LETTER TO THE EDITOR

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Comment on "GATA3 Immunohistochemical Staining in Classical Hodgkin Lymphoma and Its Diagnostic Utility in Differential Diagnosis"

"Klasik Hodgkin Lenfomada GATA3 İmmünhistokimyasal Boyamanın Tanıda ve Ayırıcı Tanıda Kullanımı" Üzerine Yorum

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To the Editor,

We would like to discuss the publication of "GATA3 Immunohistochemical Staining in Classical Hodgkin Lymphoma and Its Diagnostic Utility in Differential Diagnosis" [1] in this journal. That study was unique in assessing 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 as aberrant antigen expression in CHL is frequently a major obstacle to diagnosis. Efforts to identify new markers that can help in differentiation are critical for accurate and timely diagnosis.

However, that 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 noted, such as the lack of standardization of immunohistochemical techniques and the variety of methods for evaluating GATA3 staining results, which may lead to inter-observer variability. The definition of nuclear expression positivity, such as whether it is based on minimum cell count or on intensity level, may also affect the accuracy of the conclusion. Furthermore, there was no mention of technical controls, such as the use of internal positive controls for each biopsy.

Statistically, using a p value alone to compare various groups may reveal differences but is lacking in terms of additional clinical indicators, such as sensitivity, specificity, positive predictive value, negative predictive value, or area under the receiver operating characteristic curve, which are required for the practical application of this marker in pathological diagnosis. Furthermore, the study's findings showed that GATA3 is ineffective in distinguishing CHL from anaplastic lymphoma kinase-negative anaplastic large-cell lymphoma and mediastinal gray-zone lymphoma, which is a significant limitation because these two lymphomas are frequently included in the complex differential diagnosis of CHL, particularly when the biopsy is small or has few components.

Questions for further debate include the following: 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 artificial intelligence-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? 4) In circumstances where biopsy has limits, such as core needle biopsy, what other procedures or markers should be employed to improve the diagnostic procedure?

Future research should include investigations on other lymphoma subtypes, as well as trials in real-world settings, particularly for cases where diagnosis is challenging. In addition, multivariate analysis should be performed to determine whether GATA3 remains significant after correcting for other variables such patient age, concomitant clinical characteristics, and Epstein-Barr virus (EBV) status. The study being discussed here showed that GATA3 was more highly expressed in EBV-negative CHL, which could reflect different genetic regulatory mechanisms among CHL subtypes.

This study contributed 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 cases of some lymphomas, making it unsuitable for situations involving very small biopsies. As a result, integrating GATA3 with other markers and assessing it against clinical criteria will be a more appropriate method for reliable diagnoses in the future.

Keywords: Staining, Diagnosis, Lymphoma, Immunochemical

Anahtar Sözcükler: İmmünhistokimyasal, Boyama, Tanı, Lenfoma

Ethics

Informed Consent: Patient consent was not required for this study.

Footnotes

Authorship Contributions

Concept: H.D., V.W.; Design: H.D., V.W.; Data Collection or Processing: H.D., V.W.; Analysis or Interpretation: H.D., V.W.; Literature Search: H.D., V.W.; Writing: H.D., V.W.

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Reply from the Authors:

To the Editor,

We thank the commentators for their interest in our study titled "GATA3 Immunohistochemical Staining in Classical Hodgkin Lymphoma and Its Diagnostic Utility in Differential Diagnosis" and we appreciate their thoughtful queries regarding our publication.

Regarding standardization concerns and inter-observer variability, we acknowledge the limitations inherent to retrospective studies. With our methodology, 59 of 69 GATA3-positive classical Hodgkin lymphoma (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 a 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.

Statistical analysis beyond p values yielded clinically relevant metrics: sensitivity of 69%, specificity of 64.15%, positive predictive value of 64.49%, and negative predictive value of 68.69%. We did not perform analysis of the area under the receiver operating characteristic curve as establishing cut-off values is challenging in CHL due to abundant reactive background cells and sparse neoplastic elements. Setting arbitrary thresholds would eliminate GATA3 positivity in cases with a few positive cells, artificially inflating the diagnostic parameters.

Regarding marker combinations, all CHL cases in our cohort displayed the classic immunophenotype with CD30 and PAX5 positivity regardless of GATA3 expression. While PAX5 and EBV-LMP1 favor CHL diagnosis, studies in the literature have described PAX5 positivity in anaplastic lymphoma kinase (ALK)-negative anaplastic large-cell lymphoma (ALCL), including null phenotype cases, which creates diagnostic challenges [1,2,3]. For mediastinal gray-zone lymphoma, the size of our small cohort constituted a study limitation, although similar diagnostic complexities apply.

Concerning grading systems, the current adriamycin, bleomycin, vinblastine, and dacarbazine protocols have eliminated the prognostic significance of histologic subtypes in CHL. Artificial intelligence (AI)-based approaches incorporating GATA3 are theoretically feasible. However, a meta-analysis of 41 AI studies on lymphoma diagnosis [4] revealed methodological biases and limited clinical translation, emphasizing the need for comprehensive validation before clinical implementation [4,5,6,7].

The biological role of GATA3 in CHL pathogenesis remains speculative within our retrospective framework. Stanelle et al. [8] demonstrated that GATA3 affects interleukin-4 and interleukin-13 cytokine production and STAT4 transcription but showed no survival impact. Current evidence suggests that NF-κB and NOTCH1 drive CHL oncogenesis, with GATA3 representing a downstream consequence rather than a primary driver [8].

For limited biopsy specimens, the availability of adequate non-crushed tissue remains paramount. Since CHL lacks defining genetic alterations, liquid biopsy approaches offer minimal diagnostic benefit. The diagnosis inherently requires the combined assessment of multiple markers (CD30, CD15, PAX5, MUM1, EBV-LMP1, fascin, CD3, CD20, and IRF8), all affected by tissue adequacy limitations.

Regarding multivariate analysis and clinical correlations, Papoudou-Bai et al. [9] reported that GATA3 expression was decreased in patients over 45 years and correlated with increased β2-microglobulin in GATA3-negative cases. Our cohort of 24 pediatric and 76 adult patients with CHL 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, which is particularly problematic with small biopsies. Future investigations should be expanded to include other lymphoma subtypes with prospective validation in challenging diagnostic scenarios.

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

Sincerely,

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