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COMMENTARY

# Characterizing the immune microenvironment for nodular lymphocyte-predominant Hodgkin lymphoma

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The microenvironment of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and its relationship to presentation and outcomes has not been widely investigated. In a large cohort of patients with NLPHL, Hartmann and colleagues showed an association between microenvironmental factors and clinical presentation serving to inform future studies evaluating the prognostic impact of the immunoarchitectural patterns and cell types present.

Commentary on: Hartmann et al. Tumor cell characteristics and microenvironment composition correspond to clinical presentation in newly diagnosed nodular lymphocyte predominant Hodgkin lymphoma. Br J Haematol 2022 (Online ahead of print). doi: 10.1111/bjh.18376.

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Given the vast abundance of immune cells present in the microenvironment of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), there has been a long history of investigating clinical presentation and outcomes for patients based on morphology and immunophenotyping.[1–3] However, although the immunoarchitectural patterns found in NLPHL were described nearly two decades ago, given the rarity of NLPHL, further molecular characterization of cell populations present with assessment of clinical significance of pathologic variants has been limited.[3,4] Thus, Hartmann et al. should be commended for completing a thorough analysis of the pathologic specimens from patients diagnosed with NLPHL enrolled in the German Hodgkin Study Group prospective clinical trials HD16-HD18.[5] Patients enrolled on the HD16-HD18 trials had rigorous pathologic review with management directed by positron emission tomography representing a highly curated cohort.[6–8] They set to characterize the immune microenvironment with comparison to clinical stage and presentation, building upon their prior findings but without assessment of prognostic impact.[3]

Looking at the cohort in detail, the patients had a median age of 41, were predominantly male (74%), had early stage for the majority (59%), and almost half (45%) had either a major or minor component of variant immunoarchitectural pattern. There was an incremental increase in the percentage of patients with advanced stage when stratifying patients by major pattern with 30% for typical A/B, 46% for pattern C, 76% for pattern D, and 75% for pattern E. There was a greater proportion of male patients and those with B symptoms within the pattern E subset versus others. There were no patients with pattern F which is the most rare pattern.[9] While the association between clinical stage and variant pattern had previously been reported by Hartmann et al.,[3] their current study included immunophenotyping of the microenvironment revealing new observations for NLPHL.

Given observations of tumour associated macrophages being associated with prognosis for classic Hodgkin lymphoma,[10,11] the authors sought to determine if similar findings exist for NLPHL. They used an antibody for CD163 which has greater specificity for M2 macrophages as opposed to CD68 which was used in prior studies.[12] Interestingly, they did observe a higher percentage of CD163 positive macrophages in the microenvironment of the variant cases with higher enrichment for pattern E. It remains to be seen if the presence of CD163 positive macrophages is associated with a worse prognosis for NLPHL.

The authors observed a low percentage of IgD positivity of lymphocyte-predominant cells (13%) which as they point

out is likely due to their older cohort in contrast to prior reports for paediatric cohorts.[13] In spite of a small number of positive cases, they still observed the majority of IgD positive cases were pattern C and early stage. In agreement with these findings, Shankar et al. observed a higher proportion of patients with variant pattern and IgD positivity versus that for those with typical pattern in a cohort of primarily early stage paediatric patients.[13] Thus IgD positivity may reflect a unique pathogenesis associated with *Moraxella catarrhalis* as well as a group of patients more frequently presenting with early stage variant pattern C.[14] Future studies should further define the pattern of relapse for IgD positive NLPHL as relapses for paediatric patients tend to remain localized in contrast to adult patients who may frequently relapse with advanced stage disease which may in part be related to biologic differences represented by IgD positivity.[15–17]

Finally, Hartmann et al. observed nearly all cases (96%) had T follicular helper cell rosettes with the vast majority having PD-1 positivity. This finding in conjunction with PD-L1 positive lymphocyte predominant cells as reported in abstract form by other groups suggests check point inhibition may be a successful strategy in the treatment of NLPHL similar to results reported for classic Hodgkin lymphoma.[18,19]

Efforts by Hartmann et al. and others have set the stage for international collaboration to leverage the pathobiology that is emerging for NLPHL to assess the clinical impact of the immune microenvironment.[3,4,18,20] Large international efforts are underway to further study outcomes, patterns of failure, and the prognostic impact of variant immunoarchitectural patterns across the age spectrum for patients with all stages of NLPHL.[21] As highlighted in the updated classification by the World Health Organization, pathologists should continue to completely report the major and minor immunoarchitectural patterns present for NLPHL.[22]

Ultimately, several critical questions remain unanswered for NLPHL including which patients have truly localized disease amenable for resection or radiotherapy alone, which patients with advanced stage have a low risk of progression suitable for active surveillance, and finally, will there be a role for immunotherapy in the management of NLPHL?[15–17] To address these questions, further biologic characterization paired with clinical outcomes analyses will be necessary.

In conclusion, the findings by Hartmann et al. provide a robust resource characterizing the microenvironment of NLPHL and support the need to establish molecular staging to fuel the design of prospective studies evaluating personalized approaches for NLPHL.

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