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Cytological-Pathologic Correlation

The complementary role of insulin-like growth factor II mRNA-binding protein 3 (IMP3) in diagnosis of Hodgkin's lymphoma

Rokia Masoud, Afaf. Ibrahiem*, Dina Tantawy, Ibrahim Eldosoky

Faculty of Medicine, Mansoura University, Egypt

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ABSTRACT

Background: Hodgkin's Lymphoma (HL) is a peculiar subtype of lymphoid malignancies. The etiology of HL is still unknown. Insulin-like growth factor II mRNA-binding Protein 3 (IMP3) is a member of IMP family. In HL, IMP3 is expressed in the cytoplasmic compartment of the tumor cells (in both HRS cells & LP cells) against completely negative background of non-tumor cells except for residual germinal centers.

Materials & Methods: Of 51 cases of Hodgkin's lymphoma (HL) referred to surgical pathology laboratory at oncology center, Mansoura University (OCMU), Egypt. All cases were stained for CD20, CD3, CD15, CD30 and IMP3. Regarding IMP3 antibody, The slides were then incubated with the Anti-IMP3, mouse monoclonal antibody (1:200, clone sc-365640, concentrated, California) that was used as primary antibody for IMP3 detection for 1 hour at room temperature, followed by incubation with the secondary antibody, poly HRP (horseradish peroxidase), conjugate for mouse/rabbit, for 20 minutes.

Results: IMP3 showed cytoplasmic immunoreactivity in 43 (83%) cases while 8 cases were negative. The sensitivity of combined CD30 & CD15, combined CD30 & IMP3, combined CD15 & IMP3 were 96%, 98% and 94% respectively. On the other hand, the sensitivity of CD30, CD15 and IMP3 alone were 92.2%, 68.6% and 84.3% respectively. All 23 studied cases of NSCHL, all the 17 cases of MCCHL, 7 out of 8 cases of LRCHL and the only case of LDCHL had predominant T-lymphocytes in their background. On the other hand, the 2 cases of NLPHL and only case of LRCHL had predominant B-lymphocytes in their background.

Conclusion: IMP3 is a novel marker that is expressed in large proportion of both types of HL against nearly negative background. It has no significant increase in sensitivity in detection of the tumor cells when combined with CD30. There are insignificant relations between IMP3 expression and different clinicopathological parameters. Further studies about IMP3 on a large scale of cases are required to confirm its mechanistic role in generation of HL.

1. Introduction

Hodgkin's Lymphoma (HL) is a peculiar subtype of lymphoid malignancies. It represents about 11% of all lymphomas in the United States [1] while it represents about 28.16% of all malignant lymphomas in Egypt [2] (Fig. 1).

The etiology of HL is still unknown. However, some epidemiological and serological studies have implicated Epstein-Barr virus in pathogenesis of HL [3]. The origin of HL remained mysterious for prolonged time but now based on molecular studies, HL is considered as a germinal center B-cell (GC B)-derived neoplasm [4].

According to 2016 WHO classification, HL is classified according to the morphology and immunophenotype of the tumor cells into nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL) and 4 subtypes of classic Hodgkin's lymphoma (CHL); nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted [5].

Hodgkin's lymphoma is characterized by presence of large neoplastic cells; Hodgkin's/Reed-Sternberg cells (HRS cells) in CHL & lymphocyte-predominant (LP) cells in NLPHL surrounded by a background of mixed inflammatory cells [6]. No single marker has yet been detected for use as a specific target of clinical tests in HL.

Insulin-like growth factor II mRNA-binding Protein 3 (IMP3) is a member of IMP family that plays a critical physiological role in early embryogenesis, RNA trafficking and stabilization and regulating cell proliferation and migration [7]. Moreover, IMP3 is an oncofetal protein [8].

Overexpression of IMP3 was first detected in pancreatic cancer. Moreover, it is expressed in epithelial tumors of urinary bladder, liver, kidney, ovary, cervix, stomach, colon, lung, melanoma and testicular tumors. Other studies correlate between IMP3 overexpression and prognosis of some tumors such breast cancer, cervical cancer and neuroblastoma [9].

