Immunohistochemical expression of ICAM-1 and Cortactin as cell adhesive molecule and invasive markers in Hodgkin's and non-Hodgkin's lymphoma of the head and neck region (A comparative study)

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ABSTARCT

Background: Lymphomas are a group of diseases caused by malignant lymphocytes that accumulate in lymph nodes and cause the characteristic clinical features of lymphadenopathy. Intercellular adhesion molecule-1 (ICAM-1) (CD54) is a transmembrane glycoprotein belonging to the immunoglobulin superfamily of adhesion molecules. Cortactin was first identified as one of the major substrates for src kinase. because it localized to Cortical actin structures, The aims of this study was to evaluate and compare the immunohistochemical of ICAM-1 expression as cell adhesion molecule marker and Cortactin expression as invasive marker.

Material and Methods: This study was performed on (68) formalin-fixed, paraffin-embedded blocks, histopathologically diagnosed as lymphoma (head and neck lesions).Immunohistochemical staining of ICAM-1and Cortactin was performed on each case of the study sample.

Results: The expression of ICAM-1 was membranous and cytoplasmic, the study cases showed a 98.5% positive reaction to ICAM-1, score 2 was the most common and found in 69.1% of all cases.The expression of Cortactin was cytoplasmic, 98.5% of cases expressed positive reactions to Cortactin, score 1 was the most common and found in 42.7% of all cases.

Conclusion: Although the two markers showed a higher expression rate in all lymphomas (both HL and NHL) in this study, they can't be used to differentiate between them, nor can be used to differentiate between the subtypes of both HL and NHL. The high ICAM-1positive expression clarified that in addition to its role in cell-cell and cell-stromal interactions, it participates in proliferation, differentiation and invasion of malignant lymphoma cells.The present study is the first one that used Cortactin as an invasive marker for lymphoma.

Keywords: Lymphoma, Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), ICAM-1 (CD54), Cortactin. (J Bagh Coll Dentistry 2014; 26(2): 103-110).

INTRODUCTION

Lymphomas are a group of diseases caused by malignant lymphocytes that accumulate in lymph nodes and cause the characteristic clinical features of lymphadenopathy. Occasionally, they may spill over into blood "leukaemic phase" or infiltrate organs outside the lymphoid tissue.[(1)]

Most lymphomas encountered in routine practice belong to the B-cell origin, and the others to T-cell origin. Lymphomas are subdivided into Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL), with the latter being more common.[(2)]

The cell adhesive molecules are of importance in the establishment of normal tissue structure and function. They participate in a variety of physiological processes such as morphogenesis, embryogenesis, organogenesis, cellular proliferation, immunological function, wound healing, tissue repair, cell migration, differentiation, apoptosis, and inflammation.[(3-5)]
It is well known that many cell adhesion molecules function as tumor suppressors. These molecules exert their tumor suppressive effect mainly through cell-adhesion-mediated contact inhibition. A number of cell adhesion molecule-tumor suppressors have been reported to be capable of reducing cell migration.[(5)]

Intercellular adhesion molecule-1 (ICAM-1) (CD54) is a transmembrane glycoprotein belonging to the immunoglobulin superfamily of adhesion molecules. ICAM-1 participates as an adhesion molecule as well as a co-stimulatory molecule to improve both antigen recognition by the T-cell receptor complex and subsequent T-cell activation. ICAM-1 is also involved in lymphoid trafficking and extravasation through lymphocyte/endothelial interactions. In normal B cells it mediates homotypic adhesions. ICAM-1 is expressed on the surface of many cancer cell types and is also present in a soluble form circulating in the plasma of cancer patients at elevated levels. It has also been proposed that ICAM-1 may be involved in the process of cancer metastases, facilitating the spread of metastatic cancer cells to secondary sites. In B-cell lymphoproliferative disorders the tumor expression of ICAM-1 is closely related to the degree of cell maturation. Thus, mantle-cell-derived lymphoproliferative diseases, such as

