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Research Article

Immunohistochemical Expression of CD47 and Signal Regulatory Protein-α in B-Cell Lymphoma

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Abstract

Background: Lymphoma is one of many tumors that develop mechanisms to avoid the immune system. One mechanism of immune system evasion is CD47 interaction with various ligands, including signal regulatory protein alpha (SIRP-α). This interaction inhibits phagocytosis of lymphoma cells. ***Objectives***: To assess and compare the frequency of combined immunohistochemical expression of CD47 and SIRP-α in B cell lymphomas in addition to studying its association with some clinicopathological parameters. ***Methods***: A retrospective and prospective case series study of 51 cases of B-cell lymphomas collected randomly from the histopathological department of governmental and some private laboratories in Nineveh Province over a period of six months extending from September 2024 to February 2025. An immunohistochemistry investigation using CD47 and SIRP-α was performed, and the positive expression data were evaluated. ***Results***: The mean age was 31.29 years for HL and 62 years for NHL, with slight male predominance (51%) and (66.67%) had nodal presentation. B-cell lymphoma cases included in this study show immunohistochemical expression of CD47 and SIRP-α, but with different staining grades. 64.71% and 33.33% were high expressors vs. 35.29% and 66.67% were low expressors for CD47 and SIRPA, respectively, with no significant association. ***Conclusions***: Although CD47 and SIRPα showed divergent results, this study revealed that most B-cell lymphomas express CD47 and SIRPα proteins independently.

Keywords: B lymphoma, CD47, Signal regulatory protein alpha.

التعبير الكيميائي المناعي ل CD47 والبروتين المنظم للإشارة α في سرطان الغدد الليمفاوية للخلايا البائية

الخلاصة

الخلفية: سرطان الغدد الليمفاوية هو واحد من العديد من الأورام التي تطور آليات لتجنب جهاز المناعة. تتمثل إحدى آليات التهرب من الجهاز المناعي في تفاعل CD47 مع روابط مختلفة، بما في ذلك بروتين ألفا المنظم للإشارة (SIRP-α). هذا التفاعل يمنع البلعمة لخلايا سرطان الغدد الليمفاوية. **الأهداف**: تقييم ومقارنة تواتر التعبير الكيميائي المناعي المشترك ل CD47 و SIRP-α في الأورام اللمفاوية للخلايا البائية بالإضافة إلى دراسة ارتباطه ببعض المعلمات السريرية المرضية. **الطرائق**: دراسة سلسلة حالات بأثر رجعي ومستقبلية ل 51 حالة من الأورام اللمفاوية للخلايا البائية تم جمعها عشوائيا من قسم الأنسجة المرضية في المختبرات الحكومية وبعض المختبرات الخاصة في محافظة نينوى على مدى ستة أشهر تمتد من سبتمبر 2024 إلى فبراير 2025. تم إجراء تحليل الكيمياء المناعية باستخدام CD47 و SIRP-α، وتم تقييم بيانات التعبير الإيجابي. **النتائج**: كان متوسط العمر 31.29 سنة ل HL و 62 عاما ل NHL، مع غلبة طفيفة للذكور (51٪) و(64.7٪) كان لديهم عرض عقدي. تظهر حالات سرطان الغدد الليمفاوية للخلايا البائية المدرجة في هذه الدراسة تعبيرا كيميائيا مناعيا ل CD47 و SIRP-α، ولكن بدرجات صبغية مختلفة. 64.71٪ و 33.33٪ كانوا معبرين مرتفعين مقابل 35.29٪ و 66.67٪ كانوا معبرين منخفضين ل CD47 و SIRPA، على التوالي ، مع عدم وجود ارتباط كبير. **الاستنتاجات**: على الرغم من أن CD47 و SIRPα أظهرا نتائج متباعدة، إلا أن هذه الدراسة كشفت أن معظم الأورام اللمفاوية للخلايا البائية تعبر عن بروتينات CD47 و SIRPα بشكل مستقل.

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INTRODUCTION

B-cell lymphomas constitute approximately about 95% of all cases of lymphoma [1,2]. It is classified into Hodgkin and non-Hodgkin lymphoma depending on the presence or absence of Reed-Sternberg cells [1]. Hodgkin lymphoma (HL) includes nodular lymphocyte-predominant HL and classical HL. Classical [3]. HL has a bimodal age distribution with a prevalence not only in the elderly but also in young adults. Most patients presented with nodal site involvement [3]. HL is among the most treatable lymphomas, showing cure rates of about 80–90% with combined chemo-/radiotherapy [4]. Non-Hodgkin B cell lymphomas, a diverse category of lymphoproliferative tumors, are significantly less predictable than Hodgkin's lymphomas and are far more likely to spread to extranodal sites. Approximately 25% of NHL cases occur in extranodal sites, while the majority involve both nodal and extranodal sites [5]. It includes low-grade (indolent), intermediate, and high-grade (aggressive) B-cell lymphomas [6]. B-cell non-Hodgkin lymphomas (NHL) are most diagnosed in adults over the age of 60, with incidence increasing with age [7]. Non-Hodgkin Lymphoma (NHL) shows more