* Corresponding author.
E-mail address: afaftaha5324@mans.edu.eg (A. Ibrahiem).

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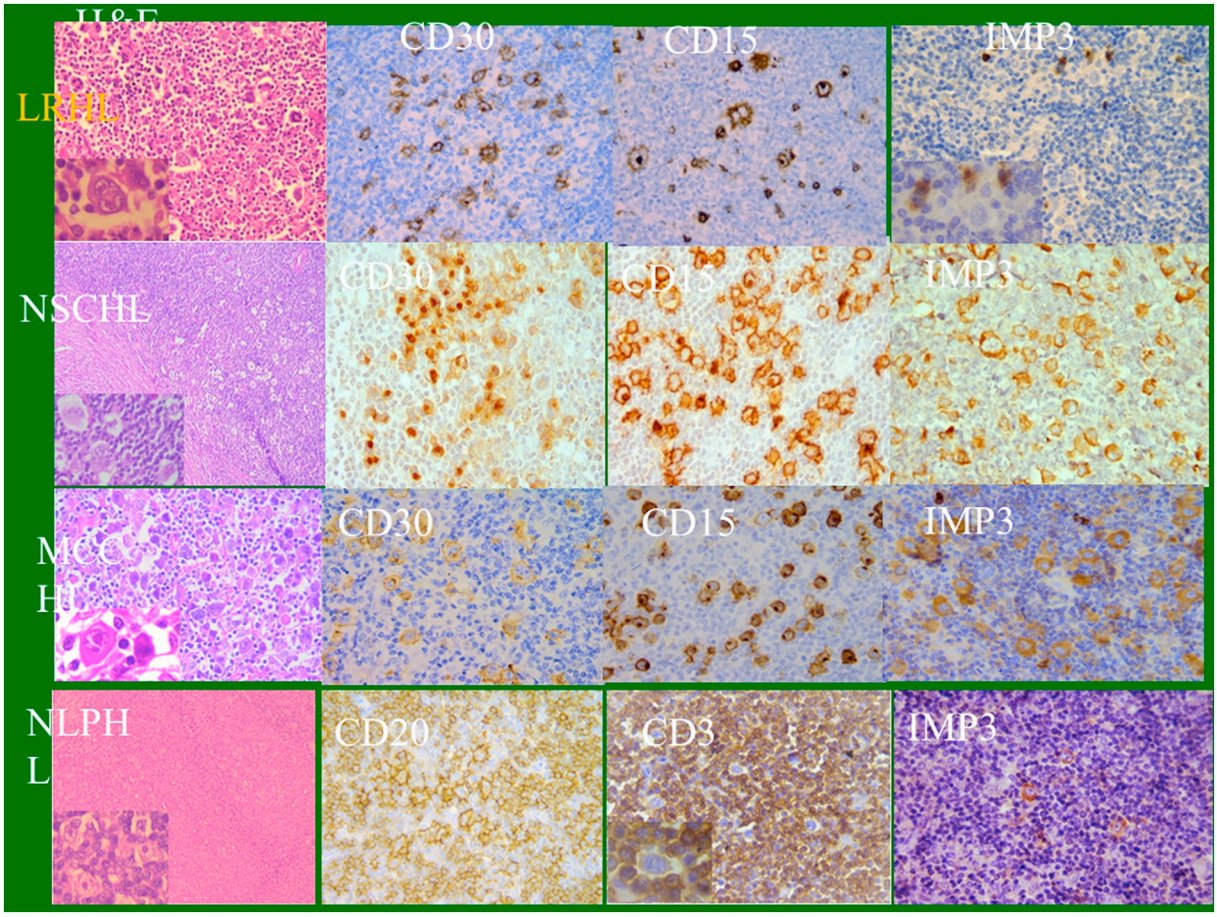

Fig. 1..

