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*Article*

# IMP3 Immunohistochemical Staining: A Valuable Tool in the Differential Diagnosis of Nodular Lymphocyte Predominant Hodgkin Lymphoma and T-Cell/Histiocyte-Rich Large B-Cell Lymphoma

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**Abstract: Introduction:** The diagnosis of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and T cell/histiocyte-rich large B-cell lymphoma (THRLBCL) can be difficult due to their overlapping histological features. Recently, insulin-like growth factor II mRNA-binding protein 3 (IMP3) has been proposed as a diagnostic marker for Hodgkin's lymphoma. The objective of this study was to evaluate the effectiveness of IMP3 in differentiating between NLPHL and THRLBCL.

**Methods:** This was a retrospective study that included formalin-fixed paraffin-embedded blocks from 56 patients. Of these, 28 were diagnosed with NLPHL and 28 with large B cell lymphoma (LBCL), including 16 THRLBCL and 12 DLBCL, NOS, based on immunohistochemistry (IHC). Samples were stained for IMP3 using IHC, and positive expression was defined as moderate to strong staining in at least 10% of tumor cells.

**Results:** The mean age of the patients was 41.25 ± 16.08 years, and the majority were male. There was a significant age difference between NLPHL (34.61 ± 16.44 years) and LBCL (47.89 ± 12.85 years) groups ($p = 0.001$). No significant difference was observed in gender or site between NLPHL and LBCL groups. The expression of IMP3 was mainly strong in the LBCL group, while it was heterogeneously distributed among NLPHL samples, ranging from weak to strong ($p < 0.001$). It was determined that strong IMP3 expression at 55.00% can differentiate LBCL from NLPHL with 71.4% sensitivity and 71.4% specificity.

**Conclusion:** Our findings showed that IMP3 may be a good complement in differentiating NLPHL cases from THRLBCL.

**Keywords:** Nodular lymphocyte predominant Hodgkin lymphoma; T cell/histiocyte-rich large B-cell lymphoma; IMP3; Immunohistochemistry

## 1. Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon type of lymphoma with distinctive clinical and pathological features. The majority of patients with NLPHL have an indolent clinical course and the disease is often diagnosed at an early stage. Localized radiation therapy is the preferred treatment for patients with early-stage disease, whereas combined-modality therapy is used for intermediate-stage NLPHL, and chemotherapy is the standard of care for advanced-stage NLPHL [1].

T cell histiocyte rich large B cell lymphoma (THRLBCL) is another rare subtype of diffuse large B cell lymphoma (DLBCL) that tends to be more aggressive than NLPHL. The prognosis of THRLBCL is similar to that of DLBCL, not otherwise specified (NOS). THRLBCL requires more intensive chemotherapy than NLPHL [2].

The neoplastic cells in NLPHL, also known as lymphocyte-predominant (LP) cells, have distinct histological features, including scant cytoplasm, a folded or multilobated nucleus, and a basophilic appearance. These cells are typically positive for CD45, CD20, CD79a, and Bcl-6, but negative for CD15, and often negative for CD30 [3].

The large cells in THRLBCL may resemble LP and Hodgkin/Reed-Sternberg (HRS) cells, but usually exhibit greater pleomorphism. Although the immunoprofile of the large cells is similar to that of LP and HRS cells, large cells are less

likely to express Bcl-6 and more likely to express IRF4/MUM1 than LP and HRS cells. As a result, differentiating between these cells based on neoplastic cell morphology alone is nearly impossible [2].

The main characteristic of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is the predominance of nodular pre-dominant background reactive B-cells expressing CD23 or CD35 in the follicular dendritic cell meshwork. In contrast, T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is mostly composed of lymphoid T-cells in a diffuse background. Thus, THRLBCL can be diagnosed by the scattered presence of neoplastic cells in a background mainly consisting of T-cell and histiocytes without small B-cells [4,5].

NLPHL variants such as pattern E are usually diagnosed in advanced stages (stage IIB and higher) [6]. The diagnosis of pattern E NLPHL (diffuse, THRLBCL-like) and THRLBCL is challenging due to their morphologic similarities. Rosette formation of PD1+ cells around neoplastic cells is a common diagnostic characteristic of NLPHL, but it may be absent in nodular forms of NLPHL, including NLPHL THRLBCL-like [7].

There is a possible reason for the observed molecular overlap between these tumor cells: the similarity in gene expression profile of NLPHL-THRBCL-like and de novo THRLBCL. However, the average genome imbalance in NLPHL is higher than that of THRLBCL (10.8 and 4.7, respectively) [7]. Recent studies on array comparative genomic hybridization show that THRLBCL has higher genomic aberrations compared to typical and THRLBCL-like variants of NLPHL. These similarities in gene expression profiling between NLPHL and THRLBCL suggest a pathobiological similarity and justify the different clinical presentations of these tumors [8].

The immunohistochemical (IHC) profile of lymphocyte-predominant (LP) and large B-cell lymphoma (LBCL) cells is quite similar, making it difficult to differentiate between them using a specific IHC marker. However, recent research has suggested that insulin-like growth factor II mRNA-binding protein 3 (IMP3/KOC), an embryo/carcinoma marker, may be useful for diagnosing classical Hodgkin's lymphoma (CHL) [9]. IMP3 belongs to a family of proteins known as insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3), which play a crucial role in RNA stability, cell growth, and migration during embryogenesis [10,11]. However, IMP3 has also been implicated as an oncogenic protein, and its overexpression has been detected in various epithelial malignancies, including bladder, liver, breast, pancreas, lung, colon, ovary, kidney, and sarcomas in several soft tissues. Therefore, IMP3 has been proposed as a diagnostic marker for some epithelial malignancies [12]. Recent studies have shown that high levels of IMP3 protein are present in 98.8% of patients with CHL and other types of Hodgkin's lymphoma, suggesting that IMP3 may be a complementary diagnostic marker for these conditions and may help distinguish them from LBCL [13]. However, a recent study found no significant difference in IMP3 expression between Hodgkin and non-Hodgkin's lymphomas [14]. Because accurate and timely diagnosis and subtyping of lymphomas are critical for successful treatment, it is essential to identify a marker that can differentiate between Hodgkin's lymphoma and LBCL. Therefore, the objective of this study was to investigate IMP3 expression in NLPHL and LBCL, especially THRLBCL, and evaluate the potential of IMP3 as an IHC marker for distinguishing NLPHL from LBCL.

## 2. Materials and methods

### 2.1. Study Design

This study was designed as a cross-sectional study and approved by the Ethics Committee of the Tehran University of Medical Sciences. It was conducted in Imam Khomeini and Dr. Shariati Hospitals, Tehran, Iran, from March 2016 to March 2020.

### 2.2. Study Population

The patients were identified through an electronic record search of the Pathology Departments in the mentioned hospitals. As THRLBCL is a rare type of lymphoma and neoplastic cells have almost the same immunophenotype with DLBC-NOS, patients with immunohistochemical (IHC) diagnosis of LBCL (including THRLBCL(preferably) and DLBCL, NOS) with NLPHL were identified. The formalin-fixed paraffin-embedded blocks of patients with a documented diagnosis of both NLPHL and LBCL were evaluated.

**Table 1.** Relationship between IMP3 expression and demographic variables

| Variable | Unstandardized beta | Standardized beta | P |
|---|---|---|---|
| Age | 0.320 | 0.159 | 0.574 |
| Gender | -6.320 | -0.111 | 0.732 |
| Site | 4.370 | 0.120 | 0.700 |

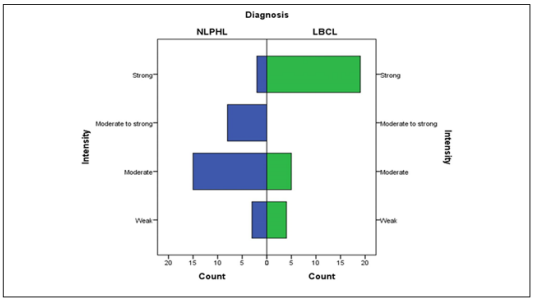


**Figure 1.** Distribution pattern of IMP3 staining intensity among NLPHL and LBCL cases

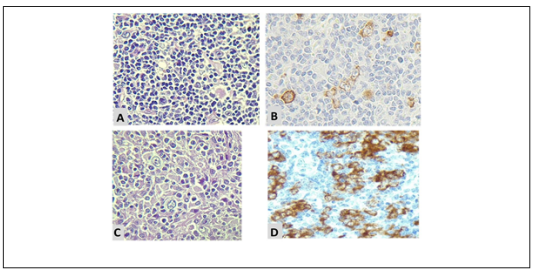


**Figure 2.** A) NLPHL, H&E(x400); B) Hetrogenous expression of IMP3 in NLPHL, IHC; C) THRLBCL, H&E(x400); D) Strong IMP3 immunoreactivity in THRLBCL

**Table 2.** Comparison of demographic characteristics of the study samples

| Variable | | Total Frequency (%) | NLPHL Frequency (%) | LBCL Frequency (%) | P |
|---|---|---|---|---|---|
| Gender | Male | 37 (66.1%) | 17 (45.9%) | 20 (54.1%) | 0.397 |
| | Female | 19 (33.9%) | 11 (57.9%) | 8 (42.1%) | |
| Site | Axillary LN | 17 (31.5%) | 8 (47.1%) | 9 (52.9%) | 0.412 |
| | Cervical LN | 17 (31.5%) | 12 (70.6%) | 5 (29.4%) | |
| | Inguinal LN | 6 (11.1%) | 4 (66.7%) | 2 (33.3%) | |
| | Para-aortic LN | 2 (3.7%) | 1 (50.0%) | 1 (50.0%) | |
| | Submandibular LN | 1 (1.9%) | 1 (100.0%) | 0 (0.0%) | |
| | Mandibular LN | 1 (1.9%) | 1 (100.0%) | 0 (0.0%) | |
| | Axillary mass | 1 (1.9%) | 1 (100.0%) | 0 (0.0%) | |
| | Vertebral lesion | 1 (1.9%) | 0 (0.0%) | 1 (100.0%) | |
| | Cervical and axillary LN | 1 (1.9%) | 0 (0.0%) | 1 (100.0%) | |
| | Skull mass | 1 (1.9%) | 0 (0.0%) | 1 (100.0%) | |
| | Sternal mass | 1 (1.9%) | 0 (0.0%) | 1 (100.0%) | |
| | Abdominal mass | 1 (1.9%) | 0 (0.0%) | 1 (100.0%) | |
| | Omentum | 1 (1.9%) | 0 (0.0%) | 1 (100.0%) | |
| | Ankle mass | 1 (1.9%) | 0 (0.0%) | 1 (100.0%) | |
| | Spleen | 1 (1.9%) | 0 (0.0%) | 1 (100.0%) | |
| | Brain | 1 (1.9%) | 0 (0.0%) | 1 (100.0%) | |

The formalin-fixed paraffin-embedded and hematoxylin and eosin (H&E) stained blocks were retrieved from hospital archives. The H&E slides were re-evaluated and previous IHC study markers for NLPHL, including CD30, CD15, CD20, CD45, and PAX5, and for LBCL, including CD20, CD3, BCL6, CD10, and CyclinD1, were reviewed to confirm the

diagnosis based on the 2016 WHO Classification of Haematolymphoid Tumors. The previously IHC-stained blocks were selected for monoclonal staining with IMP3.

The pathological features, including histological subgroup, nodal or extranodal location, clinical data, including remission status, and demographic data, including age and gender, were obtained from the Laboratory Information System and/or the surgical department records.

Patients were assigned a unique code, and their information remained anonymous. Blocks with inadequate tissue for IHC and incomplete medical records were excluded from the study.

### 2.3. IHC study

Immunohistochemistry (IHC) was conducted utilizing a monoclonal rabbit anti-human IMP3 antibody (Clone EP286, IgG isotype), which was purified from serum and prepared in 10mM PBS, pH 7.4, with 0.2% BSA and 0.09% sodium azide, utilizing Epitomics's RabMAbő technology under U.S. Patent Nos. 5,675,063 and 7,402,409. To perform the IMP3 staining, ductal adenocarcinoma of the pancreas was used as a positive control. The tissue sections were deparaffinized, rehydrated, and then subjected to heat antigen retrieval technique. The standard protocol of the manufacturer (Master Diagnostica, Spain) was used for immunostaining.

