

Original Research Article

Discordance between histopathology and immunohistochemistry and pattern of lymphoma in northern part of Bangladesh

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ABSTRACT

Background: Even in this modern era, many lymphoma patients are getting treatment based on histopathology diagnosis. The treatment plan and overall survival (OS) of lymphoma patients are adversely affected by either misdiagnosis or overdiagnosis. This study is intended to evaluate the degree of discordance between IHC and histopathological investigations, the pattern of lymphoma and various factors related to it.

Methods: This cross-sectional study was conducted in the Department of Hematology, Shaheed Ziaur Rahman Medical College Hospital, Bogura and private practice from 2019 to 2024 until 100 cases were available. Variation in diagnosis was assessed and factors such as cellular origin of lymphoma, status of CD20 positivity, any role of expert variation and justification of histopathology as a tool of treatment were assessed. Data were collected by reviewing investigation reports and documented in a checklist.

Results: Diagnostic discordance, regarding confirmed diagnosis, between histopathology and IHC was identified in 78% of patients. In 58% of cases, morphological diagnosis even failed to clarify broadly if it is malignant or not, if it is lymphoma whether it is HL or NHL. In 75% of lymphoma cases, peripheral lymph node involvement was found, about 10% of cases NHL involved bone marrow rather than peripheral LNs. CD20 was positive in 62% of lymphomas, 10% of HD and 72% of NHL.

Conclusions: Lymphoma is a potentially curable malignancy having a wide variety of treatment options depending on the type of disease. This typing is not possible without IHC. No lymphoma patient should be treated without IHC diagnosis.

Keywords: Bangladesh, Discordance, Histopathology, Immunohistochemistry, Lymphoma

INTRODUCTION

The World Health Organization classifies lymphomas into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphoma is further characterized by its stage of maturation (immature vs. mature) and cell of origin [B cell, T cell, or natural killer cell (NK) cell]. The morphologic evaluation considers the anatomical architectural changes in the lymphoid compartment.^{1,2}

Although a universal treatment protocol is usually used, lymphoma diagnosis is challenging for various reasons, mostly due to a lack of adequate and quality investigation facilities. It can be difficult to diagnose lymphoma because of the disease's subtle beginning of symptoms, difficulty obtaining a lymph node biopsy for the diagnosis, and other factors. This can cause delays in diagnosis, even in settings with the best resources.³ There is a 20% difference between expert pathologists and referrals, which directly affects patient care, according to data from the French

Lymphopath network nationwide.⁴ The influence of expert review on lymphoma management was also shown in other US and UK trials, with varying percentages of discordance (14.8 to 27.3%).^{5,6} Lymphoma diagnosis depends on the pathologist's competence, which, in the case of follicular proliferation, must clearly distinguish follicular lymphoma (FL) from follicular hyperplasia (FH). These two lesions might have very similar appearances.⁷ In addition to shape and clinical symptoms, the diagnosis and categorization of lymphoma now rely primarily on determining cell lineage, maturation, and function based on antigen expression and genetic studies. This has made immunohistochemistry (IHC) and cytogenetics an essential aspect of diagnostic hematopathology, as they are required for modern treatment, prognosis, and research.⁸ Immunohistochemistry (IHC) is a diagnostic technique that uses antigen-antibody interactions to identify specific cell proteins. This approach has various significant applications in lymphoma diagnosis, including determining the cell lineage and stage of maturation, detecting particular genetic mutations, visualizing the degree of cell proliferation, and finding treatment targets.¹

Although morphology remains the cornerstone for HL diagnosis, the morphological complexity of NHL frequently impairs the pathologist's ability to distinguish benign from malignant diseases correctly.⁹ Lymphoma is currently diagnosed through histological inspection of tissue sections at various magnification levels by a pathologist, whose suspicion is based on morphological abnormalities identified during hematoxylin and eosin (H&E) staining. Lymphoma overdiagnosis and missed diagnosis rates are unavoidably high at certain centers.⁸ This study looked into the discrepancies between histopathology and IHC findings as well as pattern of lymphoma. The findings of the following study may be taken as evidence to raise clinician awareness regarding misdiagnosis or overt diagnosis, which will ultimately benefit patients.