IMP3 is expressed in GC B-derived malignancies including Burkitt lymphoma and follicular lymphoma in high percentage. Also, IMP3 is expressed in diffuse large B-cell lymphoma in large proportion but with variable staining intensity. However, lymphomas of non-germinal center origin such as marginal zone, mantle cell, small lymphocytic, B-lymphoblastic and anaplastic large cell lymphoma are positive only in 8–20% [10].

In HL, IMP3 is expressed in the cytoplasmic compartment of the tumor cells (in both HRS cells & LP cells) against completely negative background of non-tumor cells except for residual germinal centers. Furthermore, it shows higher expression compared with other traditional markers such as CD15 and CD30. So, IMP3 has a useful supplemental role especially with CD30 for diagnosis of HL [11].

This study aimed to assess the expression of IMP3 as a novel marker in tumor cells of Hodgkin lymphoma and comparing it to results of (CD3, CD20, CD15 and CD30).

2. Materials and methods

This study is a retrospective analysis of 51 cases of Hodgkin's lymphoma (HL) referred to surgical pathology laboratory at oncology center, Mansoura University (OCMU), Egypt. It was performed through the period from January 2016 to May 2018. All patients underwent surgical excision with complete clinical data and available paraffin blocks were included in this study. Cases underwent fine needle aspiration and core needle biopsy with no recorded or available excisional biopsy or unavailable paraffin blocks were excluded from this study.

All available clinical and pathological data of the collected cases were reviewed and re-examination of their slides was performed. The clinical data includes patient's age, gender, anatomical site of the involved lymph nodes and history of recurrence. The pathological data includes the size of the involved lymph node, the lymph node architecture, histopathological subtype and bone marrow biopsy. Hx & E stained slides and previously stained IHC slides for CD3, CD20, CD15 and CD30 were reviewed by two different pathologists to confirm the diagnosis of HL and their subtypes according to 2016 WHO classification of HL.

2.1. Procedure of immunohistochemistry

Formalin fixed paraffin-embedded tissue blocks were retrieved. For immunohistochemical staining, 4 μm thick tissue sections were cut and mounted on coated slides. The sections were deparaffinized in xylene then rehydrated in a series of decreasing concentration of ethanol. After that, heat-induced antigen retrieval was done using pressure cooker and EDTA buffer (PH 8) and immersed in peroxidase-blocking solution (3% hydrogen peroxide) for 15–20 min to inhibit endogenous peroxidase activity, the slides were washed in phosphate buffer saline (PBS). All cases were stained for CD20, CD3, CD15, CD30 and IMP3. Regarding IMP3 antibody, The slides were then incubated with the Anti-IMP3, mouse monoclonal antibody (1:200, clone sc-365640, concentrated, Santa Cruz biotechnology, California) that was used as primary antibody for IMP3 detection for 1 h at room temperature, followed by incubation with the secondary antibody, poly HRP (horseradish peroxidase), conjugate for mouse/rabbit, for 20 min at room temperature. Diaminobenzedene (DAB) was the chromogen used to visualize the stain, the slides were then counterstained with Mayer's hematoxylin, dehydrated using ascending alcohol concentration, coversliped, and finally mounted with DPX.

2.1.1. Immunohistochemical interpretation

For evaluation of the IHC results, the brown cytoplasmic and membranous staining in HRS cells and their variants was considered positive.

Table 1
Tumor characteristics of the studied cases:

		Number of cases	Percent (%)
Patient's age	< 20	11	21.6
	20–40	19	37.2
	> 40	21	41.2
Patient's gender	Male	30	58.8
	Female	21	41.2
Anatomical site of the involved lymph node groups	Cervical	39	76.5
	Axillary	10	19.6
	Inguinal	2	3.9
Tumor relapse	Primary	46	90.2
	Relapsed	5	9.8
The size of the involved lymph nodes	< 2	13	25.5
	2–5	34	66.7
	> 5	4	7.8
Architecture of the involved lymph nodes	Diffuse	21	41.2
	Nodular	27	52.9
	Inter-follicular	3	5.9
Histopathological subtype	NLPHL	2	3.9
	NSCHL	23	45.1
	MCCHL	17	33.3
	LRCHL	8	15.7
	LDCHL	1	2.0
Bone marrow involvement	Negative	37	72.5
	Positive	1	2
	No available data	13	25.0