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chronic lymphocytic leukemia (CLL) or mantle-cell lymphoma, are often negative or weakly positive for ICAM-1, whereas ICAM-1 expression is more heterogeneous in germinal center cell lymphomas such as follicular or diffuse large-cell subtypes. It has been suggested that reduction of this molecule on the neoplastic lymphoid cells could impair the T-cell recognition with this contributing to neoplastic dissemination through a defective antitumor response.[6,7]

The structural organization and function of normal tissues is to a great extent determined by interactions between cells and the extra cellular matrix (ECM). Tissues are organized into compartments separated from each other by two types of ECM: basement membrane and interstitial connective tissue, each of these components of ECM is made up of collagens, glycoproteins, and proteoglycans. When invasion happens tumor cells must interact with the ECM at several stages.[8]

Cancer invasion and metastasis are landmark events that transform a locally growing tumor into a systemic, metastatic, and life-threatening disease and they are the major cause of cancer-related morbidity and mortality. The initial steps of local invasion include the activation of signaling pathways that control cytoskeletal dynamics in tumor cells and the turnover of cell matrix and cell-cell junctions, followed by active tumor cell migration into the adjacent tissue.[8,9]

Cortactin was first identified as one of the major substrates for src kinase. Because it localized to Cortical actin structures, it was named Cortactin. The strong localization of Cortactin to cell motility structures such as lamellipodia and invadopodia, sparked an early interest in the role of Cortactin in cell invasion and migration. Indeed, overexpression of Cortactin has been shown to enhance cell motility in a variety of assays, including transwell migration, wound closure, and single cell motility. Cortactin appears to play a central role in cell movement through tissues which frequently requires the degradation of ECM. Invadopodia were first identified in src kinase transformed cells and are thought to constitute the invasive cellular machinery. They are characterized by the colocalization of many proteins that are found in focal adhesions and lamellipodia, as well as membrane trafficking proteins and proteases. Related structures, podosomes, are found in osteoclasts, macrophages and other normal cells that must cross tissue barriers or remodel ECM. These downstream targets presumably function to coordinate the activities of the actin cytoskeleton, focal adhesions, protease activity, and membrane dynamics to the site of invadopodia formation. [10-12]

The aims of this study was to evaluate and compare the immunohistochemical of ICAM-1 expression as cell adhesion molecule marker and Cortactin expression as invasive marker and to correlate the expression of ICAM-1and Cortactin in Hodgkin's and non-Hodgkin's lymphoma.

MATERIALS AND METHODS

This study was performed on (68) formalin-fixed, paraffin-embedded blocks, histopathologically diagnosed as lymphoma (head and neck lesions).The diagnosis of each case was confirmed by the histological examination of the hematoxylin and eosinstained sections by two experienced pathologists. Histological classification was determined according to the world health organization (WHO) for HL (25 cases) classification and the international formulation criteria for NHL (43 cases) classification. The diagnosis of HL was confirmed by using immunohistochemical staining with CD15 and CD30, and the diagnosis of NHL was confirmed by using immunohistochemical staining with CD3, CD20 and Bcl2.

Each case was stained by ICAM-1(Anti-ICAM1 antibody [MEM-111] ab2213,Abcom, England) and Cortactin (Anti-Cortactin antibody [EP1922Y], Abcom, England), for each antibody the following procedure is done, starting by deparaffinization of a 4µm thickness section of each block mounted on positively charged microscopic slides at 65 ºC overnight, followed by dehydration, then application of hydrogen peroxidase block. Antigen retrieving was perform for ICAM-1 only (not for Cortactin) by applying the slides in hot citrate buffer solution ph 6.0 (95-99 ºC) for 10 minute, followed by protein block, then the application of primary antibody and incubation (6hr for both ICAM-1 and Cortactin), then the rabbit anti-mouse antibody unconjugated application, followed by goat anti-rabbit HRP conjugate application, and finally the application of DAB plus chromogen then hematoxylin counterstain.

