Inutility of IMP3 Marker in Differentiating Hodgkin Lymphoma from Large Cell Lymphoma

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ABSTRACT

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Background: Hodgkin's lymphoma is one of the most commonly diagnosed lymphomas in Western society. Today Reed-Sternberg cells are identified by positive staining of several biomarkers. The IMP3 (insulin-like growth factor II m-RNA-binding protein 3) marker is a member of the insulin-like growth factor II mRNA binding protein family that has been suggested as a diagnostic marker in some epithelial malignancies. In this study, we aimed to evaluate the expression profile of IMP3 in Hodgkin's lymphoma patients and compare it with those with large cell lymphoma.

Methods: In this study, patients diagnosed with Hodgkin's lymphoma between 2016 and 2018 were recruited. For the control group, patients diagnosed with large cell lymphoma were chosen. Paraffin blocks were collected and cut by a microtome machine. Immunohistochemical staining was performed on the slides for the IMP3 marker, using the Envision method. The color intensity was divided into four groups, and data on age, gender, staining intensity, sampling rate, and staining pattern entered at the end of the checklists. The collected data were analyzed using SPSS 19 software. The paired t-test has was employed, and a significant statistical level of 0.05 was considered in all tests.

Results: In this study, 145 patients in a wide range of 5 to 84 years (the mean age = 41 ± 17 years) were studied. Fifty-three patients were diagnosed with diffuse large B-cell lymphoma (36.6%), 4 cases (2.8%) with anaplastic large cell lymphoma and 88 cases with (60.7%) Hodgkin's lymphoma. Among 145 patients in the current study, 143 patients (98.6%) were positive for IMP3. IMP3 was positive in all patients with Hodgkin's lymphoma and anaplastic large cell lymphoma, and only 2 cases of diffuse large B-cell lymphoma were negative for this maker, in whom severe necrosis was noted. Consequently, there is not a vivid difference between Hodgkin's lymphoma and non-Hodgkin's lymphoma (p-value=0.153)

Conclusion: The marker is positive for Hodgkin's lymphoma with a negative background and may be used as a supplementary marker along with CD15 and CD30 to detect neoplastic cells. However, it cannot help differentiate it from large cell lymphomas because it is also positive for non-Hodgkin lymphomas.

Keywords: Hodgkin's Lymphoma; Lymphoma, Non-Hodgkin; IMP3, CD15, CD30

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INTRODUCTION:

The term 'lymphoma' is used for a group of malignant lymphoid tumors that vary greatly in terms of the degree of malignancy, clinical manifestations, and response to treatment. Hodgkin's disease (HD) is known as a lymphoma. The distinction between HD and other lymphomas is that the majority of underlying cells contain reactive non-neoplastic cells, and the neoplastic and diagnostic cells are Reed-Sternberg (RS) cells or their variants. Hodgkin lymphoma (HL) is classified into two categories, classical HL (CHL) and non-classical or nodular lymphocyte-predominant HL (NLPHL)(1).

Hodgkin's and RS cells account for less than 1% of tumor tissue. RS cells are present in a complex mixture of cells with an inflammatory background. While there is still debate about the origin of RS cells, most studies have shown that these cells originate from the germinal center (GC) B-cells(2-5). Immunohistochemical specifications play a crucial role in the routine diagnosis of HL. Today, RS cells are identified by positive staining of a few biomarkers(6-11). However, existing antibodies targeting these potential RS markers are not sufficient for a definitive diagnosis of all cases. Thus, more immunological markers are needed to improve diagnostic accuracy(12).

The IMP3 marker is a member of Insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3), including IMP1, IMP2, and IMP3 factors. The IMP3 family plays an essential physiological role in the early stages of embryogenesis and mediating RNA stability to regulate cell growth and migration(13-15). However, this oncofetal protein seems to act as a carcinogen. IMP3 overexpression has been observed in many epithelial malignancies, including bladder, liver, breast, pancreas, lung, colon, ovary, kidney, and several soft tissue sarcomas. The use of IMP3 as a diagnostic marker has also been suggested in a few epithelial malignancies(16-23). IMP3 is expressed in a high percentage of malignancies caused by GC B-cells, including Burkitt's lymphoma and follicular lymphoma. IMP3 is also expressed in a large proportion of diffuse large B-cell lymphoma (DLBCL) with variable staining intensity. However, non-GC lymphomas such as marginal zone, mantle cell, small lymphocytic lymphoma (SLL), lymphoblastic B lymphoma, and anaplastic large cell lymphoma (ALCL) are positive in only 8-20% of cases(24). In HL (both classic and non-classic), IMP3 is expressed in the cytoplasmic compartment of tumor cells against a completely negative background of non-tumor cells other than the remaining GCs. In addition, IMP3 shows more expression than other traditional markers such as CD15 and CD30. Therefore, IMP3 plays a beneficial supplementary role, especially with CD30 for HL detection(25).

Therefore, considering the small number of articles on IMP3 expression in lymphoid tissues, the present study aims to evaluate the immunohistochemical specifications of IMP3 expression on HL patients and compare it with large cell lymphoma patients.

METHODS:

This cross-sectional study was performed on 145 patients diagnosed with Hodgkin's lymphoma, diffuse large B-cell lymphoma, and anaplastic large cell lymphoma, who referred to Rasoul Akram and Firoozgar hospitals between 2016 and 2018. The previous diagnosis of these patients was confirmed by needle biopsy or removal of the lymph nodes and microscopic and immunohistochemical examination by the pathologist. In this study, patients diagnosed with large cell lymphoma were considered as evidence group. Hematoxylin-eosin-colored slides, immunohistochemical slides, and paraffin blocks were collected from laboratories. Paraffin blocks were cut by a microtome machine and stained for the IMP3 marker using the Envision method, which included the following steps:

The samples were stored in the laboratory for immu-

nohistochemistry (IHC) examination. The slides were placed in the oven at 37°C for 24 hours before IHC and at 60°C for 10–15 minutes. Deparaffinization, dehydration, and tissue blocking were done using xylenol, serial ethanol alcohol (absolute and 96 degrees), and methanol (containing hydrogen peroxidase), respectively. Then, the tissue samples were placed inside the autoclave for 20 minutes in a container containing a suitable buffer (pH = 6 citrate) for retrieval antigen. Afterward, the tissues were incubated with the primary antibody for a certain period of time (1 hour or overnight, if necessary), then secondary antibodies were placed. The staining was performed using a pre-prepared DAB solution and then hematoxylin. Stained slides were observed under the microscope and interpreted by a pathologist. All information was recorded according to the tumor block number.

Staining intensity is divided into the following four groups:

Group 1: Non-staining

Group 2: Weakly staining

Group 3: Moderate staining

Group 4: Strong staining

Staining pattern is divided into the following groups:

Group 1: Nuclear staining

Group 2: Cytoplasmic staining

Group 3: Membranous staining

It should be noted that the Clone EP286 (ready-to-use type) marker was used, which is manufactured by the Master Diagnostica Co., Spain.

Age, sex, color intensity, staining rate, and staining pattern were entered in the relevant checklists and analyzed using SPSS software version 19. The statistical significance level of 0.05 was considered in all tests.

Data Analysis

The descriptive part of the results was expressed through tables of frequency distribution, mean, standard deviation, and percentage. The individual error was also determined using a paired t-test. Chi-square test was used to compare the staining extent, staining intensity, and staining pattern in the two groups.

RESULTS:

A total of 145 patients with a mean age of 41±17 years were included in the present study. Among 145 patients, 54 (37.2%) were female, and 91 (62.8%) were male. Furthermore, out of 145 patients studied, 53 were diagnosed with DLBCL (36.6%), 4 with ALCL (2.8%), and 88 with HL (60.7%). Of the 88 HL patients, 48 cases (54.5%) were CD15-positive and 87 cases (98.9%) were CD30-positive.

Also, out of 145 patients enrolled in the present study, 143 patients (98.6%) were IMP3-positive, and cytoplasmic staining pattern was observed in all cases. All HL patients were IMP3-positive, and two large B-cell patients were IMP3-negative (3.8%). In both IMP3-negative large B-cell patients, there was severe necrosis. As a result, there is not a meaningful difference between HL and NHL (p-value=0.153). The intact residual GCs were strongly stained with IMP3, and the plasma cells were IMP3-positive in one case.

In the present study, out of 53 patients with large B-cell lymphoma, two patients (3.8%) did not have IMP3 staining, 6 patients (11.3%) had +1 staining, 36 patients (67.9%) had +2 staining, and 9 patients (17%) had +3 staining. Also, among 4 patients with ALCL, one patient (25%) had +2 staining and 3 patients (75%) had +3 staining, and among HL patients, 4 patients (4.5%) had +1 staining, 29 patients (33%) had +2 staining, and 55 patients (62.5%) had +3 staining (**Figure 1**), which was statistically significant (p-value=0.001) (**Table 1**). Moreover, among HL patients with negative CD15, one person (2.5%) had IMP3 + 1 staining, 17 (42.5%) had +2 staining and 22 (55%) had +3 staining. Among HL patients with positive CD15, 3 (6.3%) had + 1 staining, 12 (25%) had + 2 staining and 33 (68.8%) had +3 stain-
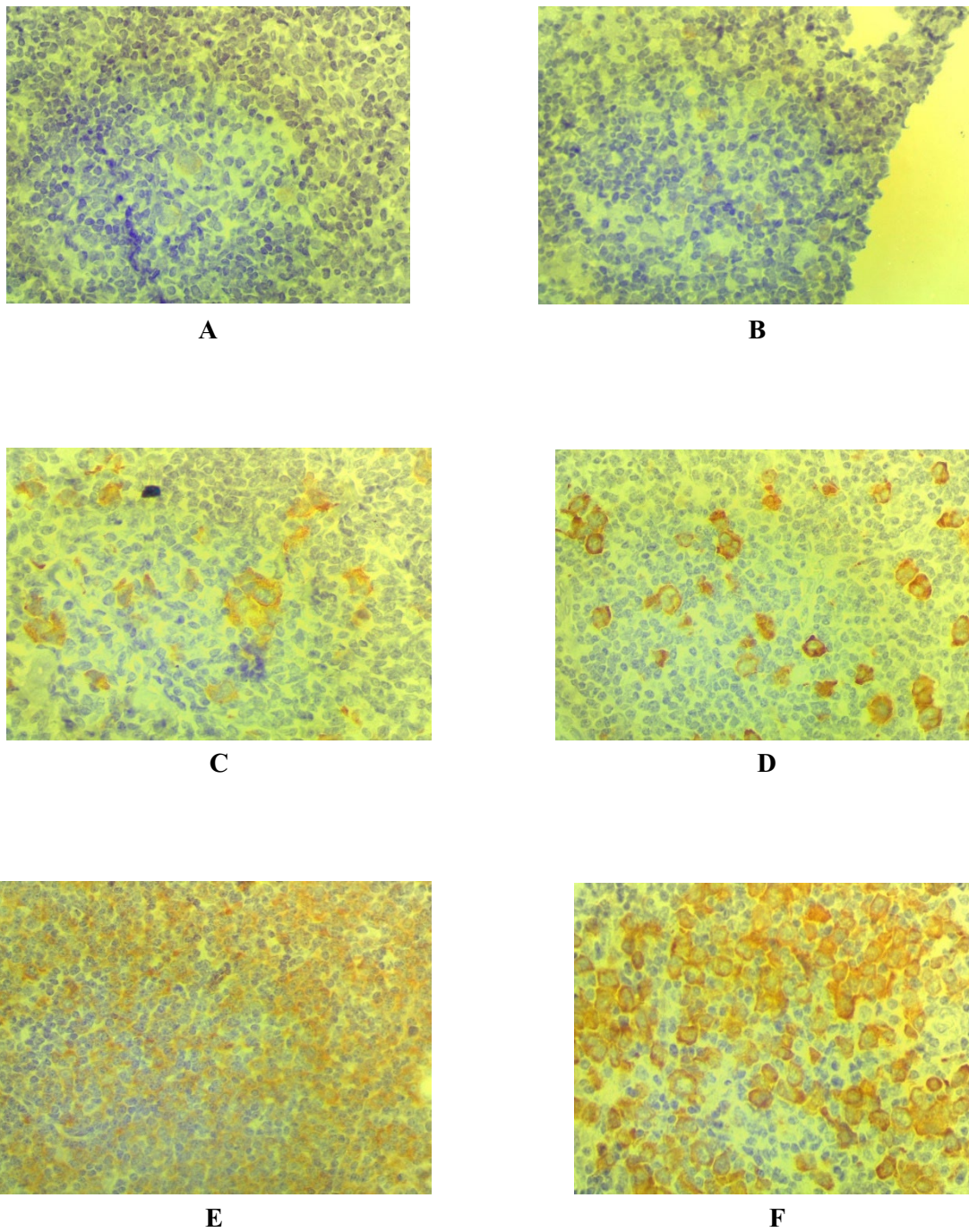
Figure 1. A & **B)** Weakly staining (+1) of Hodgkin's lymphoma; C) Moderate staining (+2) of Hodgkin's lymphoma; **D**) Strong staining (+3) of Hodgkin's lymphoma; **E**) Moderate staining (+2) of diffuse large B-cell lymphoma; **F**) Strong staining (+3) of anaplastic large-cell lymphoma

