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Case Report

Activated B-cell signet ring lymphoma: A case report and a comparative review of the literature

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ABSTRACT

Signet ring cell lymphoma is an exceedingly rare subtype of non-Hodgkin lymphoma that was originally thought to be a morphologic variant of follicular lymphoma. To date, 56 cases have been reported, with the majority occurring in lymph nodes and bone marrow. Herein, we report a case of a 37-year-old female who presented with a left inguinal mass and high suspicion of lymphoma that was rendered on MRI. A successful ultrasound-guided core biopsy was performed. Pathologic examination revealed a diffuse large B-cell lymphoma (DLBCL) with unique signet ring histology and post-germinal center phenotype. In-situ hybridization showed an isolated BCL-6 gene rearrangement and confirmed the absence of a double-hit phenotype. This case would be situated as the second case of activated B-cell (ABC) signet ring lymphoma and the first case to arise in this anatomic location. The patient recently initiated therapy with a standard six-cycle regimen of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Introduction

Pathologists have recognized signet ring features as a specialized type of cell that is round and filled with light blue mucin that pushes the cell's nucleus to the side. Although gastric and breast carcinomas are the most common cancers with signet ring features, these features could be seen with other mucin-producing adenocarcinomas and in some rare types mesotheliomas [1,2]. This paper presents a rare case of (ABC)-DLBCL, which had unique signet ring histology. Other tumors with signet ring features are significant differential diagnosis considerations. This association can present clinically and radiologically as a single retroperitoneal mass. Careful microscopic examination using H&E followed by immunohistochemistry is required for diagnosis.

Case presentation

A 37-year-old female presented with a 6.9 cm rapid-growing firm left upper medial thigh mass. The patient did not experience any activity change, appetite change, chills, and fever, and there was no significant past medical history. The mass had internal vascularity measuring 5.4 × 5.2 × 4.2 cm on ultrasound. The enlarged lymph node was favored, given the rapid development. MRI revealed a 6.9 × 5.2 × 4.2 cm enlarged mass, which was increased compared to the previous ultrasound's size. Further evaluation with CT showed lobulated soft tissue mass in the left anterior pelvis measuring up to 9.7 cm in diameter (Fig. 1A). Multiple enlarged and coalescent pathologic lymph nodes were suspected. In addition, there was a 6.9 cm diameter mass in the proximal left thigh, which is typically consistent with an enlarged lymph node. Subsequently, the patient underwent an ultrasound-guided biopsy of a left medial upper thigh/groin mass. The specimen displayed three tan white soft tissue cores, each measuring (2.3–2.4 cm in length and 0.1 cm in diameter). A portion of each core was saved in RPMI, and two touch preps were made. Flow cytometry of the peripheral blood didn't show a monotypic B-cell population, phenotypically abnormal *T*-cell population, or blast cell population detected. Microscopic examination revealed dyscohesive sheets of large lymphoid cells with abundant cytoplasm and distinct cytoplasmic vacuoles, resembling signet ring cells (Fig. 1B). The cells with a signet ring appearance comprised around 60–70 % of the total number of tumor cells. In minor areas without signet ring, intermixed small to intermediate-sized lymphocytes were seen in a background of apoptosis and cellular lysis, indicative of a delicate cytoplasmic membrane.

By immunohistochemistry, the neoplastic cells were strong and diffusely positive for CD45 (membranous), CD20 (membranous), PAX-5 (nuclear), CD30 (membranous), BCL-6 (nuclear), BCL-2 (cytoplasmic), and MUM-1 (nuclear) and negative for pan-cytokeratin (AE1/AE3),