Table 2
Different markers' expression by tumor cells:

() Total number of cases	Positive, N (%)	Negative, N (%)
IMP3: Total (51)	43 (84.3%)	8 (15.7%)
-CHL (49)	42 (85.7)	7 (14.3)
-NLPHL (2)	1(50)	1(50)
CD30:		
-CHL (49)	47 (96%)	2 (4%)
-NLPHL (2)	0 (0%)	2 (100%)
CD15		
-CHL (49)	35 (71.4%)	14 (28.6%)
-NLPHL (2)	0 (0%)	2 (100%)
CD20		
-CHL (49)	3 (6%)	46 (94%)
-NLPHL (2)	2 (100%)	0 (0%)

Table 3
Sensitivity of different markers' expression in relation to combined CD15 and CD30 sensitivity in cases of CHL (49 cases).

	Positive, N (%)	Negative, N (%)
CD15	35 (71.4%)	14 (28.6%)
CD30	47 (96%)	2 (4%)
IMP-3	42 (85.7%)	7 (14.3)
CD15 + IMP3	48 (98%)	1 (2%)
CD30 + IMP3	49 (100%)	0 (0%)
CD15 + CD30 + IMP3	49 (100%)	0 (0%)
Combined CD15 and CD30	49 (100%)	0 (0%)

The residual germinal center B-cells were used as internal control if present. The GC in five reactive lymph nodes ***as shown in photomicrograph 1***, two tonsils and one adenoid was positive for IMP3 staining. In addition to pancreatic adenocarcinoma ***as shown in photomicrograph 2*** that was used also as external control. Cases of both CHL and NLPHL in which tumor cells revealed weak, moderate or intense cytoplasmic staining for IMP3 in > 10% of tumor cells were considered positive [11].

I. Tumor characteristics of the studied cases:

The distribution of the studied cases according to patient's age, patient's gender, anatomical site of the involved lymph node groups, tumor relapse, the size of the involved lymph nodes, and architecture of the involved lymph nodes, histopathological subtype and bone marrow involvement is shown in Table 1.

Table 4
Relation between histopathological subtype and predominant background lymphocytes.

	T-lymphocytes, N (%)	B-lymphocytes, N (%)
NLPHL	0	2 (100%)
NSCHL	23(100%)	0
MCCHL	17 (100%)	0
LRCHL	7 (87.5%)	1(12.5%)
LDCHL	1(100%)	0

Table 5
Relation between IMP3 expression and different clinicopathological parameters.

		IMP3		*p* value
		Positive N (%)	Negative N (%)	
Age	< 20	10 (23.1%)	1 (12.5%)	0.27
	20–40	14 (32.6%)	5 (62.5%)	
	> 40	19 (44.2%)	2(25.0%)	
Gender	Male	26 (60.5%)	4(50.0%)	0.43
	Female	17 (39.5%)	4(50.0%)	
Anatomical site of the involved lymph node	Cervical	34 (79.1%)	5 (62.5%)	0.33
	Axillary	8 (18.6%)	2 (25.0%)	
	Inguinal	1(2.3%)	1 (12.5%)	
Recurrence	Primary	39 (90.7%)	7 (87.5%)	0.59
	Recurrent	4(9.3%)	1 (12.5%)	
Greatest dimension of the involved lymph node	< 2	10 (23.3%)	3 (37.5%)	0.52
	2–5	29 (67.4%)	5 (62.5%)	
	> 5	4 (9.3%)	0	
Architecture	Diffuse	19 (44.2%)	2 (25.0%)	0.36
	Nodular	21 (48.8%)	6 (75.0%)	
	Partial effacement	3 (7.0%)	0	
Histopathological subtype	NLPHL	1 (2.3%)	1 (12.5%)	0.17
	NSCHL	18 (41.9%)	5 (62.5%)	
	MCCHL	17 (39.5%)	0	
	LRCHL	6 (14.0%)	2 (25.0%)	
	LDCHL	1 (2.3%)	0	
Bone marrow involvement	Negative	32 (96.9%)	5(100%)	0.65*
	Positive	1 (3.1%)	0	

* Significant p value (< 0.05).