Table 1. Relationship between Staining intensities for IMP3 in different types of lymphoma

	Large B-cell		ALCL		Hodgkin's		P-value
	Number	Percent	Number	Percent	Number	Percent	
Negative	2	3.8	0	0	0	0	0.001
1+	6	11.3	0	0	4	4.5	
2+	36	67.9	1	25	29	33	
3+	9	17	3	75	55	62.5	

ing which was not statistically significant (p-value = 0.186).

However, HD patients, only one person (2.5%), had a negative CD30 marker due to excessive tissue necrosis and had IMP3 + 1 staining. Among the positive CD30 patients, 3 (6.3%) had +1 staining, 29 (33.3%) had +2 staining and 55 (63.2%) had +3 staining which was statistically significant (p-value=0.001) (**Table 2**).

DISCUSSION:

Hodgkin's lymphoma (HL) is a B-cell-derived neoplasm originating from the GC and accounts for 11% of all lymphomas in the United States(26). Accurate diagnosis of HL is essential for the initiation of a timely and appropriate treatment strategy. Thus, improvement of the patient's prognosis and survival is of great importance. While morphological and immunohistochemical characteristics of RS cells are the current diagnostic standards, no single marker has been identified for clinical trial use to detect HL(27). The current panel of markers helps to identify RS cells, but there are some limitations, and the interpretation of the results is somewhat subjective. For example, the differential diagnosis is distorted by the expression of CD30 in ALCL(28). Therefore, more biological markers need to be identified that may help to improve the immunohistochemical

Table 2. Relationship between IMP3 Staining intensity in HL patient with negative and positive CD30 marker

	CD30			
	Negative		Positive	
	Number	Percent	Number	Percent
+1	1	100	3	3.4
+2	0	0	29	33.3
+3	0	0	55	63.2
P-value	0.001			

diagnosis of HL.

Insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3, also known as IMP3) is a member of the IMP family, which includes IMP1 and IMP2. It is also known as a protein containing the K homology domain-containing protein overexpressed in cancer (KOC). Members of this family are an influential physiological factor in primary embryogenesis, RNA trafficking, stabilization, and regulation of cell proliferation and migration(29). Besides, IMP3, which is an oncofetal protein extinguished after birth, is seen at low levels in the normal tissue of adults and is expressed in several malignancies, including lymphomas(30).

IMP3 expression in normal tissue is limited to specific tissues or cells. IMP3 is expressed in the placenta, testicular spermatogonia, mucin-secreting cells of the endocervix, fallopian tube ciliated cells, ciliated and secretory cells of the bronchial mucosa, mucin-secreting cells of the submandibular and sublingual glands, ileal absorptive cells, epithelial cells of the rectum and adenohypophyseal cells of the pituitary gland(31). IMP3 expression is also limited to the lymph nodes, spleen, and tonsillar GCs(32). This marker is expressed in cells of centrocytes, centroblasts, and thymocytes but not in bone marrow cells(33).