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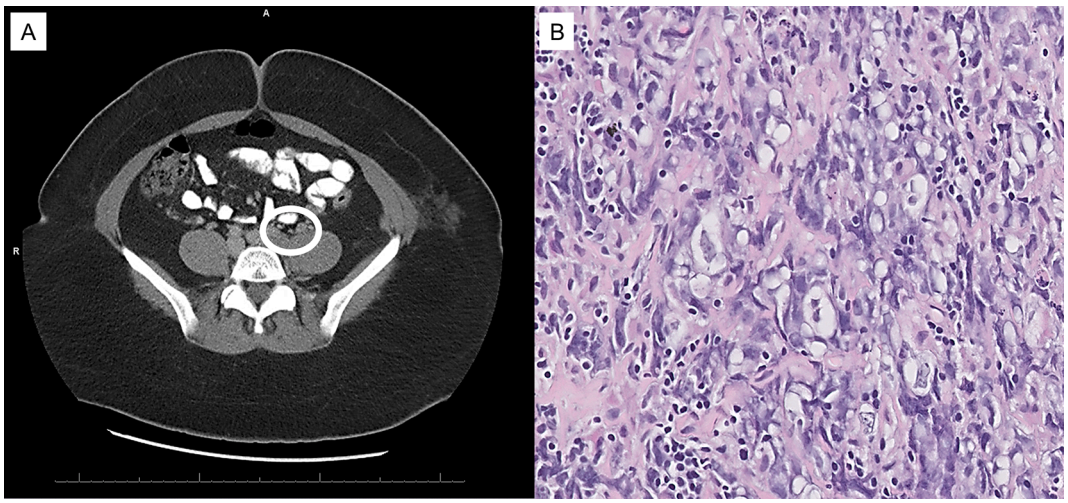

Fig. 1. CT scan and Microscopic Image of the Mass (20X). (A) CT imaging shows a left anterior pelvis (9.7 cm in diameter) (B) A Microscopic image (20X) shows diffuse malignant lymphocytic infiltrate with signet ring features.

mucicarmine, CD10, CD5, CD3, BCL-1, EBER, ALK-1 (Fig. 2A-2F). CD21 and CD23 were negative for the presence of follicular dendritic meshwork. In addition, the Ki-67 proliferation index showed 80 % positivity and C-MYC was negative (less than 40 %). Fluorescent in-situ hybridization (FISH) showed BCL-6 gene rearrangement but lacked MYC and BCL-2 rearrangement, confirming the absence of a double-hit phenotype. The findings were consistent with a non-germinal center diffuse large B cell lymphoma.

A recent review of the clinical notes showed that the patient recently initiated therapy with a standard six-cycle regimen of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Discussion

We performed an extensive literature search using the available PubMed database for previous reports of signet ring lymphomas (Table 1) [3–16]. To the best of our knowledge, signet ring features in non-Hodgkin lymphoma have been documented in 56 cases, the majority of which presented as low-grade B-cell lymphoma either in the form of MALT or follicular lymphomas. MALT lymphomas were identified in 26 cases with the morphology and gastric mucosal tissue location, which could be easily misdiagnosed as signet ring carcinomas [10]. In contrast, follicular lymphomas have been reported in 20 cases either as a predominant pattern or as a minor component [3, 4, 5, 14, 15, and 16]. Four instances of follicular lymphoma in the inguinal lymph nodes were observed. Only one case of immunoblastic post-germinal center signet ring lymphoma has been reported by Nakamura et al., located at cervical lymph nodes [13].

DLBCL is considered the most common and aggressive type of non-Hodgkin lymphoma (NHL), classically characterized by diffuse proliferation of neoplastic B lymphoid cells with a nuclear size exceeding normal histiocyte nuclei [17]. The molecular mechanism of DLBCL is not entirely understood; however, studies have shown that DLBCL is mainly caused by heterogeneous genetic alterations involving NF-κB regulator, MYC, PIM1, PTEN, PIK3CA, B-cell lymphoma 2 (BCL-2), and BCL-6 pathways [18]. Besides, approximately 35 % of DLBCL contain a t (14:18), which leads to ectopic expression of the BCL-2 oncogene [19]. While DLBCL often occurs de novo, the transformation from pre-existing lymphoid malignancies, such as follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL), must always be considered [20].

Generally, DLBCL is more common in the old age group with a median age of 70 years; however, it can affect young and adolescents age groups, as in our case, and is considered the most prevalent NHL in this age group, with exceptional outcomes in response to CHOP regimens [21]. The clinical presentation of DLBCL is nonspecific; it often presents as a rapidly progressive symptomatic mass or enlarged lymph node, most commonly in specific anatomic locations such as the groin, axilla, and neck [22]. Furthermore, some DLBCL patients can present with constitutional symptoms such as fever, night sweats, weight loss, and shortness of breath, or they may be asymptomatic in about 40 % of cases. Therefore, successive imaging would be optimal to detect the mass and evaluate its progressive growth.

Our case established that the classic microscopic features of DLBCL are not always present, and overlapping with other differential diagnoses could easily occur. One of the most challenging diagnostic mimickers is signet ring carcinoma, which have some features that could help with this differentiation such as the cohesive glandular or papillary architecture and the intracytoplasmic mucin inclusions. Such "Signet ring carcinoma" category includes a broad spectrum of tumors involving the breast, stomach, bladder, ovary, and lungs [23]. Therefore, a definitive diagnosis requires a correlation between the clinical and morphologic features, supplemented by immunohistochemistry using epithelial, lymphoma, and mucin, and immunoglobulin markers. Furthermore, the flow cytometry analysis in our case was not diagnostic as various lymphomas, metastatic tumors, or other neoplasms cannot be detected by flow cytometric analysis [24].

In addition, the distinct classification of DLBCL into germinal center B-cell-like (GCB) DLBCL, activated B-cell type (ABC) DLBC, and Double-Hit DLBCL have led to significant prognostic and predictive implications [25]. ABC DLBCL or non-germinal center DLBCL is associated with significantly worse outcomes with standard chemoimmunotherapy compared to GCB DLBCL. Strategies to distinguish these subtypes using Hans's immunohistochemistry algorithms play a significant role in treatment selection, specifically with R-CHOP therapy [26]. Therefore, the diffuse expression of BCL6, MUM-1, and the complete absence of CD10 by IHC and MYC amplification by FISH in our case, confirmed the diagnosis of activated B-cell type (ABC) DLBCL. Moreover, useful IHC markers such as CD45, CD 20, PAX-5, CD30, CD5, CD3, BCL-1, EBER, ALK-1, and Ki-67 can help differentiate and classify DLBCL.

Finally, considering the biological and clinical heterogeneity of DLBCL, signet ring morphology may indicate distinct genetic or molecular alterations that need further investigation in these cases to identify possible avenues for management options. Due to the inherit sampling limitations of a needle core biopsy, a concurrent or antecedent low grade B-cell lymphoma such as follicular lymphoma cannot be excluded and may impact the clinical management. Therefore, an excisional or incisional biopsy is typically recommended, in the proper clinical context.