The expression for all markers was evaluated semi-quantitatively. It was obtained by counting the number of tumor cells in 5 fields (using 40X objective in most represented areas of sections) and calculates the percentage of tumor cells that labeled a brown cytoplasmic. Labeling index for each field was calculated using the following equation: (number of positive cells/ number of total cells); the mean value of labeling indices for the five fields was considered to be the label index for the case.

The scoring categories for each antibody;

1-ICAM-1; the tumor cells labeled by antibody display a brown cytoplasmic and membrane staining pattern, immunoreactivity was classified as:(1) <10%, (2) 10%-50% and (3) >50%. [13]

2-Cortactin; The tumor cells labelled by antibody display a brown cytoplasmic staining pattern, immunoreactivity was classified: (1) < 25%, (2) 25%-50%, (3) > 50%. [14]

Computerized statistical program (Statistical Package for Social Sciences, SPSS version 15) was used for the statistical analysis of data.

RESULTS

The expression of ICAM-1 was membranous and cytoplasmic. A 67 cases were positive (98.5%), and one case was negative (1.5%), the positivity for HL was 100% and for NHL was 97.7%."Score 2" represent 64% and 72.1% of both HL and NHL respectively. No statistically significant difference was found between the two types of lymphoma in ICAM-1 expression, the details of ICAM-1 Scoring categories is shown table 1

The expression of ICAM-1 in Hodgkin's lymphoma cases according to its subtypes is shows that the commonest category was “Score 2” (64%) followed by "Score 3" (36%), as seen in table 2. However, no statistical significant difference was found in the expression of ICAM-1 between the subtypes of HL.

Figure 1 shows the expression of ICAM-1 in HL case.

The expression of ICAM-1 in non-Hodgkin lymphoma cases found that the most common expression was “Score 2” in 31 cases (72.1%), followed by "Score 3"(table 3). As in HL, regarding the scoring of ICAM-1 there was no significant different between the NHL subtype. Fig 2 and 3 shows the expression of ICAM-1 in NHL case

Cortactin expression was cytoplasmic; there were 67 positive cases (98.5%) and only one case negative (1.5%), the numbers of lymphoma cases according to scoring categories for Cortactin are shown in the following table, No statistically significant correlation was found between the types of lymphoma related to the scoring category for Cortactin, as seen in table 4.

All cases of HL were positive for Cortactin, "Score 2" and "Score 3" where the most common scores and represent 36% for both of all HL cases, followed by "Score 1" (28%). The cytoplasmic expression of Cortactin in HL is shown in Fig 4 and 5. No correlation was found between the subtype of HL in relation to the score categories of Cortactin as showed in table 5.

The percentage of positive expression of Cortactin in NHL cases was 97.7%, the highest expression was found in "Score 1” with 22 cases (51.2%), followed by "Score 2" which was 32.6%. The cytoplasmic expression of Cortactin in NHL is seen in fig 6. As in HL, there was no significant correlation found between the subtypes of NHL regarding the score of Cortactin. Details of Cortactin expression according to the subtypes of NHL found in table 6.

The correlation between percentages of expression of the ICAM-1 and Cortactin in HL and NHL cases was analyzed using Spearman's rank correlation coefficient (Spearman's rho).The results of CD54 expression in HL cases showed that the CD54 expression correlated significantly with that of Cortactinat level p= 0.05. In NHL cases also the CD54 expression correlated significantly with that of Cortactinbut at level p= 0.01.

DISCUSSION

Hayes & Seigel [7] studied the level of expression of ICAM-1 in different tissue and tumor types and found that tumors of the lymphatic system had the highest average ICAM-1 scores. This is in agreement with the results of the present study were the percentage of ICAM-1 was 98.5% of all cases of study sample. The higher levels of ICAM-1 seen in lymphoid tumors is most likely due to the fact that ICAM-1 is normally found in lymphoid tissues and would seem to be a favorable environment for ICAM-1 expression.