METHODS

This cross-sectional study was conducted in the Hematology Department of Shaheed Ziaur Rahman Medical College Hospital, Bogura and private practice from 2019 to 2024 until 100 cases were available. Patients diagnosed as lymphoma, either by cytological or histopathological investigation, irrespective of age and gender, were included. The primary aim was to find the discordance between IHC and cytological investigations and the pattern of lymphoma in the northern part of Bangladesh. Exclusion criteria were Absent identifiers or essential clinical/path data needed for classification/discordance assessment (age, sex, site, biopsy date, specimen type, H&E diagnosis, IHC panel/results), and those who are not willing provide information in this study. Factors such as cellular origin of lymphoma, pattern of tissue involvement, status of CD20 positivity and justification of histopathology as a tool of treatment were further analyzed. Data were collected by

reviewing investigation reports and documented in a checklist. Data was analyzed by SPSS software version 22 according to the set objectives.

RESULTS

Distribution of the patients according to the demographic characteristics

Table 1 shows that the majority of patients (32%) were in the 40-59 age range, with 26% of patients being in the 20-39 age range. The mean age of the patients was 41.44 ± 19.423 years. The majority (67%) of patients were male, as shown in the Table 1.

Table 1: Demographic characteristics of the patients (n=100).

Characteristics	Group	Frequency	Percentage
Age in years (in group)	0 -19	18	18
	20 -39	26	26
	40-59	32	32
	60 and above	24	24
	Mean $\pm$ SD (Years)	41.44 ± 19.423	
	Min-Max (Years)	5-82	
Gender	Male	67	67
	Female	33	33

Broad category of lymphoma diagnosed by histopathology

The study included 100 patients who had been diagnosed with lymphoma histopathologically. We followed the protocol; if a patient was suspected of lymphoma by FNA or histology, we did IHC. Although 100 lymphoma patients were cytopathologically or histopathologically diagnosed, after final IHC diagnosis, 13% were found non-malignant, 6% were non-hematological malignancies, and 81% were confirmed as lymphoma (Table 2).

Table 2: Histopathological diagnosis of the patients (n=100).

Categories	Frequency	Percentage
HL	23	23
NHL	57	57
Other malignancy	6	6
Non-malignant	13	13
LPD could not be typed	1	1

According to Table 3, among lymphomas, 28% (23/81) were Hodgkin. Most cases were found to be Non-Hodgkin's lymphoma (NHL), 72% (58/81). According to the results, 21 cases were classical HL and 2 cases were nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Table 3 also demonstrates that diffuse large B-

cell lymphoma (DLBCL) was the most common variety among NHL.

Table 3: Pattern of lymphoma according to immunohistochemistry (n=81).

Categories	Frequency	Percentage
Hodgkin lymphoma (classical)	21	25.61
DLBCL	20	24.39
Follicular lymphoma	6	7.31
PTCL	6	7.31
T cell lymphoblastic lymphoma	5	6.09
B NHL	5	6.09
AITCL	3	3.65
Mantle cell lymphoma	2	2.44
Burkitt lymphoma	2	2.44
Histiocytic sarcoma	2	2.44
NLPHL	2	2.44
SLL	2	2.44
Anaplastic large cell lymphoma	1	1.21
B-cell lymphoblastic lymphoma	1	1.21
Extranodal MZL	1	1.21
Marzinal zone lymphoma	1	1.21
Lymphoma but cannot be categorized	1	1.21

Diagnostic discordance between histopathology and IHC was identified in 78% of patients according to Table 4.

Table 4: Discordance between histopathology and immunohistochemistry findings (n=100).

Attributes	Categories	Frequency	Percentage
Discordance between histopathology and IHC	Yes	78	78
	No	22	22
Broad categorical difference in histopathology and IHC	Yes	58	58
	No	42	42

Table 5: Distribution of histopathological diagnosis and the broad category of IHC (n=100).

