLBCL by Paschold and colleagues in this issue of *Haematologica*. Immunoglobulin heavy chain next-generation sequencing and IgD staining were employed to study of collected paraffin-embedded tissue blocks from patients with 5 newly-diagnosed cases of NLPHL that did not relapse or transform (single samples, cohort 1), 16 NLPHL cases with paired samples at diagnosis and time of relapse (cohort 2), 10 paired samples at diagnosis of NLPHL at diagnosis and time of relapse as transformation (cohort 3) and 28 single sample control cases (10 nonspecific lymphadenitis, 4 progressive transformation of germinal centers, 10 DLBCL, ABC subtype, and 4 T-cell/histiocyte-rich large B-cell lymphoma, cohort 4).

Initial samples from cases that later transformed were IgD negative and had absence of the most characteristic lymphocyte predominant cell IGHV3/IGHD3/IGHJ6 LP gene rearrangement, high repertoire clonality and patients were older, as compared with cases that did not transform. Phylogenetic trees within the malignant clone in initial and relapsed and transformed samples were established. In cases that relapsed but did not
transform, the LP IGH gene rearrangement was identical in initial and relapsed samples. Cases that transformed showed more complex trajectories with strong intraclonal diversification. Clonal evolution of the founder clone was seen in some transformed samples while in others, a clone from a different cell of origin was identified. The data identify high B-cell repertoire clonality with dominant intraclonal LP cell diversification in initial NLPHL diagnostic biopsies to be a predictor of subsequent transformation compared with cases that did not transform and controls and suggest a significant role of antigen drive.

Another study of recombinantly-expressed B-cell receptors from micro-dissected LP cells from IgD-positive cases suggest that bacterial antigens from Moraxella bacterial species bind to the B-cell receptor. Of interest, almost 1/3rd of the IgD-negative cases in the present study share the characteristic IGHV/D/J rearrangement as IgD-positive cases possibly suggesting a similar pathogenesis. Moraxella catarrhalis is associated with several common childhood infectious illnesses and could be an antigen driver.

This is an interesting study that is a contribution to understanding the biology and pathogenesis of NLPHL and its transformation. Next generation sequencing is performed on whole biopsy samples and avoids the difficulties of microdissection. The concept that infectious antigen-drive may be important in pathogenesis, as suspected by Jackson and Parker 77 years ago, is very intriguing.

References: