RESEARCH ARTICLE

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# GATA3 Immunohistochemical Staining in Classical Hodgkin Lymphoma and Its Diagnostic Utility in Differential Diagnosis

## Klasik Hodgkin Lenfomada GATA3'ün İmmünohistokimyasal Boyanması ve Ayırıcı Tanıda Kullanılabilirliği

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## Abstract

**Objective:** Classical Hodgkin lymphoma (CHL) is a common lymphoid neoplasm with a wide range of differential diagnoses. Although it has a specific immunophenotype, aberrant expression of antigens can cause problems at its diagnosis. In this study we evaluated the usefulness of GATA3 in the differential diagnosis of CHL.

**Materials and Methods:** One hundred cases of CHL and a control group of 106 lymphoma cases, which included anaplastic large-cell lymphoma both positive and negative for anaplastic lymphoma kinase (ALK), Epstein-Barr virus (EBV)-positive large B-cell lymphoma, T-cell/histiocyte-rich B-cell lymphoma, primary mediastinal large B-cell lymphoma, nodular lymphocyte-predominant Hodgkin lymphoma, and mediastinal gray-zone lymphoma, were included in the study. GATA3 immunohistochemistry was applied to all cases and nuclear expression was accepted as positive. Expression status of GATA3 was compared between the CHL group and the control group, as well as among each lymphoma subtype. In addition, whether the biopsy type affected diagnostic performance was assessed. For CHL, the relationship with EBV status and GATA3 expression was evaluated.

**Results:** GATA3 expression was significantly higher in CHL cases compared to the control group ($p<0.001$). When compared among individual subgroups, GATA3 was found to be useful in the differential diagnosis of all except for ALK-negative anaplastic large-cell lymphoma ($p=0.678$) and mediastinal gray-zone lymphoma ($p=0.327$). GATA3 expression was significantly higher in EBV-negative CHL ($p=0.02$). In core-needle biopsies, the diagnostic performance was limited ($p=0.178$).

**Conclusion:** GATA3 is a useful marker for differentiating CHL from B-cell non-Hodgkin lymphomas but its efficiency is limited in ALK-negative anaplastic large-cell lymphoma and mediastinal gray-zone lymphoma. Due to heterogeneous reactions, its diagnostic value is limited in core-needle biopsies.

**Keywords:** Classical Hodgkin lymphoma, GATA3, Anaplastic large-cell lymphoma, Incisional/excisional biopsy

## Öz

**Amaç:** Klasik Hodgkin lenfoma (KHL), geniş bir ayırıcı tanı yelpazesine sahip, sık görülen bir lenfoid neoplazidir. Özgün bir immünofenotipe sahip olmasına rağmen beklenenin dışında olabilen immünofenotiplerde tanısal zorluk olabilir. Bu çalışmada GATA3'ün KHL ayırıcı tanısındaki kullanışlılığı değerlendirilmiştir.

**Gereç ve Yöntemler:** Yüz KHL olgusu ve anaplastik büyük hücreli lenfoma (ALK [+] ve ALK [-]), Epstein-Barr virüsü (EBV) (+) büyük B-hücreli lenfoma, T-hücreleri ve histiyositlerden zengin büyük B-hücreli lenfoma, primer mediastinal büyük B-hücreli lenfoma, nodüler lenfosit predominant Hodgkin lenfoma ve mediastinal gri zon lenfomadan oluşan 106 olguluk kontrol grubu çalışmaya alındı. Tüm olgulara GATA3 immünohistokimyası uygulandı ve çekirdek boyanması pozitif olarak kabul edildi. GATA3 ifadesi KHL grubu ile bir bütün olarak kontrol grubu ve onu oluşturan lenfoma alt grupları ile karşılaştırıldı. Ayrıca biyopsi tipinin GATA3'ün tanısal performansına etkisi ve KHL grubu içerisinde GATA3 ifadesinin EBV ile olan ilişkisi değerlendirildi.