The expression of IMP3 in HL has been investigated in several previous studies. King et al.(34) investigated the overexpression of IMP3 in neoplastic lymphoid tissues. They showed differential expression among different types of lymphomas so that IMP3 overexpression was reported in 100% of HLs and 80% of DLBCLs, Burkitt's lymphoma, and follicular lymphoma. Hartmann et al.(35) investigated the functional role of IMP3 overexpression in mantle cell lymphoma and demonstrated its proliferative function.

IMP3 has been shown to be a new diagnostic marker expressed in classic Hodgkin's lymphoma (CHL) and non-classical or nodular lymphocyte-predominant HL (NLPHL). Besides, these cells exhibited selective staining of tumor cells without background staining(31, 36). The present study showed that the positivity of the IMP3 marker was high in both HL and non-HL (NHL) groups (100% vs. 96.5%). However, the high staining intensity (+3) was 62.5% in the HL group and 21.1% in the NHL group. Positive staining of the Hodgkin lymphomas was observed for CD15 (54.5%), CD30 (98.9%), and IMP3 (98.6%). This result is comparable to the results of other studies. For example, Tang et al.(25) depicted that the IMP3 marker was positive in 98.8% of HL patients. Of these, 72.8% of patients had strong staining. The frequency of strong staining in HL patients who participated in the present study was 62.5%, which is lower than the Tang's study. Tang(25) also showed that the CD15 and CD30 markers were positive in 65.4% and 82.7% of cases, respectively. While in the present study, this rate was 55% and 99%, respectively. Although the present study has relied more on the positivity of the CD30 marker in the detection of HL, lower positivity of the CD15 marker in the present study seems to be due to the use of existing slides and differences in antibody clones for CD15 detection. Although Tang did not compare IMP3 in HL and NHL patients, he considered it a suitable marker for detecting HL considering the high positive cases of IMP3. However, the present study showed that this marker is not able to differentiate HL from large cell lymphomas.

In another study, Masoud et al.(37) investigated the IMP3 marker in HL patients. They observed the positive IMP3 marker in 85.7% of cases, which is lower than the present study. The CD15 marker was positive in 71.4% of cases, which was higher than the present study. The CD30 marker was also reported in 96% of cases, which is comparable to the results of the present study. Masoud et al. found no relationship between IMP3-positive and clinicopathological features. Although IMP3 is a useful marker for the detection of HL, it will not help

to increase the sensitivity of HL diagnosis(37). The results of the mentioned study are consistent with the results of the present study.

CD30 and CD15 are commonly observed in the membrane and Golgi area of the RS and Hodgkin cells, but this expression pattern makes their staining extent less visible than IMP3. Another limitation regarding CD15 and CD30 detection includes their negative response to Hodgkin's NLPHL specimens. Also, since CD15 is also detected in reactive B and T lymphocytes, these limitations may be partially eliminated by using IMP3. The present study showed that IMP3 positivity in NHL was as high as HLs (96.5% vs. 100%). Even so, the IMP3 staining extent of cells varies between HL and NHL so that HLs have a higher staining intensity. Marker staining extent is an eye variable. Therefore, the error rate can vary greatly. Although the IMP3 positivity in HL and RS cells was high, due to the positivity of this marker in NHL patients, it is not superior to other common markers, and the only difference is that these cells are stained in an entirely negative background. Considering the inability of the IMP3 marker to differentiate HL from large cell lymphoma, it seems that the results of the Tang et al. 's study could not help improve the diagnosis and differentiation of HL patients and the change in staining intensity is not a useful feature ensuring differentiation.

CONCLUSION:

To the best knowledge of the authors, this is the first study that evaluates and compares the IMP3 marker among HL and NHL patients. Although IMP3 positivity cannot increase the diagnostic accuracy of HL, the extent of IMP3 positivity can help diagnose Hodgkin's cells and RS cells due to the limitations of existing markers. Also, considering the IMP3 positivity in DLBCL and ALCL patients, it can be concluded that this marker does not help to differentiate HL from the NHL.

Finally, as a recommendation, due to the strong staining of the IMP3 marker in comparison to routine markers and vivid staining in the negative background, it could play a valuable role in the detection of HL relapse in patients with a previously confirmed diagnosis.

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