### 2.4. IHC staining interpretation

The immunohistochemical (IHC) staining analysis of the samples was conducted using a 4-tiered system with a high magnification (400x) light microscope by two independent pathologists, namely F.A and T.B. Both pathologists were unaware of the patients' clinicopathologic parameters and outcome. A positive cytoplasmic staining was considered when the immunoreactivity was observed in at least 10% of the tumor cells [15]. The staining intensity was further categorized as weak (1+), moderate (2+), or strong (3+) based on the degree of positive stained tumor cells. In case of any discrepancy between the pathologists' interpretations, a consensus was reached through mutual agreement.

### 2.5. Statistical analysis

The study employed the statistical software package for social sciences (SPSS) version 16 to conduct data analysis. Normality distribution of continuous variables was evaluated using the Shapiro-Wilk test. Mean and standard deviation (SD) or minimum and maximum values were used to present continuous variables, based on normality. Frequency and percentage were used to present categorical variables. Comparison of continuous variables between groups was performed using the independent t-test, while the distribution pattern of categorical variables between groups was compared using the chi-square test. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off for IMP3 expression in differentiating between LBCL and NLPHL. The analysis reported the area under the curve (AUC), 95% confidence interval (CI) for AUC, cut-off, and its sensitivity and specificity. The level of statistical significance was considered as $p < 0.05$. Relevant references were used in the study to support the analysis.

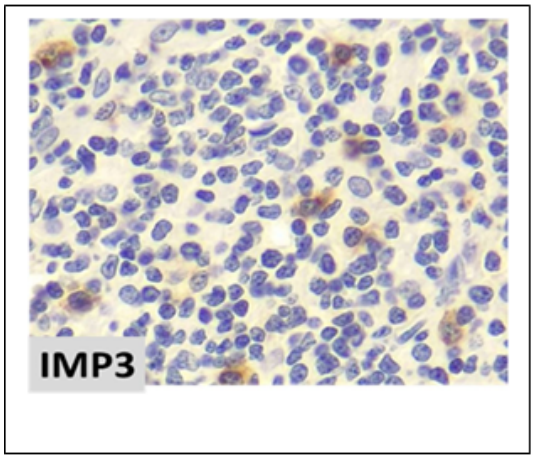


**Figure 3.** Scattered IMP3 immunreactivity in background non-neoplastic lymphoid cells in NLPHL (x400)

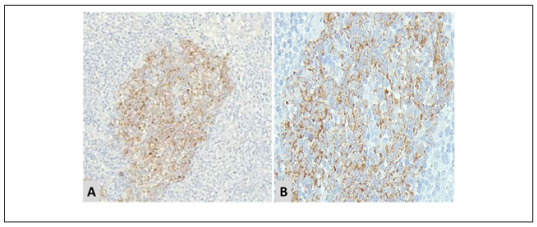


**Figure 4.** A(x100) & B(x400): IMP3 expression in reactive lymphoid germinal centers

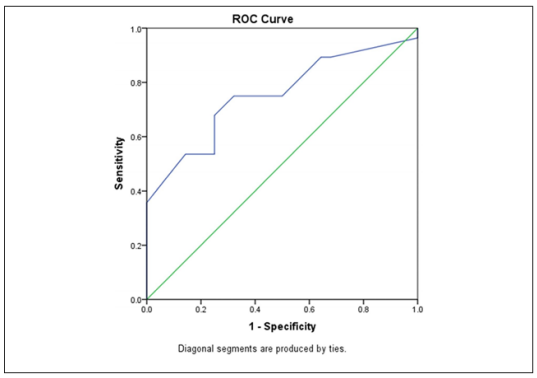


**Figure 5.** ROC curve for IMP3 expression in differentiating LBCL( including THRLBC & DLBCL,NOS) from NLPHL

## 3. Results

A total of 56 samples were analyzed in this study, consisting of 19 females (33.9%) and 37 males (66.1%), with a mean age of 41.25 ± 16.08 years. The study included an equal number of NLPHL and LBCL samples, with 28 samples in each group. Among these, 16 samples were THRLBCL and 12 samples were DLBCL, NOS. The most common tumor sites were axillary and cervical lymph nodes, followed by inguinal lymph nodes and para-aortic lymph nodes. A significant age difference was observed between NLPHL and LBCL groups, with NLPHL patients being younger than LBCL patients. However, there was no significant difference in gender and site between the two groups.