II. Immunohistochemical characteristics of the studied cases:

A. Expression of CD20 and CD3 in the background lymphocytes:

Forty-eight cases of CHL had a background rich in T-lymphocytes. On the other hand, three cases had a background rich in B-lymphocytes including the two cases of NLPHL and one case of CHL.

B. Expression of immunohistochemical markers by tumor cells:

As shown in Table 2, CD30 revealed positive immunoreactivity in 47 cases of CHL. However, CD15 was positive in 35 cases of CHL. The cases of NLPHL were negative for CD30 and CD15.

The cells showed positive reaction for CD20 in cases of NLPHL and only 3 cases of CHL.

As regard IMP3 staining, it revealed positive cytoplasmic immunoreactivity in 43 cases (42 case of CHL and one case of NLPHL) while 8 cases were negative.

C. Sensitivity of different markers expressed by HRS cells in CHL:

Table 6.
Relation between IMP3 expression and different clinicopathological parameters.

		IMP3		p value
		Positive N (%)	Negative N (%)	
Age	< 20	10 (23.1%)	1 (12.5%)	0.27
	20–40	14 (32.6%)	5 (62.5%)	
	> 40	19 (44.2%)	2(25.0%)	
Gender	Male	26 (60.5%)	4(50.0%)	0.43
	Female	17 (39.5%)	4(50.0%)	
Anatomical site of the involved lymph node	Cervical	34 (79.1%)	5 (62.5%)	0.33
	Axillary	8 (18.6%)	2 (25.0%)	
	Inguinal	1(2.3%)	1 (12.5%)	
Recurrence	Primary	39 (90.7%)	7 (87.5%)	0.59
	Recurrent	4(9.3%)	1 (12.5%)	
Greatest dimension of the involved lymph node	< 2	10 (23.3%)	3 (37.5%)	0.52
	2–5	29 (67.4%)	5 (62.5%)	
	> 5	4 (9.3%)	0	
Architecture	Diffuse	19 (44.2%)	2 (25.0%)	0.36
	Nodular	21 (48.8%)	6 (75.0%)	
	Partial effacement	3 (7.0%)	0	
Histopathological subtype	NLPHL	1 (2.3%)	1 (12.5%)	0.17
	NSCHL	18 (41.9%)	5 (62.5%)	
	MCCHL	17 (39.5%)	0	
	LRCHL	6 (14.0%)	2 (25.0%)	
	LDCHL	1 (2.3%)	0	
Bone marrow involvement	Negative	32 (96.9%)	5(100%)	0.65
	Positive	1 (3.1%)	0	

* = significant p value (< 0.05) *R = reference group.

As shown in Table 3, CD15 was significantly lower in its results in relation to the currently used method which make it not suitable for diagnosis of this tumor if it used alone. However, there was no difference in the rest of different antibodies combination when compared with CD15/CD30. The sensitivity of combined CD30 & CD15, combined CD30 & IMP3, combined CD15, CD30 & IMP3 were equal (100%). However, it was a little lower for CD15/IMP3 (98%). On the other hand, the sensitivity of CD30, CD15 and IMP3 alone were 96%, 71.4% and 85.7% respectively.

III. Relation between histopathological subtype and background lymphocytes of the studied cases:

As shown in Table 4, there was a high statistically significant relation between the histopathological subtype and the background lymphocytes of the studied cases. All 23 studied cases of NSCHL, all the 17 cases of MCCHL, 7 out of 8 cases of LRCHL and the only case of LDCHL had predominant T-lymphocytes in their background. On the other hand, the 2 cases of NLPHL and only case of LRCHL had predominant B-lymphocytes in their background.

IV. Relation between IMP3 expression and different clinicopathological parameters:

As shown in Table 5, there was an insignificant relationship between IMP3 expression and different clinicopathological data. These include patient's age, patient's gender, the involved groups of lymph node, tumor recurrence, the size and the architecture of the involved nodes, the histopathological subtype or bone marrow involvement (Table 6).