Histopathological diagnosis	Broad category of IHC					Total
	HL	NHL	Other malignancy	Non-malignant	Lymphoma but cannot be defined	
HL	11	3	0	2	0	16
NHL	2	33	4	8	1	48
Normal	1	0	0	1	0	2
Others	9	21	2	2	0	34
Total	23	57	6	13	1	100

In this study, we found that 80% (65/81) of lymphomas originated from B-cells and 20% from T-cells. 71% of NHL originated from B-cells and 29% from T-cells. None of the Hodgkin lymphomas originated from T-cells. Regarding tissue involvement, in 75% of lymphomas,

Histopathology failed to accurately diagnose in 78%. In 58% of cases, it even failed to clarify broadly whether it is malignant or not, if it is lymphoma, whether it is HL or NHL. In our study, according to the initial histopathological diagnosis, 16 cases were HL. Of which, after IHC, 11 were diagnosed as HL, the diagnostic accuracy was about 69%.

Histopathological diagnosis and the broad category of immunohistochemistry

Total 23 cases were diagnosed as HL. Initially 16 cases were HL, of them 11 were confirmed as HL after IHC. Histopathology failed to diagnose 52%(12/23) of HL. NHL was diagnosed in 48 cases; after IHC, 33 were NHL, 2 HL, 4 other than hematological malignancies and 8 were found non-malignant. In 2 cases, FNA was suggestive of lymphoma, later commented as normal tissue in histopathology, but after final diagnosis, one of them was HL. Most importantly, histopathology put nonspecific comments like atypical lymphoid hyperplasia, lymphoproliferative disorder, etc., in 34 cases. After final diagnosis by IHC 21 NHL, 9 HL, 2 other than haematological malignancies and 2 cases were found non-malignant.

The average age of the patients was 41.44 years, with ages ranging from 5 to 82 years. The 40-59-year age group had the highest proportion of cases, accounting for 32% of the total. About 39% (9/23) HL patients were under 20 years whereas NHL was only 5%. Table 6. shows that HL was more prevalent in the youngest age group, while NHL was the dominant type in patients older than 20 years.

peripheral lymph node involvement was found. In 87% (20/23) of Hodgkin lymphoma, peripheral lymph nodes were involved, and about 71% (41/57) of NHL peripheral lymph nodes were involved. About 10% of NHL cases involved bone marrow rather than peripheral lymph nodes.

Table 6: Distribution of the broad category of IHC according to the age group (n=100).

Age group (in years)	Broad category of IHC					Total
	HL	NHL	Other malignancy	Non-malignant	Lymphoma but cannot be defined	
0-19	9	3	0	2	0	16
20-39	9	33	4	8	1	48
40-59	3	0	0	1	0	2
60 and above	2	21	2	2	0	34
Total	23	57	6	13	1	100

Table 7: Distribution of the broad category of IHC according to the type of cell involvement and tissue sample (n=100).

Attributes	Category	Broad category of IHC					Total
		HL	NHL	Others	Non-malignant	Lymphoma cannot be categorized	
Cell involvement	B-cell	23	40	0	1	1	65
	T-cell	0	15	0	1	0	16
	Not applicable	0	0	1	8	0	9
	Others	0	2	5	3	0	10
Tissue sample	Lymph node	20	40	3	8	1	72
	Trephine biopsy	0	6	1	0	0	7
	CT-guided core biopsy	2	3	1	3	0	9
	Others	1	8	1	2	0	12

DISCUSSION

This study evaluated histological and immunohistochemical (IHC) findings in lymphoma patients in northern part of Bangladesh and explored the degree of discordance and various factors relating to lymphoma. Our findings revealed a predominance of male patients and Hodgkin's lymphoma (HL) being the most commonly diagnosed type among the youngest age group. Similar trends of male predominance have been documented in retrospective hospital-based studies from both India and Sweden.^{10,11} In the current study, 72% of the lymphoma cases were classified as NHL, aligning with data reported in prior research. Relevant studies in India also observed a higher prevalence of non-Hodgkin lymphoma (NHL) compared to HL.^{10,12} Sharma et al found that of the total NHL cases, 76% were B-cell NHL, whereas the remaining were T-cell NHL.¹² According to the findings, 80% of lymphomas originated from B-cells and 71% of NHLs originated from B-cells in the current study. This finding matched with a relevant study in Bangladesh by Akhter et al that found B-cell lymphoma comprised 86.25% of the NH lymphomas. Naresh et al found that B-cell lymphoma accounted for 79.1% of NHLs and DLBCL was the most common subtype.^{13,14} DLBCL was the commonest variety of NHL with a frequency of 24.39% in the current study which is quite similar according to the International non-Hodgkin's Lymphoma Study Group Series, the most common was DLBCL with 31% cases.¹² Second most common NHL was FL 7.31%. In their study Jain et al also found FL as second common NHL (10.81%).¹⁰ In this