Similarly, Ruco et al [15] stated that, expressed ICAM-1 is a characteristic feature of H/RS cells in lymph node from patients with HL, also Vihinenet al [16] found that ICAM-1 was strongly expressed in involved tissues of HL. Uchihara et al [17] examined the expression of ICAM-1 in 4 HL cell lines and found that ICAM-1 was seen in all HL cell lines. This is in agreement with the result of the present study were the expression of ICAM-1 was found in all cases of HL, with no significant difference among the subtypes. This could be related to the fact that in HL the origin of the malignant cells (Hodgkin and Reed-Sternberg cells) are of B-cell origin and these malignant cells constitute only a small fraction of all cells present in the nodes, the majority of which represent inflammatory cells, including lymphocytes, plasma cells, eosinophils and histiocytes. It has been demonstrated that interactions between neoplastic and surrounding reactive cells, mediated by adhesive molecules which play an important role in the pathogenesis of HL.[18]

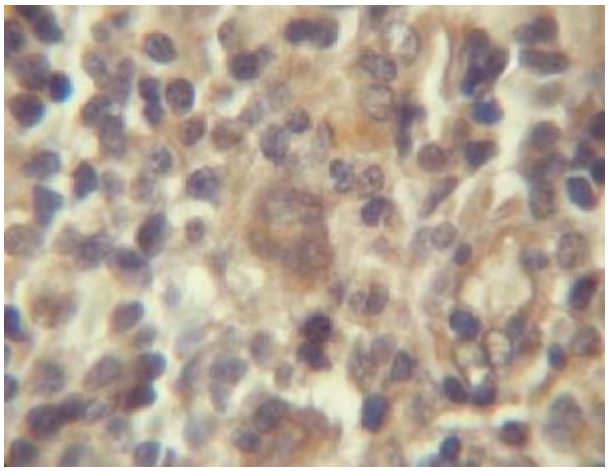

Fig. 1: The expression of ICAM-1 in a HL case (mixed cellularity subtype) (×100)

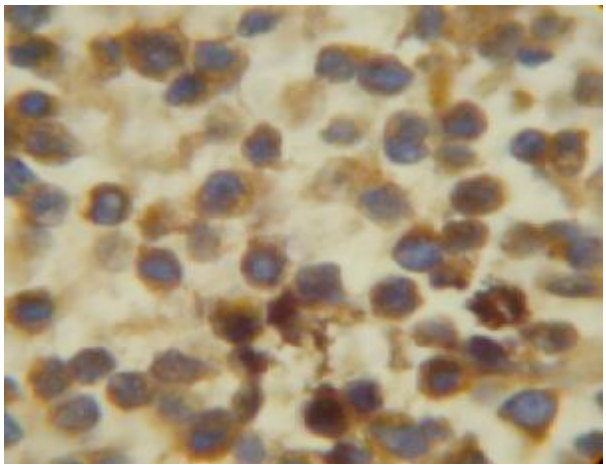

Fig. 2: The expression of ICAM-1 in NHL case (low grade), (×100)

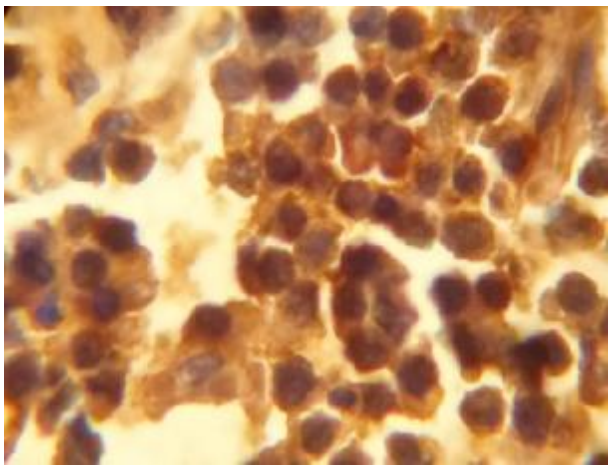

Fig. 3: The expression of ICAM-1 in NHL case (high grade), (×100)