**Bulgular:** KHL olguları ile kontrol grubu kıyaslandığında GATA3 ifadesi KHL olgularında anlamlı şekilde yüksek bulunmuştur ($p<0,001$). Alt gruplarla karşılaştırıldığında GATA3'ün, ALK (-) anaplastik büyük hücreli lenfoma ($p=0,678$) ve mediastinal gri zon lenfoma ($p=0,327$) dışında ayırıcı tanıda yararlı olduğu görülmektedir. EBV (-) KHL'lerde GATA3 ekspresyonu anlamlı derecede yüksektir ($p=0,02$). İğne biyopsilerinde ise GATA3'ün tanısal performansı sınırlıdır ($p=0,178$).

**Sonuç:** GATA3, KHL'yi B-hücreli non-Hodgkin lenfomalardan ayırmak için yararlı bir belirteçtir ancak ALK (-) anaplastik büyük hücreli lenfoma ve mediastinal gri zon lenfomada katkısı sınırlıdır. Ayrıca kısmi pozitiflik gösterebilmesi nedeniyle iğne biyopsisi gibi sınırlı örneklemelerde tanısal katkısı sınırlı olabilmektedir.

**Anahtar Sözcükler:** Hodgkin lenfoma klasik tip, GATA3, Anaplastik büyük hücreli lenfoma, İnsizyonel/eksizyonel biyopsi

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## Introduction

Classical Hodgkin lymphoma (CHL) is a relatively common lymphoid neoplasm with a distinct morphology and immunohistochemical profile [1]. Although it is a B-cell neoplasm, most of the B-cell antigen expression is lost due to defective B-cell programming. Furthermore, aberrant T-cell antigen expression can be detected [1]. Due to morphological and immunohistochemical properties, there is a wide range of differential diagnoses including T-cell and B-cell non-Hodgkin lymphomas (NHL) [1,2,3]. Diagnosis might be challenging, especially in cases of limited biopsies, because of the overlapping features among entities.

GATA3 is a transcription factor that differentiates T helper cells to the Th2 subtype [4] and is reported to be aberrantly expressed in CHL [4,5]. There are a few studies suggesting it as a useful marker in the differential diagnosis of CHL [6,7,8], but they did not cover the entire spectrum of entities included in the differential diagnosis of CHL. Therefore, its diagnostic utility remains unclear. We aimed to assess the usefulness of GATA3 in the differential diagnosis of CHL by evaluating the expression status of GATA3 in CHL and a wide range of entities that are included in the differential diagnosis.

## Materials and Methods

### Case Selection

One hundred CHL cases diagnosed between 2006 and 2023 were included in the study. The control group consisted of 106 cases, which included anaplastic lymphoma kinase (ALK)-positive (10 cases) and ALK-negative (46 cases) anaplastic large-cell lymphoma (ALCL), Epstein-Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) (10 cases), T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) (15 cases), primary mediastinal large B-cell lymphoma (PMLBCL) (10 cases), nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) (10 cases), and mediastinal gray-zone lymphoma (MGZL) (5 cases).

Ethics approval was received from İstanbul University's İstanbul Faculty of Medicine Ethics Board (approval no: 22, case no: 2022/2042, date: 09/12/2022). Because this was a retrospective archive study and no identifying information was used, patient consent was not sought for the research.

### Immunohistochemical Analysis

GATA3 (mouse monoclonal L50-823, Biocare, Pacheco, CA, USA) immunohistochemistry (IHC) was performed on 3-µm-thick sections of formalin-fixed paraffin-embedded tissues representing the tumor, using an automated immunostainer (Benchmark XT/ISH Staining Module, Ventana Medical Systems, Oro Valley, AZ, USA). Nuclear staining was accepted as signifying positivity regardless of staining extent and intensity. Cases with a staining extent of less than 50% of neoplastic cells were accepted as partially positive.

### Statistical Analysis

Chi-square and Fisher exact tests were performed for statistical analysis. Values of $p<0.05$ were accepted as statistically significant.

## Results

The demographic features of the CHL group and the control group are summarized in Table 1. CHL subtypes included in the study were as follows: 39 nodular sclerosis (NS), 21 mixed cellularity (MC), 20 lymphocyte-rich (LR), and 20 lymphocyte-poor (LP) cases. Seventeen of the NS subtype cases were grade 2 and 2 were the syncytial variant. For the LR subtype, 11 cases showed nodular and 9 cases showed diffuse growth patterns. Information about EBV status, determined by EBV latent membrane protein 1 (LMP1) IHC, was available for 88 CHL cases. Epstein-Barr encoding region (EBER) in situ hybridization results were available for one case. Thirty-three cases (44%) (9 NS, 15 MS, 8 LR, and 1 LP) were EBV-positive. Eighty-three of the CHL cases (83%) were diagnosed by excisional biopsy (29 NS, 18 MC, 17 LR, and 19 LP) and 17 (17%) were diagnosed by core-needle biopsy (CNB) (10 NS, 3 MC, 3 LR, and 1 LP). Sixty-nine of the CHL cases (69%) were positive for GATA3 (29 NS, 13 MC, 13 LR, and 14 LP) (Figure 1). Partial positivity was observed in 10 CHL cases (4 NS, 2 MC, 3 LR, and 1 LP). In most cases, staining was observed in the majority of cells but not all. Staining intensity was also more prominent than the background T lymphocytes. GATA3 expression did not differ among CHL histological subtypes ($p>0.05$).

In the control group, 61 diagnoses entailed excisional biopsies (5 ALK-positive ALCL, 27 ALK-negative ALCL, 8 EBV-positive DLBCL, 10 THRLBCL, 9 NLPHL, and 2 MGZL), while 45 entailed CNB (5 ALK-positive ALCL, 19 ALK-negative ALCL, 2 EBV-positive DLBCL, 5 THRLBCL, 10 PMLBCL, 1 NLPHL, and 3 MGZL). Thirty-eight of 106 cases (36%) (3 ALK-positive ALCL, 30 ALK-negative ALCL, 1 EBV-positive DLBCL, 1 THRLBCL, 1 PMLBCL, and 2 MGZL) showed GATA3 positivity (Figure 2). Partial positivity was observed in 10 cases (2 ALK-positive ALCL, 5 ALK-negative ALCL, 1 EBV-positive DLBCL, 1 THRLBCL, and 1 PMLBCL).

GATA3 positivity was significantly higher in CHL than in the control group ($p<0.001$). When the control group was divided into B-cell and T-cell NHL cases, the difference was statistically significant for B-cell NHL (EBV-positive DLBCL, THRLBCL, PMLBCL, and MGZL) ($p<0.001$), whereas the difference was insignificant for T-cell NHLs (ALCL) ($p=0.221$). When the expression of GATA3 in CHL was compared for each lymphoma subtype, GATA3 positivity was still significantly higher in CHL versus EBV-positive DLBCL ($p<0.001$), CHL versus THRLBCL ($p<0.001$), CHL versus PMLBCL ($p<0.001$), and CHL versus NLPHL ($p<0.001$). However, the differences between CHL and ALCL

| **Table 1. Demographic features and biopsy types of cases.** | | | |
|---|---|---|---|
| **Classical Hodgkin lymphoma (n=100)** | | | |
| Gender | Male: 61 | | |
| | Female: 39 | | |
| Age, years, median (range) | 33 (4-88) | | |
| Biopsy type | Excisional: 83 | | |
| | Core-needle biopsy: 17 | | |
| Anaplastic large cell lymphoma, ALK-positive (n=10) | | | |
| Gender | Male: 6 | | |
| | Female: 4 | | |
| Age, years, median (range) | 20.5 (10-40) | | |
| Biopsy type | Excisional: 5 | | |
| | Core-needle biopsy: 5 | | |
| Anaplastic large cell lymphoma, ALK-negative (n=46) | | | |
| Gender | Male: 36 | | |
| | Female: 10 | | |
| Age, years, median (range) | 50 (14-85) | | |
| Biopsy type | Excisional: 27 | | |
| | Core-needle biopsy: 19 | | |
| EBV-positive diffuse large B-cell lymphoma (n=10) | | | |
| Gender | Male: 8 | | |
| | Female: 2 | | |
| Age, years, median (range) | 54 (11-81) | | |
| Biopsy type | Excisional: 8 | | |
| | Core-needle biopsy: 2 | | |
| T-cell and histiocyte-rich large B-cell lymphoma (n=15) | | | |
| Gender | Male: 12 | | |
| | Female: 3 | | |
| Age, years, median (range) | 45 (27-83) | | |
| Biopsy type | Excisional: 10 | | |
| | Core-needle biopsy: 5 | | |
| Primary mediastinal large B-cell lymphoma (n=10) | | | |
| Gender | Male: 3 | | |
| | Female: 7 | | |
| Age, years, median (range) | 39 (17-62) | | |
| Biopsy type | Excisional: 0 | | |
| | Core needle biopsy: 10 | | |
| Nodular lymphocyte-predominant Hodgkin lymphoma (n=10) | | | |
| Gender | Male: 7 | | |
| | Female: 3 | | |
| Age, years, median (range) | 36.5 (10-65) | | |
| Biopsy type | Excisional: 9 | | |
| | Core-needle biopsy: 1 | | |
| Mediastinal gray-zone lymphoma (n=5) | | | |
| Gender | Male: 2 | | |
| | Female: 3 | | |
| Age, years, median (range) | 27 (15-72) | | |
| Biopsy type | Excisional: 2 | | |
| | Core-needle biopsy: 3 | | |
| Comparison of GATA3 expression between CHL and control group | | | |
| | **GATA3-positive** | **GATA3-negative** | **p** |
| CHL (n=100) | 69 | 31 | p<0.001 |
| Control group (n=106) | 38 | 68 | |

ALK: Anaplastic lymphoma kinase; EBV: Epstein-Barr virus; GATA3: GATA binding protein 3; CHL: classical Hodgkin lymphoma.

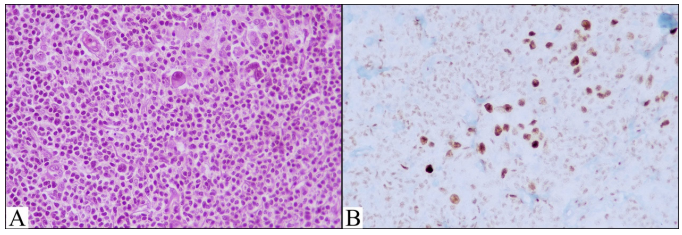


**Figure 1.** (A) Classical Hodgkin lymphoma nodular sclerosis subtype. Hematoxylin and eosin, 400x. (B) GATA3 positivity in Hodgkin and Reed-Sternberg types of neoplastic cells. GATA3 staining intensity is greater than that of the background T lymphocytes. Immunohistochemistry, 400x.

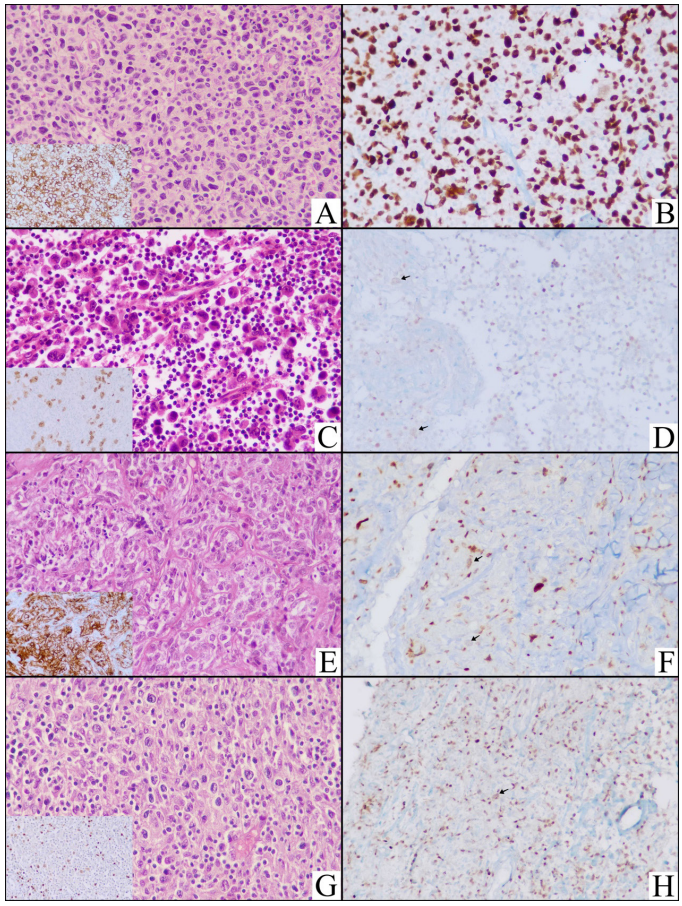


**Figure 2.** (A) Anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (inset: CD30). Hematoxylin and eosin, 400x. (B) Diffuse and strong GATA3 positivity in neoplastic cells. Immunohistochemistry, 400x. (C) ALK-positive anaplastic large cell lymphoma (inset: ALK1). Hematoxylin and eosin, 400x. (D) Weak GATA3 positivity observed in very few neoplastic cells. Immunohistochemistry, 400x. (E) Primary mediastinal large B-cell lymphoma (inset: CD23). Hematoxylin and eosin, 400x. (F) Weak to moderate GATA3 positivity detected in few neoplastic cells. Immunohistochemistry, 400x. (G) T-cell and histiocyte-rich large B-cell lymphoma (inset: Pax5). Hematoxylin and eosin, 400x. (H) Weak to moderate GATA3 positivity detected in very few neoplastic cells. Immunohistochemistry, 400x.

and between CHL and MGZL were not statistically significant (p=0.221 and p=0.327, respectively). Comparing ALCL subgroups individually, GATA3 positivity in CHL versus ALK-positive ALCL was statistically significant (p=0.031), but the significance disappeared for CHL versus ALK-negative ALCL (p=0.678).

To determine whether EBV influences GATA3 expression in CHL, we compared the expression status of GATA3 in EBV LMP1-positive and EBV LMP1-negative CHL cases. GATA3 positivity was significantly higher in EBV-negative CHL cases (p=0.02).

Finally, as GATA3 is not expressed in all neoplastic cells, we analyzed whether biopsy type affected the utility of GATA3 in differential diagnosis. Although GATA3 expression was significantly different between CHL excisional versus control excisional biopsies (p<0.001), the statistical significance was lost for CHL CNB versus control CNB setting (p=0.178).

Details regarding GATA3 expression and related statistical analyses are summarized in Table 2.

## Discussion

CHL, with its morphological and immunohistochemical features, has a wide variety of entities included in its differential diagnosis, which require different clinical management. In this study, we evaluated the usefulness of GATA3 in the differential diagnosis of CHL.

Although it is a mature B-cell neoplasm, CHL has a defective B-cell program that results in the loss of the expression of most of the B-cell antigens and aberrant expression of other antigens as well as T-cell markers [1,2]. GATA3 is one such transcription factor reported to be expressed in Reed-Sternberg cells, which is normally expressed in T lymphocytes and regulates Th2 differentiation [4]. It is speculated that NF-κB and Notch-1 activation in CHL causes GATA3 expression [5].

In our study, GATA3 was found to be a reliable marker in the differential diagnosis of CHL and B-cell NHLs such as EBV-positive DLBCL, THRLBCL, PMLBCL, and NLPHL. Our results are consistent with other studies [6,8], excluding the findings for PMLBCL. In their study, Kezlarian et al. [6] reported GATA3 positivity in 75% of the PMLBCL cohort, whereas we only had one case showing partial positivity with GATA3. Kim et al. [7] reported results similar to ours. Compared to the CHL cases, the positivity of GATA3 in abovementioned B-cell NHLs tends to be limited and the staining intensity of GATA3 is equal to that of reactive T lymphocytes that reside in the microenvironment. In CHL, however, GATA3 staining intensity is generally higher than that of accompanying T cells. In their recent study, Papoudou-Bai et al. [9] discussed the staining extent of GATA3 in CHL cases and proposed a cut-off value of 26% for GATA3 positivity. The extent of staining is important for most immunohistochemical markers, and more diffuse and

homogeneous expression increases their diagnostic reliability. However, in neoplasms like CHL that contain dispersed and relatively small numbers of neoplastic cells, we believe that drawing conclusions on the extent of staining is difficult and can be unreproducible. In our cohort, when GATA3 positivity was present, it was seen in most of the neoplastic cells. For cases that showed partial positivity, roughly less than 50% of cells had GATA3 expression. It also should be noted that GATA3 expression is not a requirement for CHL diagnosis. Our data and the literature indicate positivity rates of 69%, 80% [6], and 54% [9], respectively. GATA3 positivity is a supportive feature for the diagnosis of CHL and its differential diagnosis from B-NHL and NLPHL, but its negativity does not exclude the diagnosis of CHL.

**Table 2. Expression status of GATA3 among subgroups.**

| | |
|---|---|
| **Comparison of GATA3 expression between CHL and control group (n)** | |
| CHL (100) vs. control group (106) | p<0.001 |
| CHL (100) vs. B-NHL group (40) | p<0.001 |
| CHL (100) vs. ALCL (56) | p=0.221 |
| CHL (100) vs. ALK (+) ALCL (10) | p=0.031 |
| CHL (100) vs. ALK (-) ALCL (46) | p=0.678 |
| CHL (100) vs. EBV (+) DLBCL (10) | p<0.001 |
| CHL (100) vs. THRLBCL (15) | p<0.001 |
| CHL (100) vs. PMLBCL (10) | p<0.001 |
| CHL (100) vs. NLPHL (10) | p<0.001 |
| CHL (100) vs. MGZL (5) | p=0.327 |
| **Comparison of GATA3 expression between CHL subtypes** | |
| NS (39) vs. non-NS (61) | p=0.397 |
| NS grade 1 (20) vs. NS grade 2 + syncytial variant (19) | p=0.461 |
| NS (39) vs. MC (21) | p=0.347 |
| NS (39) vs. LR (20) | p=0.490 |
| NS (39) vs. LP (20) | p=0.765 |
| MC (21) vs. LR (20) | p=0.837 |
| MC (21) vs. LP (20) | p=0.585 |
| LR (20) vs. LP (20) | p=0.736 |
| **Comparison of GATA3 expression between EBV-positive and E BV-negative CHL cases** | |
| EBV (+) (33) vs. EBV (-) (56) | p=0.02 |
| **Comparison of biopsy types between CHL and control group** | |
| CHL CNB (17) vs. control CNB (45) | p=0.178 |
| CHL excisional (83) vs. control excisional (61) | p<0.001 |

CHL: Classical Hodgkin lymphoma; GATA3: GATA binding protein 3; B-NHL: B-cell non-Hodgkin lymphoma; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; EBV: Epstein-Barr virus; DLBCL: diffuse large B-cell lymphoma; THRLBCL: T-cell and histiocyte-rich large B-cell lymphoma; PMLBCL: primary mediastinal large B-cell lymphoma; NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma; MGZL: mediastinal gray-zone lymphoma; NS: nodular sclerosis; MC: mixed cellularity; LR: lymphocyte-rich; LP: lymphocyte-poor; CNB: core-needle biopsy.