3. Discussion

Hodgkin's lymphoma is a B-cell derived neoplasm mostly of germinal center origin. It represents about 11% of all lymphomas in the United States [1]. Early diagnosis and standard treatment (chemotherapy and/or radio therapy) is associated with increase possibility of remission and long-term survival [11].

HRS cells are identified by positive immunoreactivity for CD30, CD15, PAX5, MUM1 and fascin. However, LP cells show positive immunoreactivity for CD45, CD20 and EMA in addition to PAX5 but lack the expression of CD15 and CD30 [6]. There are many problems concerning those commonly used traditional markers in diagnosis of HL. The activation marker of lymphocytes, CD30, is expressed in cases of infectious mononucleosis [11]. It is also expressed in lymphomas other than HL. These include anaplastic large cell lymphoma, primary mediastinal large B-cell lymphoma and angioimmunoblastic T-cell lymphoma [12].

CD15 is not expressed in all cases of HL. Also, there is a background staining in granulocytes [13,14]. The other commonly used markers PAX5 and MUM1 have further limitation for diagnosis of HL. PAX5 that shows weak nuclear staining in tumor cells is stronger in the background B-lymphocytes [13]. Also, MUM1 is expressed in the activated B-lymphocytes [15]. This may lead to difficulty in interpretation of the results of immunohistochemistry [11].

The actin-binding protein, fascin, is expressed in virtually all HRS cells of CHL only [16,17]. However, fascin is not specific for HL as it is expressed in about 50% of ALCL. This makes fascin less useful in this differential diagnosis [18].

CD20 expression in HRS cells is predominantly negative or best described as faint and/or heterogeneous positive in < 20% of HRS cells [19]. However, the diagnosis of CHL should be excluded if homogeneous or strong CD20 expression is seen in > 20% of the tumor cells. Instead, the diagnosis of T-cell/histiocyte-rich large B-cell lymphoma, NLPHL, diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma should be considered [20].

So, the available antibodies targeting these markers are not adequate to provide an absolute diagnosis for all cases of HL. Identification of additional immunoreactive markers is important for more diagnostic accuracy [11].

Insulin-like growth factor II mRNA-binding Protein 3 (IMP3) is a member of IMP family which also includes IMP1 and IMP2. It is also known as K-homology domain-containing protein overexpressed in cancer (KOC). These family members play a critical physiological role in early embryogenesis, RNA trafficking and stabilization and regulating cell proliferation and migration [7]. Moreover, IMP3 is an oncofetal protein as it is silenced after birth, detected in low levels in normal adult tissue and re-expressed in several malignancies including lymphomas [8].

The mature human deglycosylated IMP3 is formed of 263 amino acids and has a molecular mass of 28.7 kDa. The primary structure of IMP family is formed of three distinct domains and other subdomains or functional motifs which are critical for their diverse actions. The main domains are the conserved N-terminal domain, the highly variable midregion and the conserved C-terminal domain [21]. The conserved N-terminal domain carries two RNA-recognition motifs (RRM1&RRM2) and the C-terminal part carries four hnRNP-K homology (KH) domains [22].

All members of IMP family bind to mRNA facilitated by KH-domains. In the cytoplasm, IMP members form ribonucleoproteins granules mainly in the perinuclear region and they are detected in the neurites of the developing neurons. These findings support the role of IMP in promoting mRNA localization [22].

IMP family sequestrates their targeted mRNA in cytoplasmic protein-RNA complexes, termed mRNPs. This prevents premature decay of specific target transcript such as PTEN, MYC and CD44 mostly by limiting release of protein associated transcript [23].

Recruitment of targeted mRNAs to cytoplasmic mRNPs is directed by IMP family. This is very important for controlling mRNA translation and transport. Caging of the transcript in the cytoplasmic mRNPs is controlled by several signaling events. This allows controlled release of silenced mRNA to induce mRNA decay (mRNA degradation) or protein synthesis (mRNA translation) [24].