variable response rates, depending on subtype. with overall response rates (ORR) varying from 35% to 90%, especially in relapsed/refractory settings [8,9]. Immunohistochemistry has an important role in confirmation of diagnosis, accurate typing of lymphoma, and predicting treatment response. Leukocyte common antigen (LCA), B-cell markers (CD20 and CD79a), T-cell markers (CD3 and CD5), and other markers like MUM1, CD23, BCL-2, BCL-6, CD10, cyclin D1, CD15, CD30, ALK-1, PD-L1, and CD138 (based on cyto-architectural pattern) are also included in the panel of markers, which is chosen based on morphologic differential diagnosis (no single marker is specific) [10-14]. Originally known as integrin-associated protein (IAP), Cluster of Differentiation 47 (CD47) is a 50 kDa, highly glycosylated cell surface protein that is a member of the immunoglobulin superfamily [15]. It is encoded by the CD47 gene, which is found on the human chromosome's 3q13.12 region [16]. CD47 can interact with various ligands and, by binding to these ligands, influences a number of target cell biological processes. Examples of extracellular ligands include signal regulatory protein alpha (SIRP-α), thrombospondin-1 (TSP-1), integrins (α2B1, α4B1, α5B1, and α6B1), CD36, CD95, and signal regulatory protein gamma. In contrast, Bcl-2/adenovirus E1B 19-kDa interacting protein 3 and Gi proteins are examples of intracellular ligands [17,18]. SIRPα is an inhibitory receptor with the highest affinity for CD47; it is a membrane protein of the SIRP protein family, which is composed of five members (SIRPα, SIRPβ1, SIRPβ2, SIRPγ, and SIRPδ). SIRPα is also referred to as PTPNS1, SHPS1, CD172A, and P84 [19]. It is encoded by the 20p13 chromosome's gene cluster [17]. CD47 inhibits phagocytosis of neoplastic lymphoma cells by interacting with the signal-regulating protein alpha (SIRPα) on the surface of phagocytic cells. Interaction with CD47 facilitates SIRPα localization to the phagocytic synapse by activating Src homology region 2 domain-containing phosphatase-1 (SHP-1). Phosphatase then stops non-muscle myosin IIA from building up at the cell membrane, which stops engulfment of malignant cells. [20]. This study aims to assess and compare the frequency of combined immunohistochemical expression of CD47 and SIRP-α in both Hodgkin and non-Hodgkin B cell lymphomas, while also examining its association with various clinicopathological parameters, including age, gender, and the site of presentation (nodal versus extranodal).

METHODS

Study design and setting

This study was a retrospective and prospective case series study of 51 cases of B-cell lymphomas collected randomly from histopathology departments of governmental and some private laboratories in Nineveh Province from September 2024 to February 2025.

Sample selection

Patient data, including age, gender, and primary site of disease at presentation, were retrieved from archive records. Inclusion criteria include paraffin blocks with adequate tissue and high tumor density, while cases with paraffin blocks with less tumor material, extensive necrosis, badly preserved specimens, or patients who received chemotherapy were excluded.

Analysis of samples and scoring

Immunohistochemical (IHC) examination was conducted on formalin-fixed, paraffin-embedded (FFPE) tissue sections utilizing specific antibodies targeting CD47 and SIRPα, in accordance with the protocols supplied by the respective manufacturers (Medaysis, USA). The identification of target antigens was accomplished utilizing the Mouse/Rabbit PolyDetector Plus DAB HRP Brown detection system (Bio SB, USA). External affirmative controls of colon epithelial samples were employed to validate the staining process. A certified pathologist examined the hematoxylin and eosin-stained sections and conducted the interpretation to evaluate the expression and location of CD47 and SIRPα in tissue specimens. The scoring method used was the Allred score [21]; staining intensity was classified as 0 (absent), 1 (weak), 2 (moderate), and 3 (strong); and the percentage of chromatosis cells was classed as 0 (none), 1 (1–10%), 2 (11–50%), 3 (51–80%), and 4 (greater than 80%). Multiply these two numbers: 0–2 is classified as (−); 3–4 as (+); 5–8 as (++); and 9–12 as (+++). 0–1+ was classified as low expression, whereas 2–3+ was deemed high expression [21]. Meanwhile, the SIRP-α leukocyte proportions score was calculated by taking the highest number of leukocytes stained by SIRP-α in high power fields (HPF) [22]. The median (10 positive cells per HPF) was regarded as the cutoff value, with cases below 10 per HPF regarded as low SIRPA expression, while cases with 10 or above per HPF were regarded as high SIRPA expression.