Our results for ALCL and MGZL present a different story. Although GATA3 is still useful in the differential diagnosis of CHL and ALK-positive ALCL, the important issue is GATA3 positivity in ALK-negative ALCL. GATA3 positivity is reported for primary cutaneous ALCL [10], but, to our knowledge, its positivity in systemic ALK-negative ALCL has not been discussed in the literature. We believe that this finding is important because in some cases an antigenic overlap between CHL and ALK-negative ALCL can cause a serious diagnostic dilemma [1,2]. GATA3, along with TBX-21 (T-bet), is used for subclassifying peripheral T-cell lymphoma NOS to Th1 (TBX-21 expression) and Th2 (GATA3 expression) subgroups via gene expression profiling [11]. With target cytokines CCR5 and CXCR3, respectively, a four-antibody IHC panel has been proposed for the differentiation of Th1 and Th2 [11]. This subgrouping approach has not been previously reported for ALCL and thus we do not know its relationship with the current ALK-negative ALCL subtypes. There are reported similarities in oncogenic pathways in ALCL and CHL, like BATF3 and STAT3 [12]. STAT3 activation can be important regarding GATA3 because STAT3 activation is also seen in the PTCL-GATA3 subgroup [11,13]. GATA3 expression in CHL and ALCL can be a byproduct of this similarity.

We evaluated the relationship between GATA3 expression and EBV status based on EBV LMP1 in CHL. The expression of GATA3 was significantly lower in EBV LMP1-positive CHL. Although our finding was based on EBV LMP1 and not confirmed by EBER, it is in concordance with GATA3 negativity in EBV-positive DLBCL. This can be attributed to EBV-positive cases having fewer genetic mutations, especially in NF-κB and the JAK/STAT pathway [14,15,16] in CHL.

As an alternative to excisional biopsy, CNB of lymph nodes is a widely accepted procedure for diagnosis. As the evaluated tissue is limited in CNBs, the differential diagnosis of CHL can become challenging due to the polymorphic background that may mask the neoplastic cells. Furthermore, heterogeneous immunoreactions in neoplastic cells increase the diagnostic difficulty. Reliable diagnostic markers play an important role in making results more conclusive and reducing the risk of misdiagnosis. The effect of the biopsy type on GATA3's diagnostic utility was not previously discussed in the literature. In this study, we evaluated whether GATA3's contribution to diagnosis differed depending on the biopsy type. Its contribution to diagnosis was not significant in CNBs, which is probably due to the heterogeneous expression of GATA3 in neoplastic cells.

### Study Limitations

The main limitations of this study were the limited EBV status detection by EBER in situ hybridization and the unavailability of ALK-negative ALCL subgrouping by DUSP22 and TP63 fluorescence in situ hybridization. For the first limitation, the latency type of EBV (type 2a) in CHL helps us to overcome the

problem. EBV LMP1 is enough to confirm EBV presence. The second situation arose due to the unexpected high expression of GATA3 in ALK-negative ALCL cases. Although the lack of subgroup information for ALK-negative ALCL did not affect the interpretation of GATA3, whether GATA3 expression is higher in any specific ALK-negative ALCL subgroups is a question to be answered.

## Conclusion

GATA3 is a useful marker in the differential diagnosis of CHL from B-cell NHLs and NLPHL. However, it does not have additive value in the differential diagnosis of CHL versus ALK-negative ALCL and MGZL. Since it is not expressed in all neoplastic cells, its contribution to diagnosis is limited in CNB.

### Ethics

**Ethics Committee Approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the İstanbul University İstanbul Medical Faculty (approval no: 22, case no: 2022/2042, date: 09.12.2022).

**Informed Consent:** Retrospective study.

### Footnotes

### Authorship Contributions

Concept: A.Y.A., G.Y.; Design: A.Y.A., G.Y.; Data Collection or Processing: A.Y.A., B.Y.E.; Analysis or Interpretation: A.Y.A., G.Y., B.Y.E.; Literature Search: A.Y.A., B.Y.E.; Writing: A.Y.A., G.Y.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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