study, average age for HL is about 28 years and for NHL it is about 48 years. The majority of Hodgkin's lymphoma (HL) cases were detected in patients under the age of 40. About 39% of HL patient belonged to below 20 years where as only about 9% in case of NHL. In a hospital-based analysis in Dhaka Medical College and Hospital found that the majority of NHL patients were in the 31-55 years age group and the mean age of the HL patients was 30 years. Though the age pattern for HL was quite similar, a variation was observed in NHL.¹³ Our findings were also similar to that.

A diagnostic discrepancy between histopathology and immunohistochemistry (IHC) was observed in 78% of cases in this study. Notably, in 58% of these cases, histopathology alone failed to determine whether the lesion was malignant, and if so, whether it was Hodgkin's lymphoma (HL) or Non-Hodgkin lymphoma (NHL). A prior study conducted in Bangladesh in 2018 reported that 60.3% of lymphoma cases were diagnosed as NHL based solely on histopathology, which increased to 73.5% when both histopathology and IHC were used. That study also documented a 27% rate of diagnostic discordance.¹⁸ In this study we also found about 72% of lymphoma as NHL broadly. Similar diagnostic discrepancies have been reported in other South Asian countries. For instance, a 2024 study from India revealed a 75% concordance rate between histopathological and IHC findings in identifying malignant lymphomas. In this study degree of discordance is very high in comparison to others because very few studies available on discordance between histopathology

and IHC. Most of the studies compared both histopathology and IHC with review or second opinion. Important point is, here we considered discordance by pin point final diagnosis not merely by either Hodgkin or Non-Hodgkin lymphoma. In the current study, 16 cases were histopathologically diagnosed as HL but only 11 of these were confirmed as HL after IHC, reflecting a diagnostic accuracy rate of approximately 69%. Our total Hodgkin lymphoma cases were 23. So, 12 cases were not identified by histopathology, the rate of misdiagnosis was 52%. But we know, because of characteristics finding diagnostic accuracy of HL is far greater than NHL by histopathology. An important observation of this study is, in 2 cases, FNA was suggestive of lymphoma, later commented as normal tissue in histopathology, but after final diagnosis, one of them was HL.

Now a days treatment decision is based on final diagnosis. Different varieties of NHL have different treatment protocol. Furthermore, secondary reviews have shown that patients with concordant diagnoses had improved five-year overall survival, whereas those with discordant findings were at a significantly greater risk of mortality.¹⁹ Cai et al., in a trend analysis of NHL, highlighted that in South Asia, diagnostic challenges including resource limitations, interpretive errors, and lack of high-quality pathological services have contributed to poorer patient outcomes. These findings underscore the essential role of IHC in enhancing diagnostic precision and reducing misclassification in lymphoma cases.

This study has few limitations. Although most of the IHCs were done in a renowned laboratory with high reliability, some also done at different centers. It was a single-center study. The main limitation is lack of review or second opinion, which was not included in the study design, as diagnostic approaches and available resources can differ across institutions and regions. Additionally, the relatively small sample size may not adequately reflect the diverse range of lymphoma subtypes or allow for strong conclusions regarding the frequency of diagnostic discrepancies. Although most of the histopathology and IHC done at same center where IHC may could have influence histopathology reports. Furthermore, the involvement of a limited number of pathologists in the diagnostic process could introduce subjectivity and inter-observer variability, potentially impacting the reliability of the results.

CONCLUSION

This study revealed a significant rate of diagnostic discrepancies in lymphoma cases, particularly highlighting the limitations of relying solely on histopathology. A substantial proportion of cases showed misclassification between malignant and non-malignant forms, as well as between Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). These diagnostic inaccuracies can severely impact patient management, influencing prognosis, treatment decisions, and overall survival. To

minimize such errors, incorporating expert pathology review panels and combining histological analysis with immunohistochemistry (IHC) is recommended. Additionally, increased investment in diagnostic infrastructure and the recruitment of skilled personnel at district and higher healthcare levels are essential to ensure timely and precise diagnosis.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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