Ethical considerations

This study was conducted based on the principles of ethics that have their origin in the Declaration of Helsinki, and it was approved by the Research Ethics Committee, Nineveh Health Directorate, with a reference number (2024155) on September 4, 2024, to get this approval.

Data analysis

The gathered data were systematically arranged and tabulated utilizing the statistical package for society study (SPSS) version 26. Descriptive statistics were employed to encapsulate demographic information. The Fisher exact test and chi-square test were employed to

examine relationships among tumor classifications. A p-value < 0.05 was considered statistically significant.

RESULTS

The study sample included 51 cases of B-cell lymphoma, 27 cases (53%) of HL vs. 24 (47%) cases of NHL. In HL, the age of patients ranged from 4 to 70 years (mean 31.29 years) (median 28 years) and peaked at 20-29 years (8/27), while in NHL, the age of the patients ranged from 23 to 84 years (mean 62 years) (median 66 years) and peaked at ≥ 60 years (18/24). Thirty-three cases (64.7%) had nodal presentation (24 HL and 9 NHL), while extranodal presentation was noticed in 18 cases (35.3%) (3 HL and 15 NHL). 26 cases (51%) of the study sample were males, while 25 (49%) were females. In HL there is female predominance (55.56%), while in NHL there is male predominance (58.34%). In the current study, the expression level of CD47 was categorized according to the Allred score (56); 6 cases (11.8%) were negative, while 45 cases (88.3%) were positive with different grades, as shown in Table 1.

Table 1: CD47 expression in B-cell lymphoma

Histological type	CD 47 expression					p-value
	-	+	++	+++	Total	
HL	2(4)	9(17.6)	12(23.5)	4(7.8)	27(52.9)	
NHL	4(7.8)	3(5.9)	14(27.5)	3(5.9)	24(47.1)	0.2 *
Total	6(11.8)	12(23.5)	26(51)	7(13.7)	51(100)	

Values are presented as frequencies and percentages. *Fishers exact test.

Thirty-three cases (64.71%) of the study sample were high CD47 expression, while 18 cases (35.29%) were low CD47 expression. In HL cases, 59.25% and 40.74% had high and low CD47 expression, respectively, while in NHL cases, 70.84% and 29.17% had high and low CD47 expression, respectively. The distribution of the study sample according to SIRPα showed that 34 cases (66.67%) of the study sample were low SIRPα expression, while 17 cases (33.33%) were high. Comparison of the expression of CD47 with SIRP-α across lymphoma subtypes (B-cell, Hodgkin, and Non-Hodgkin) is demonstrated in Table 2.

Table 2: Comparison of the Expression of CD47 with SIRP-α Across Lymphoma Subtypes (B-cell, Hodgkin, and Non-Hodgkin)

Lymphoma type	SIRP-α	CD47 Low	CD47 High	Total	p-value*
B-cell Lymphoma	Low	10(55.6)	24(72.7)	34(66.7)	0.1
	High	8(44.4)	9(27.3)	17(33.3)	
Hodgkin Lymphoma	Low	5(45.5)	9(56.3)	14(51.9)	0.4
	High	6(54.5)	7(43.8)	13(48.1)	
Non-Hodgkin Lymphoma	Low	5(71.4)	15(88.2)	20(83.3)	0.3
	High	2(28.6)	2(11.8)	4(16.7)	

Values are presented as frequencies and percentages *Fishers exact test.

The difference between the high and low SIRPα expression in relation to CD47 expression in the total cases and in subtypes (B-cell, Hodgkin, and Non-Hodgkin) was statistically not significant (p-value= 0.1, 0.4, and 0.3, respectively). It revealed that the strongest association was in Non-Hodgkin Lymphoma (NHL) between SIRP-α high and low CD47 (15/20) (75%), while the lowest association was between SIRP-α low and low CD47 (5/20) (25%) in NHL. The IHC expression pattern of CD47 and SIRP-α in B-cell lymphoma is shown in Figure 1.