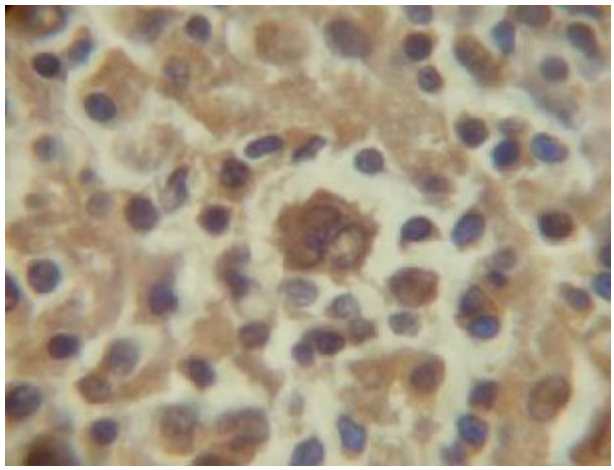

Fig. 4: The expression of Cortactin in HL case (nodular sclerosing). (×100)

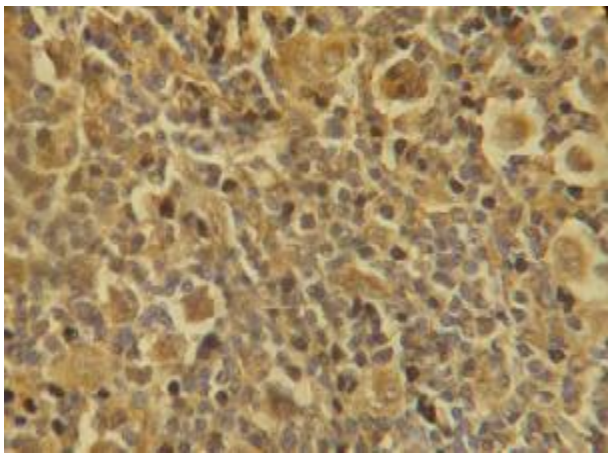

Fig. 5: The expression of Cortactin in HL case (mixed cellularity). (×40)

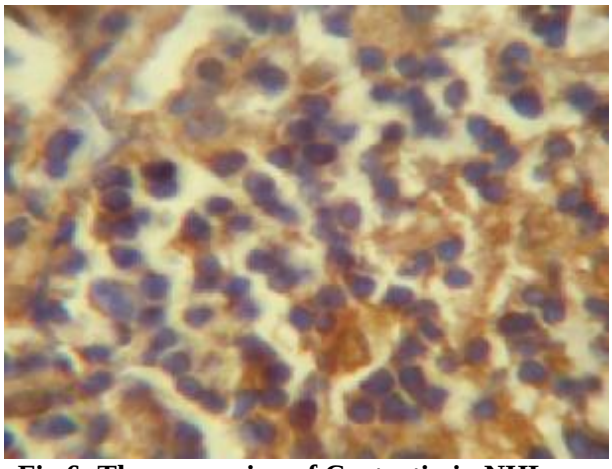

Fig 6: The expression of Cortactin in NHL case (intermediate grade). (×100)

Table 1: The numbers of lymphoma cases according to scoring categories for ICAM-1

Lymphoma types		ICAM-1				Total
		Negative	Score 1	Score 2	Score 3	
HL	No.	0	0	16	9	25
	% total	0%	0%	23.5%	13.3%	36.8%
	%HL	0%	0%	64%	36%	100%
NHL	No.	1	0	31	11	43
	% total	1.5%	0%	45.6%	16.2%	63.3%
	%NHL	2.3%	0%	72.1%	25.6%	100%
Total	No.	1	0	47	20	68
	%	1.5%	0%	69.1%	29.4%	100%