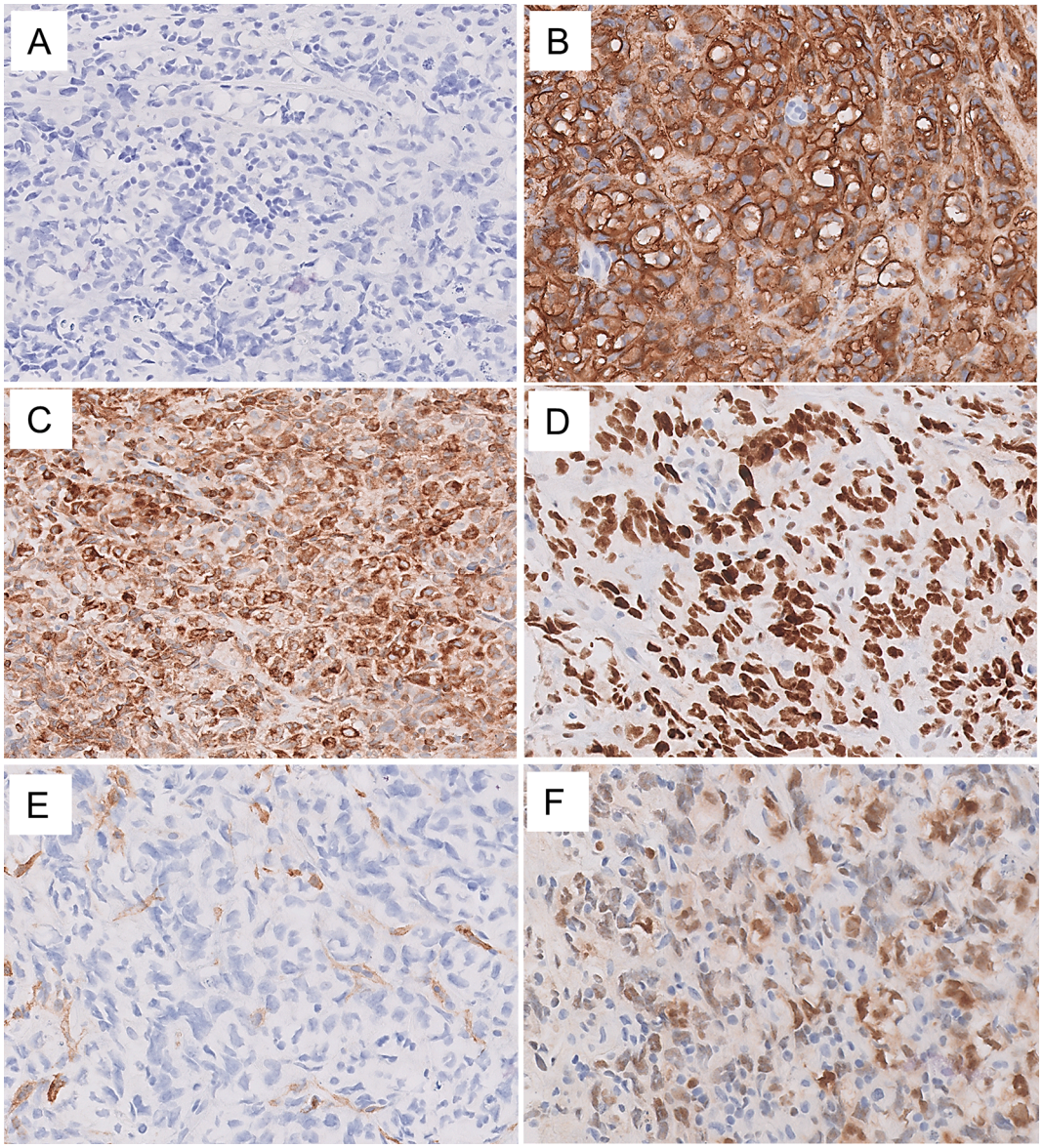

Fig. 2. Immunohistochemistry of the Signet-Ring Cells (20X). (A-F) IHC (20X) demonstrates that the neoplastic cells are (A) negative for pan-cytokeratin, (B-D) positive for CD20 (membranous), BCL2 (cytoplasmic), BCL6 (nuclear) (E-F) and negative for CD10 and positive for MUM1 (nuclear).

Conclusions

In conclusion, activated B-cell (ABC) signet ring lymphoma (SRL) should be approached with caution with the primary intent to exclude various malignancies which exhibit overlapping histology. Given this tumor's limited occurrence, its origin and prognostic determinants have yet to be fully determined. Gene expression profiling and comparative genomic hybridization with other cases may help better to situate this entity within the existing classification framework.

Ethics Statement including Patient Consent Statement

This study adhered to the guidelines set forth by the Office of Human Research Protection that is supported by U.S. Department of Health & Human Services. Informed telephone consent was obtained from the patient for publication of this report and any accompanying images.

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Author Contributions

Writing the manuscript: AIY; Reviewing and proofreading the manuscript: AIY, MMM, MV, and MDR; Supervision and oversight: MV and MDR.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1
Summary of previously published case reports of signet-ring lymphoma.

Reference	Number of Cases	Diagnosis	Anatomic Location
Kim et al. 1978 [3]	7 cases	Follicular lymphoma	(2) Mesenteric LN, (1) Submaxillary LN, (1) Post auricular LN, (1) Supraclavicular LN, (1) Submandibular LN, and (1) Inguinal LN
Harris et al. 1981 [4]	1 case	Follicular lymphoma	Inguinal LN
Spagnolo et al. 1982 [5]	3 cases	Follicular lymphoma	N/A
Weiss et al. 1985 [6]	2 cases	T-cell lymphoma	Skin (Thigh and Inguinal area)
Grogan et al. 1985 [7]	1 case	T-cell lymphoma	Skin (Scalp)
Lee et al. 1987 [8]	1 case	Burkitt's-like lymphoma	Cervical LN
Cross et al. 1989 [9]	1 case	T-cell lymphoma	Skin (Chin)
Zamboni et al. 1996 [10]	26 cases	MALT lymphoma	Gastric associated lymphoid tissue
Falini et al. 1997 [11]	1 case	Anaplastic large cell lymphoma	Supraclavicular LN
Ramnani et al. 1999 [12]	1 case	CLL/SLL	Axillary LN
Nakumara et al. 2003 [13]	1 case	Immunoblastic post germinal center	Cervical LN
Wu et al. 2013 [14]	3 cases	Follicular lymphoma	Inguinal LN, Mesenteric LN, and peripancreatic mass
Zhang et al. 2017 [15]	7 cases	4 Follicular lymphomas, 1 GC DLBCL, 1 DLBCL with FL, and 1 DLBCL with MZL	N/A
Patel et al. 2020 [16]	1 case	GC DLBCL with minor FL	Inguinal LN

Summary of previous case reports of signet ring lymphomas published in the literature [3–16]. (FL) follicular lymphoma, (GC) germinal center, (MZL) marginal zone lymphoma. (N/A) indicates limited access to this article to determine the anatomic location.

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