IMP3 expression in normal tissue is limited to certain tissues or specific cells. It is expressed in placenta spermatogonia of the testis, mucin secreting cells of endocervix, ciliated cells in Fallopian tube, ciliated and secreting cells of bronchial mucosa, mucin secreting cells of submandibular and sublingual glands, ileal absorptive cells, rectal

epithelial cells and cells of adenohypophysis of pituitary gland [25]. Also, IMP3 expression is restricted to germinal centers of lymph nodes, spleen and tonsils [26]. It is expressed in centrocytes, centroblasts and thymocytes. However, it is not expressed in bone marrow cells [27].

Insulin-like growth factor II mRNA-binding protein 3 (IMP3) expressions in HL is reviewed in previous few studies. These found that IMP3 is a novel diagnostic marker that expressed in both CHL and NLPHL. Moreover, it showed selective staining of the tumor cells without a background staining [17,25,28]. This is the first study in our locality to use IMP3 aiming to use it as a routine in diagnosis of HL and comparing its results to commonly used markers such as CD30, and CD15.

This study is a retrospective analysis of collected 51 cases of Hodgkin's lymphoma referred to surgical pathology laboratory at oncology center. These include 2 cases of NLPHL 23 cases of NSCHL, 17 cases of MCCHL, 8 cases of LRCHL and 1 case of LDCHL. It was performed through the period from January 2016 to May 2018. All patients underwent surgical resection were included in this study. Cytoplasmic and membranous staining for IMP3 in > 10% of tumor cells were considered positive [18].

This study found that IMP3 showed cytoplasmic and membranous staining in 43/51 of HL cases (42/49 of CHL, 85.7% & 1/2 of NLPHL, 50%) representing about 84%. The staining may be weak, moderate or strong. The background cells were negative except for plasmacytoid cells, our results were similar to Tang et al. results in which 98.8% of Hodgkin lymphomas were reactive for IMP3 (70/71 of CHL, 98.6% & 10/10 of NLPHL, 100%) [11], while it was positive in 64.3% of CHL (53 of 83) cases and 92.3% (12 of 13) of NLPHL in the study performed by Zhang et al. [29].

On the other hand, CD30 and CD15 are expressed in 47/49 (96%) and 35/49 (71.4%) of CHL cases respectively. These markers show membranous and dot-like positivity in the HRS cells or their variants. Moreover, CD15 shows positive staining in the background granulocytes. However, the cases of NLPHL are negative for CD30 & CD15.

Also, the results documented that the sensitivity of combined CD15 and CD30 (traditionally used markers) is about 100% in diagnosis of CHL. There were equal results in using the combination of CD30/IMP3 & CD30/CD15/IMP3. The sensitivity is little lower when using CD15/IMP3 (98%). So, we can depend on CD30/IMP3 for detection of neoplastic cells for diagnosis of CHL. Moreover, IMP3 can be used in detection of NLPHL. However, this requires more studies on large number of cases.

There was no significant relationship between IMP3 expression and different clinicopathological parameters. These include patient's age, patient's gender, the involved group of lymph nodes, tumor recurrence, the size of the involved lymph node, the architecture of the involved nodes, the histopathological subtype, bone marrow involvement, CD30 expression, CD15 expression, CD20 expression or background lymphocytes.

CD30 has a significant relation with the involved groups of lymph node and the histopathological subtype of studied HL cases. However, no statistically significant relation between its expression and the other clinicopathological parameters. CD15 has only a statistically significant relation with the histopathological subtype of studied HL cases.

In this study, we concluded that IMP3 is a novel marker that is expressed in large proportion of both types of HL against nearly negative background. It has no significant increase in sensitivity in detection of the tumor cells when combined with CD30. There are insignificant relations between IMP3 expression and different clinicopathological parameters.

Further studies about IMP3 on a large scale of cases are required to confirm its mechanistic role in generation of HL. Also, these are required for testing its diagnostic and prognostic value as well as therapeutic strategies for HL. Also, more studies are recommended to detect ability of IMP3 to differentiate between HL and their mimics.

Fund

Nil.

Declaration of Competing Interest

No conflict of interest.

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