Chi-squared value 0.72, DF 1, Significance level P (2 sided) = 0.3961

Table 2: Expression of ICAM-1 in HL cases of the study sample

Subtypes of HL		ICAM-1			Total
		Score 1	Score 2	Score 3	
Lymphocyte-rich	No.	0	1	0	1
	% total	0%	4%	0%	4%
	%subtype	0%	100%	0%	0%
Mixed cellularity	No.	0	4	3	7
	%total	0%	16%	12%	28%
	%subtype	0%	57.1%	42.9%	100%
Nodular sclerosing	No.	0	11	6	17
	%total	0%	44%	24%	68%
	%subtype	0%	64.7%	35.3%	100%
Total	No.	0	16	9	25
	%	0%	64%	36%	100%

Chi-squared value 0.709, DF 2, Significance level P (2 sided) = 0.7015

Table 3: Expression of ICAM-1 in NHL cases of the study sample

Subtypes of NHL		*ICAM-1*				Total
		Negative	Score 1	Score 2	Score 3	
Low grade	No.	1	0	3	2	6
	%total	2.3%	0%	10%	4.7%	14%
	%subtype	16.7%	0%	50%	33.3%	100%
Intermediate grade	No.	0	0	12	4	16
	%total	0%	0%	27.9%	9.3%	37.2%
	%subtype	0%	0%	75%	25%	100%
High grade	No.	0	0	16	5	21
	%total	0%	0%	37.2%	11.6%	48.8%
	%subtype	0%	0%	76.2%	23.8%	100%
Total	No.	1	0	31	11	43
	%	2.3%	0%	72.1%	25.6%	100%

Chi-squared value 0.567, DF 2, Significance level P (2 sided) = 0.7531

Table 4: Expression of Cortactin in lymphoma study cases

Lymphoma types		Cortactin				Total
		Negative	Score 1	Score 2	Score 3	
HL	No.	0	7	9	9	25
	%total	0%	10.4%	13.2%	13.2%	36.8%
	%HL	0%	28%	36%	36%	100%
NHL	No.	1	22	14	6	43
	%total	1.5%	32.3%	20.6%	8.9%	63.2%
	%NHL	2.3%	51.2%	32.6	13.9%	100%
Total	No.	1	29	23	15	68
	%	1.5%	42.7%	33.7%	22.1%	100%

Chi-squared value 5.485, DF 2, Significance level P (2 sided) = 0.0644.

Table 5: The expression of Cortactin in HL study cases

Subtypes of HL		Cortactin				Total
		Negative	Score 1	Score 2	Score 3	
Lymphocytic rich	No.	0	1	0	0	1
	%total	0%	4%	0%	0%	4%
	%subtype	0%	100%	0%	0%	100%
Mixed cellularity	No.	0	1	3	3	7
	%total	0%	4%	12%	0%	28%
	%subtype	0%	14.4%	42.8%	42.8%	100%
Nodular sclerosing	No.	0	5	6	6	17
	%total	0%	20%	24%	0%	68%
	%subtype	0%	29.4%	35.3%	35.3%	100%
Total	No.	0	7	9	9	25
	%	0%	28%	36%	36%	100%

Chi-squared value 3.241, DF 4, Significance level P (2 sided) =0.518

Table 6: The expression of cortactin in NHL study cases

Subtypes of NHL		Cortactin				Total
		Negative	Score 1	Score 2	Score 3	
Low grade	No.	0	1	3	2	6
	%total	0%	2.3%	7%	4.7%	14%
	%subtype	0%	16.6%	50%	33.4%	100%
Intermediate grade	No.	1	8	3	4	16
	%total	2.3%	18.6%	7%	9.3%	37.2%
	%subtype	6.3%	50%	43.7%	25%	100%
High grade	No.	0	13	8	0	21
	%total	0%	30.2%	18.6%	0%	48.8%
	%subtype	0%	61.9%	38.1%	0%	100%
Total	No.	1	22	14	6	43
	%	2.3%	51.2%	32.6%	13.9%	100%