**Table 3**

| Lymphoma type | | | Intensity of IMP3 expression | | Total |
|---|---|---|---|---|---|
| | | Negativea | Variable ) weak to moderate) | Strong above 55% | |
| LBCL- sub- | THRLBCL | 2 | 4 | 10 | 16 |
| type | DLBCL,NOS | 0 | 1 | 11 | 12 |
| NLPHL | | 3 | 22 | 3 | 28 |

The study found that the mean IMP3 expression percentage among all samples was 55.80% (ranging from 5.00 to 100.00). The mean IMP3 expression percentage was significantly higher in LBCL than in NLPHL (70.89% vs. 40.71%, respectively). The distribution of IMP3 expression intensity levels was also significantly different between the two groups. LBCL samples had mainly strong IMP3 expression, while IMP3 expression in NLPHL samples was heterogeneously distributed, ranging from weak to strong. IMP3 expression was observed in the background lymphoid cells and germinal centers of reactive lymphoid follicles.

There was no significant relationship between IMP3 expression and demographic variables such as age and gender. The ROC curve analysis indicated that IMP3 expression intensity can differentiate NLPHL from LBCL with 71.4% sensitivity and 71.4% specificity at a cutoff value of 55.00%. The area under the ROC curve was 75.4, suggesting that IMP3 expression can differentiate these two neoplasms to a certain extent.

In this study, the researchers conducted a ROC analysis to determine if IMP3 expression could be used to differentiate between THRLBCL and NLPHL. The results showed that the area under the curve for the ROC curve was 64.3%, indicating that IMP3 expression intensity is capable of differentiating these two neoplasms. They found that IMP3 expression at 55% can differentiate THRLBCL type from NLPHL with 56.3% sensitivity and 71.4% specificity. Based on this cut-off, the researchers presented a box plot indicating the mean, standard deviation, and range of the data.

NLPHL and THRLBCL share a common pathological feature, which is the presence of scattered large neoplastic B-cells in a background of benign lymphocytes and macrophages. The THRLBCL-like variant of NLPHL and de novo THRLBCL may show significant morphologic and immunophenotypic overlap, making their diagnosis challenging. However, it is critical to differentiate between these two neoplasms due to differences in prognosis and treatment. NLPHL has a favorable overall prognosis, except in advanced stages, while THRLBCL is often refractory to the chemotherapy regimens currently in use.

The IMP family, including IMP1, IMP2, and IMP3, play an important role in primary embryogenesis, RNA trafficking, stabilization and regulation of proliferation, and migration of embryonic cells. Not all normal tissues express IMP3, and in lymphoid tissue, IMP3 is only expressed in lymph nodes, spleen, and tonsillar germinal centers. IMP3 expression was also reported in centrocytes, centroblasts, and thymocytes, while IMP3 is not expressed in bone marrow cells.