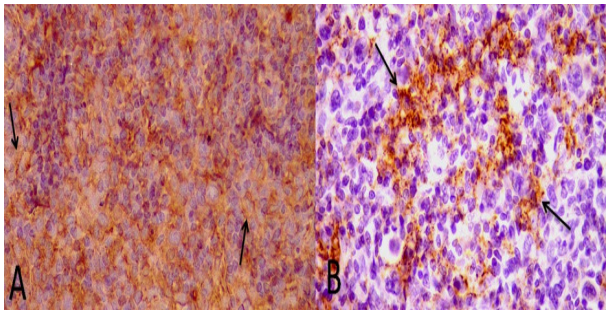

Figure 1: IHC expression model of CD47 and SIRP-α in B-cell lymphoma. **A)** Strong membranous expression, brown DAB staining of CD47on non-Hodgkin lymphoma cells (black arrow) (×400); **B)** Cytoplasmic brown DAB staining of >10 cells/HPF SIRP-α expression (black arrow) (×400).

DISCUSSION

CD47 overexpression in many malignant tumors prevents tumor cell phagocytosis and initiates tumor progression. As an integrin-associated protein, CD47 interacts with a CD47 ligand known as Signal regulatory protein-α (SIRPα). This interaction promotes a dephosphorylation cascade that prevents phagocytosis [23]. In the present study, the age distribution of HL cases is comparable to studies reported in Iraq, including the western region (mean 29.33) [24] and the northern region (mean 32.57) (median 28 years) [25], in addition to other neighboring countries like Iran (mean 31) [26] and Bahrain (median 31 years) [27], along with Germany (median 33 years) [2]. Indonesia and the US show the same age group range (32.34% and 24.86%), respectively [28,29]. While in this study NHL patients were older than HL patients, this aligns with global data linking NHL to advanced age [30]; a similar finding was also reported in nearby countries like Lebanon (mean 53.52) [31], Turkey (median 53 years) [32], Saudi Arabia (35% in the age group above sixty) [33], and Bahrain (median 56 years) [27]. This is anticipated due to the global aging population, as cancer predominantly affects the elderly, while the Middle Eastern population possesses a younger age pyramid, indicating a reduced

number of individuals reaching the age demographics where lymphoma prevalence is highest [34]. The current study revealed that nodal presentation was the predominant form. These findings are consistent with those reported by Balikó et al., Babu et al., and Okap et al., where nodal presentation comprises 75%, 61.6%, and 55.8%, respectively [35-37]. This agrees with the clinical behavior of lymphoma, as the majority of HL and more than 70% of NHL have nodal presentation [38, 39]. In the present study, the distribution of the study sample according to gender shows a slight male predominance, a similar finding in Saudi Arabia (57.4%) [31], Yemen (60.6%) [40], and Bahrain (57.01%) [27]. This predominance may be attributed to the protective effect of estrogen and its role in the modulation of the immune system [41,42] and greater occupational exposure to some carcinogenic substances like agricultural pesticide chemical groups among males compared to females, in addition to the role of smoking and alcohol [43-45]. In this study, the relationship between CD47 and SIRP-α expression in B-cell lymphoma and in subtypes B-cell, Hodgkin, and Non-Hodgkin was statistically not significant, a similar result obtained by Gholiha *et al*. on cHL [46] and Kazama *et al*. in Japan on DLBCL [22]. These results indicate that higher SIRP-α levels in the microenvironment may not always accompany high CD47 expression on tumor cells, and each protein may be regulated separately; for instance, oncogenic signaling may cause CD47 to be increased, whereas cytokine profiles or immune cell infiltration may influence SIRP-α expression. Additionally, the results may show that CD47-mediated immune evasion can happen independently of SIRP-α abundance, perhaps as a result of downstream signaling suppression or functional saturation [47]. In the present study, although high CD47 and high SIRP-α co-expression were not statistically significant, they were seen more in Hodgkin lymphoma compared to NHL cases. According to Cho *et al*. (2020) and Gholiha *et al*. (2020), HL had higher levels of SIRP-α and CD47 co-expression than NHL [48,49]. HL patients frequently have a dense infiltration of macrophages, which produce a functionally active inhibitory axis by expressing high amounts of SIRP-α. A worse prognosis and less macrophage-mediated clearance are associated with high CD47 expression in HL, as when CD47 is high, it binds to SIRP-α on macrophages, sending the "don't eat me" signal. This inhibits macrophage activity, so tumor cells are not cleared effectively. This immune evasion leads to disease progression and worse prognosis [46, 50].

Limitation of the study

The current study has some limitations, including a small sample size, lack of case diversity, absence of patient follow-up, and a restricted number of references. This research topic is relatively new in the local context, and published literature remains limited.

Conclusion

This study revealed that most B-cell lymphomas express CD47 and SIRP-α proteins independently, which warrants cautious attention in future large-scale investigations due to their potential therapeutic and prognostic significance. Targeting the CD47–SIRP-α axis may represent a promising strategy to improve patient outcomes and advance the management of B-cell lymphomas.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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