Chi-squared value 9.403, DF 4, Significance level P (2 sided) = 0.0517

The level of ICAM-1 expression in NHL in the present study was 97.7% which is slightly lower than that of HL, the expression in intermediate and high grades was non-significantly higher than that of low grade and this in agreement with Maio et al [19], who stated that, in in B-cell NHL, ICAM-1 expression appears to correlate with the differentiation stage of malignant cells, "High-grade" and "intermediate grade" B-cell NHL express in general a higher level of ICAM-1 than "low-grade", ICAM-1 was not detected on malignant T cells. Jacob et al [20] stated that, B-lymphocytes in high grade NHL express higher levels of cellular adhesion molecules than low grade subtypes which are similar to the findings of this study.

Terol et al [21] in their study on NHL found that 80% of cases where positive to ICAM-1 and no significant relationship was found in ICAM-1 expression and the lymphoma histologic subtype, these findings are in agreement with the present results.

To the best of our knowledge, this is the first study which demonstrates the cortactin expression in lymphoma. Early study done by Miglarese et al [22] on murine B lymphoid tumor cell lines hypothesize that cortactin expression is associated with transformed plasma cells and not with the terminal differentiation of normal B lymphocytes to plasma cells.

The results of the present study show that the positive expression of Cortactin was 98.5% and with no significant different between the types of lymphoma and between the subtypes of each type, this high expression indicate the invasiveness of all types of lymphomas were the tumor involves initially single lymph node, from where it spreads contiguously from one group of lymph nodes to another, and some time it spread to an extranodal sites.

In this study the Cortactin expression of tumor cells was cytoplasmic; similarly other studies found the same pattern of expression is similar.[14, 23, 24]

As for Cortactin on the basis of current knowledge regarding all the published studies, no definite study could be found that used this marker to estimate its effect in the diagnosis of lymphoma of its all types and subtypes. It is worth-mentioning that in this study cortactin gave remarkable positive results. It was shown that 98.5% of all study cases were positive, HL cases show high scores than in NHL but there was no significant different between them. This suggest that additional information should be taken in consideration regarding this marker and more diffused studies should be made in this field to determine its exact effect considering lymphoma in general and its types and subtypes in more specific.

A correlation was detected in ICAM-1 expression with cortactin expression in both HL and NHL in the present work. Cortactin is a cytoskeletal protein and src kinase substrate that is frequently overexpressed in cancer and cortactin overexpression increases tumor aggressiveness, possibly through promotion of tumor invasion and metastasis. Primary tumors with invasive properties usually display reduced intercellular adhesion, which allows cells to break away from the parental cell mass. Tumor cells invasion the adjacent tissues either together in tightly or loosely associated cell groups, this suggests that cancer cells retain some cell-cell adhesion, even as they break away from the primary tumor. Invasion of the target organ during metastasis requires certainly more stable interactions, probably mediated by various CAMs, which are present at the endothelial–endothelial and tumor–endothelial boundaries [25], and this could explain the correlation s between the ICAM-1 and Cortactin.

In conclusions, the high ICAM-1 positive expression in this study clarified that in addition to its role in cell-cell and cell-stromal interactions, it participates in proliferation, differentiation and invasion of malignant lymphoma cells. The high expression of ICAM-1in HL could be related to the fact that the malignant cells interact with the surrounding reactive cells and this interaction is mediated by adhesive molecules which play an important role in the pathogenesis of HL. In NHL the expression of ICAM-1 in intermediate and high grades was non-significantly higher than that of low grade suggesting that low grade subtypes are less aggressive in its course. The present study is the first one that used Cortactin as an invasive marker for lymphoma, the highly positive expression in 100% for HL and 97.7% for NHL, may be related to the fact that all types of lymphomas could not be restricted to single site of lymph node and once it starts all the node will be affected and sometimes the lymphoma could affect tissues other than lymphoid tissues as in extranodel involvement.

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