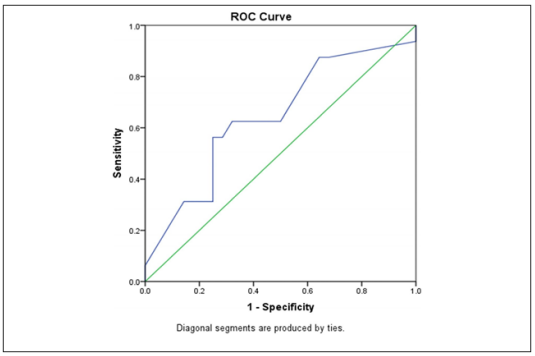


**Figure 6.** ROC curve for IMP3 expression in differentiating THRLBCL from NLPHL

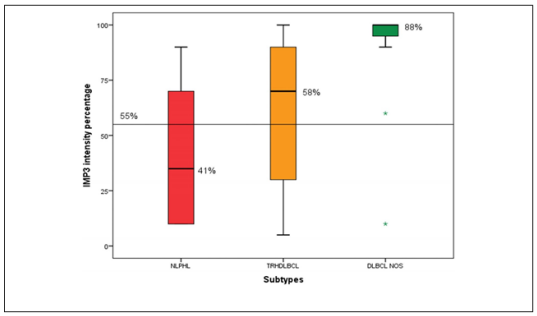


**Figure 7.** Box plot for mean, standard deviation, and range of the intensity percentage of IMP3 among NLPHL, THRLBCL and DLBCL,NOS subtypes with respect to 55% cut-off

The study conducted in [16] aimed to investigate whether IMP3 expression could differentiate between THRLBCL type and NLPHL. The ROC analysis revealed that IMP3 expression intensity could differentiate these two neoplasms with an area under curve of 64.3% (95% CI: 46.8% and 81.7%). The identified cut-off point of 55% IMP3 expression could differentiate 56.3% of THRLBCL type from NLPHL with 56.3% sensitivity and 71.4% specificity (Fig. 6). Furthermore, a box plot presenting the mean, standard deviation, and range of the data with respect to the 55% cut-off is presented in Fig. 7.

NLPHL and THRLBCL share a common pathological feature of scattered large neoplastic B-cells in a benign background of lymphocytes and macrophages. However, significant morphologic and immunophenotypic overlap between the THRLBCL and NLPHL, especially THRLBC-like variant, makes their diagnosis challenging. This differentiation is critical, as NLPHL has a favorable prognosis except in advanced stages, while THRLBCL is an aggressive disease often refractory to current chemotherapy regimens [17].

The IMP family, including IMP1, IMP2, and IMP3, play a crucial role in primary embryogenesis, RNA trafficking, and regulation of cell proliferation and migration. In lymphoid tissue, IMP3 is only expressed in lymph nodes, spleen, and tonsillar germinal centers. Moreover, IMP3 expression was also reported in centrocytes, centroblasts, and thymocytes, while it is not expressed in bone marrow cells [18].

The study examined the expression of IMP3 as a diagnostic marker in differentiating between Hodgkin lymphoma subtypes, including NLPHL and LBCL. The results showed that IMP3 was highly positive in both NLPHL and LBCL cases, with LBCL cases showing significantly higher expression levels compared to NLPHL. The study also found a significant difference in the distribution of IMP3 expression intensity levels between NLPHL and LBCL, with LBCL cases showing predominantly strong expression of IMP3, while NLPHL cases showed more heterogeneous and variable staining.

The study identified a cutoff of strong IMP3 expression higher than 55% to differentiate 71.4% of DLBCL tumors from NLPHL, with better differentiation of DLBCL NOS subtype from NLPHL compared to THRLBCL. The study suggested that IMP3 could be used as a complementary marker for the diagnosis of NLPHL, as neoplastic cells in NLPHL are mainly negative for CD30. The study also noted that IMP3 was expressed in the residual germinal centers of non-neoplastic lymphoid follicles of lymphoma cases, while other parts of lymphoid follicles were negative.

The study compared its findings with previous studies and identified differences in staining intensity and inclusion criteria, which could account for some of the variations in results. Further studies are required to determine whether IMP3 intensity and percentage can differentiate LBCL from NLPHL. The study also suggested investigating the expression of IMP3 in activated B and T cells, as it was expressed in background lymphoid cells.

## 4. Conclusion

The different staining patterns of IMP3 in NLPHL and LBCL, particularly THRLBCL, could potentially be a diagnostic feature of these lymphoma subtypes. However, this hypothesis requires further investigation and validation through additional studies. Additionally, the functional role of IMP3 in the pathogenesis of Hodgkin's lymphoma and its potential as a prognostic or therapeutic marker should also be explored in future research.

**Author Contributions:** All authors contributed equally to the writing of this paper. All authors read and approved the final manuscript.

**Conflicts of Interest:** "The authors declare no conflict of interest."

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