LETTER TO THE EDITOR
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Comment on "S GATA3 Immunohistochemical Staining in Classical Hodgkin Lymphoma and Its Diagnostic Utility in Differential Diagnosis"

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Dear Editor,
The publication on "GATA3 Immunohistochemical Staining in Classical Hodgkin Lymphoma and Its Diagnostic Utility in Differential Diagnosis [1]" is hereby discussed. This study is unique in its ability to assess the potential of GATA3, a transcription factor commonly used in the classification of epithelial tumors, as a biomarker for distinguishing classical Hodgkin lymphoma (CHL) from other lymphomas, particularly in cases where aberrant antigen expression in CHL is frequently a major obstacle to diagnosis. As a result, efforts to identify new markers that can help differentiate are critical for accurate and timely diagnosis.
However, the study used a cross-sectional retrospective design, which, although somewhat suitable for the analysis of marker expression in tissues, has some limitations that should be mentioned, such as the lack of standardization of IHC and the variety of methods for evaluating GATA3 staining results, which may lead to inter-observer variability. The definition of what "nuclear expression" is considered positive (e.g., minimum cell count or intensity level), may affect the accuracy of the conclusion. And there is no mention of technical controls, such as the use of internal positive controls in each biopsy.
Statistically, using p-value alone to compare various groups, while it can find differences, lacks additional clinical indicators, such as sensitivity, specificity, PPV, NPV, or AUC, which are required for the practical application of this marker in pathological diagnosis. Furthermore, the study's findings show that GATA3 is ineffective in distinguishing CHL from ALK-negative anaplastic large-cell lymphoma (ALCL) and mediastinal gray-zone lymphoma, which is a significant limitation because these two lymphomas are frequently included in the complex differential diagnosis with CHL, particularly when the biopsy is small or has few components.
Questions for further debate include: (1) Can GATA3 be used in conjunction with other markers, such as PAX5, CD30, or LMP1, to improve the accuracy of CHL diagnosis? (2) Is it possible to construct a grading system or AI-based histopathology that includes GATA3 in the model? (3) Does GATA3 expression have a direct biological function in the pathogenesis of CHL, or is it simply a co-marker? And (4) In circumstances where biopsy has limits, such as core needle biopsy, what other procedures or markers should be employed to improve diagnosis?
Future research should include investigations on other lymphoma subtypes, as well as trials in real-world settings, particularly in cases when diagnosis is challenging. In addition, multivariate analysis should be performed to see if GATA3 remains significant after correcting for other variables such patient age, concomitant clinical characteristics, and EBV status. This study discovered that GATA3 was more highly expressed in EBV-negative CHL, which could reflect different genetic regulatory mechanisms amongst CHL subtypes.
Finally, this study adds to the development of a new tool for distinguishing comparable lymphomas, particularly CHL, which, despite the presence of unique markers, sometimes causes uncertainty in interpretation. However, GATA3's efficacy remains restricted in some lymphomas, making it unsuitable for situations involving tiny biopsies. As a result, integrating GATA3 with other markers and assessing it against clinical criteria will be a more appropriate method for reliable diagnosis in the future.

References

1. Altay AY, Yeni B, Yegen G. GATA3 Immunohistochemical Staining in Classical Hodgkin Lymphoma and Its Diagnostic Utility in Differential Diagnosis. Turk J Hematol 2025;42:9-14

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HP 50 % ideas, writing, analyzing, approval
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Reply from the Authors
To the Editor,
We thank the commentators for their interest in our manuscript titled "GATA3 Immunohistochemical Staining in Classical Hodgkin Lymphoma and Its Diagnostic Utility in Differential Diagnosis" and appreciate their thoughtful queries regarding our publication.
Regarding standardization concerns and inter-observer variability, we acknowledge these limitations inherent to retrospective studies. In our methodology, 59 of 69 GATA3-positive CHL cases demonstrated 75-80% expression, with the lowest staining extent being 30-40% in partially positive cases. We intentionally avoided setting minimum thresholds as even few positive cells can be diagnostically significant in small biopsies. Internal controls (T cells) were available in every case, providing standardization for baseline GATA3 expression and ensuring procedure quality.
The statistical analysis beyond p-values yields clinically relevant metrics: sensitivity 69%, specificity 64.15%, positive predictive value 64.49%, and negative predictive value 68.69%. We did not perform AUC analysis as establishing cut-off values proves challenging in CHL due to abundant reactive background cells and sparse neoplastic elements. Setting arbitrary thresholds would eliminate GATA3 positivity in cases with few positive cells, artificially inflating diagnostic parameters.
Regarding marker combinations, all CHL cases in our cohort displayed classic immunophenotype with CD30 and PAX5 positivity regardless of GATA3 expression. While PAX5 and EBV-LMP1 favor CHL diagnosis, literature reports describe PAX5 positivity in ALK-negative ALCL, including null phenotype cases, which creates diagnostic challenges (1-3). For mediastinal gray-zone lymphoma, our limited cohort represents a study limitation, though similar diagnostic complexities apply.
Concerning grading systems, current ABVD protocols have eliminated the prognostic significance of histologic subtypes in CHL. AI-based approaches incorporating GATA3 are theoretically feasible. However, Fu et al.'s meta-analysis of 41 AI studies in lymphoma diagnosis revealed methodological biases and limited clinical translation, emphasizing the need for comprehensive validation before clinical implementation (4-7).
The biological role of GATA3 in CHL pathogenesis remains speculative within our retrospective framework. Stanella et al. demonstrated that GATA3 affects IL-4 and IL-13 cytokine production and STAT4 transcription but showed no survival impact. Current evidence suggests NF-κB and NOTCH1 drive CHL oncogenesis, with GATA3 representing a downstream consequence rather than a primary driver (8).
For limited biopsy specimens, adequate non-crushed tissue remains paramount. Since CHL lacks defining genetic alterations, liquid biopsy approaches offer minimal diagnostic benefit. The diagnosis inherently requires combined assessment of multiple markers (CD30, CD15, PAX5, MUM1, EBV-LMP1, fascin, CD3, CD20, IRF8), all affected by tissue adequacy limitations.
Regarding multivariate analysis and clinical correlations, Papoudou-Bai et al. reported GATA3 expression decreases in patients over 45 years and correlates with increased β2-microglobulin in GATA3-negative cases. Our cohort of 24 pediatric and 76 adult CHL patients showed no statistical age-related differences in GATA3 expression ($p=0.430$). Similarly, comparing patients under versus over 45 years revealed no significant difference ($p=0.504$).
We acknowledge GATA3's limitations in distinguishing CHL from ALK-negative ALCL and mediastinal gray-zone lymphoma, particularly problematic in small biopsies. Future investigations should expand to other lymphoma subtypes with prospective validation in challenging diagnostic scenarios.

In conclusion, while GATA3 represents a valuable addition to the diagnostic tools for CHL, its integration with established markers and clinical correlation remains essential for reliable diagnosis in routine practice.
Sincerely,

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References

1. Ong DM, Cummins KD, Pham A, Grigoriadis G. PAX5-expressing ALK-negative anaplastic large cell lymphoma with extensive extranodal and nodal involvement. BMJ Case Rep. 2015 Jul 17;2015:bcr2015211159. doi: 10.1136/bcr-2015-211159.
2. Fratoni S, Niscola P, Zhao XF, Larocca LM, Capalbo A, Fabbretti M, Bernardini L, Abruzzese E. ALK-negative anaplastic large cell lymphoma with "Hodgkin-like" cytomorphology and nuclear expression of PAX5. Pathol Res Pract. 2020 Feb;216(2):152724. doi: 10.1016/j.prp.2019.152724.
3. Salyana MA, Khan S, Zhang X. ALK-negative anaplastic large cell lymphoma, null type with aberrant expression of PAX5 and CD138: A diagnostic pitfall. Diagn Cytopathol. 2021 Oct;49(10):E395-E399. doi: 10.1002/dc.24821.
4. Fu Y, Huang Z, Deng X, Xu L, Liu Y, Zhang M, Liu J, Huang B. Artificial Intelligence in Lymphoma Histopathology: Systematic Review. J Med Internet Res. 2025 Feb 14;27:e62851. doi: 10.2196/62851. PMID: 39951716; PMCID: PMC11888075.
5. Motmaen I, Sereda S, Brobeil A, Shankar A, Braeuninger A, Hasenclever D, Gattenlöhner S. Deep-learning based classification of a tumor marker for prognosis on Hodgkin's disease. Eur J Haematol. 2023 Nov;111(5):722-728. doi: 10.1111/ejh.14066.
6. Shankar V, Yang X, Krishna V, Tan B, Silva O, Rojansky R, Ng A. LymphoML: An interpretable artificial intelligence-based method identifies morphologic features that correlate with lymphoma subtype. Proceedings of Machine Learning Research. 2023;225:528–558.
7. Soltane S, Alshreef S, Eldin SM. Classification and diagnosis of lymphoma's histopathological images using transfer learning. Computer Systems Science and Engineering. 2022;40(2):629–44. doi: 10.32604/csse.2022.019333.
8. Stanelle J, Döring C, Hansmann ML, Küppers R. Mechanisms of aberrant GATA3 expression in classical Hodgkin lymphoma and its consequences for the cytokine profile of Hodgkin and Reed/Sternberg cells. Blood. 2010 Nov 18;116(20):4202-11. doi: 10.1182/blood-2010-01-265827.