CASE REPORT

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A Rare Case of Signet Ring Cell Lymphoma and Review of the Literature

ABSTRACT

Signet ring cell lymphoma (SRCL) is a non-Hodgkin's lymphoma with a very rare variant. Although this morphology is frequently seen in follicular lymphoma, it can also be observed in the group of diffuse large B-cell lymphomas. A seventy-six year old woman with known diagnosis of gastric adenocarcinoma, tubular type, moderately differentiate presented with a mesenteric lymphadenopathy with high FDG uptake (SUVmax: 21.3) in PET/CT during follow-up. A tru-cut biopsy was performed for histopathological diagnosis. Diffuse infiltrative singet ring neoplastic cells showed negativity for PanCK, CK7, CK20, S100, SMA, calretinin and vimentin. The panel was then expanded to include SRCL, a rare variant of lymphoma. Additional immunohistochemical evaluation revealed positivity for CD20, CD19, PAX-5 and Bcl-2. Ki-67 proliferation index was about 80%. CD3, CD30, Myc, Bcl-6, ALK, Cyclin-D1, CD23, CD10, CD21, and MUM-1 were negative. EBER was also negative by chromogen in situ hybridization (CISH). Based on these data, diffuse large B-cell lymphoma (DLBCL) was considered. We herein reported a case of signet ring cell lymphoma discussed its clinical and morphological features with regard to the literature.

Keywords: Signet Ring Cell, Lymphoma, Diffuse Large B-Cell Lymphoma, Post Transplant.

Nadir Bir Taşlı Yüzük Hücreli Lenfoma Olgusu ve Literatürün Gözden Geçirilmesi

ÖZET

Taşlı yüzük hücreli lenfoma, Hodgkin dışı lenfomaların oldukça nadir görülen bir varyantıdır. Bu morfoloji sıklıkla foliküler lenfomada görülmekle birlikte diffüz büyük B hücreli lenfomalar grubunda da görülebilmektedir. Bilinen tübüler tip mide adenokarsinomu tanısı olan 76 yaşında kadın hasta, takip sırasında PET/BT'de FDG tutulumu yüksek (SUVmax: 21,3) mezenterik lenfadenopati ile başvurdu. Histopatolojik tanı için tru-cut biyopsi yapıldı. Diffüz infiltrasyonlu taşlı yüzük görünümündeki neoplastik hücreler PanCK, CK7, CK20, S100, SMA, kalretinin ve vimentin için negatiflik gösterdi. Panel daha sonra nadir bir lenfoma çeşidi olan SRCL'yi içerecek şekilde genişletildi. Ek immünhistokimyasal incelemede CD20, CD19, PAX-5, Bcl-2'nin pozitif olduğu ve Ki-67 proliferasyon indeksinin %80 civarında olduğu görüldü. CD3, CD30, Myc, Bcl-6, ALK, Cyclin-D1, CD23, CD10, CD21, MUM-1 negatifti. EBER, kromojen in situ hibridizasyon (CISH) ayrıca negatifti. Bu verilere dayanarak diffüz büyük B hücreli lenfoma (DLBCL) düşünüldü. Burada taşlı yüzük hücreli bir lenfoma olgusu sunulmuş olup morfolojik ve klinik özelliği literatür eşliğinde tartışılmıştır.

Anahtar Kelimeler: Taşlı Yüzük Hücreli, Lenfoma, Diffüz Büyük B Hücreli Lenfoma, Transplantasyon Sonrası

INTRODUCTION

Signet ring cell morphology consists of cells with transparent cytoplasm and irregular nuclei that are pushed aside. Signet ring cell morphology is seen in many types of cancer such as melanoma (1-4), adenocarcinoma (5-7), mesothelioma (8,9), multiple myeloma (10,11), lymphoma, liposarcoma (7).

SRCL is a very rare morphologic variant of non-Hodgkin's lymphoma. In the literature, this variant is generally considered to be a follicular lymphoma. In some case reports (12, 13), this morphologic appearance is also present in DLBCL, although more rarely. Here, we presented a case of lymphoma with signet ring cell morphology and discussed with the literature.

CASE REPORT

Our case was seventy-six-year-old female patient with a history of chronic kidney disease (renal transplant 12 years ago), type 2 diabetes mellitus, primary hypertension, and a history of total abdominal hysterectomy and bilateral salpingo-oophorectomy due to endometrial carcinoma 20 years ago. A biopsy taken from the skin of the chin 2 years ago was reported as squamous cell carcinoma. Since it was an early stage squamous cell carcinoma, no specific treatment was clinically initiated.

The patient was referred to an external center with complaints of dyspepsia, heartburn and abdominal pain that started 2 years ago. The endoscopic biopsy result was interpreted as chronic inactive atrophic gastritis, intestinal metaplasia and mild to moderate dysplasia. Due to gastrointestinal bleeding, a biopsy performed 1 year ago at an external center revealed gastric adenocarcinoma, tubular type, moderately differentiated. After submucosal dissection, PET/CT showed a 1 cm lymphadenopathy with SUVmax: 8 in the mesenteric fat plane in the descending colon and was interpreted as a metastasis. When the patient returned for follow-up, the March 2024 PET/CT showed a mass lesion with an SUVmax of 15.2 in the jejunal wall and a 4 cm diameter lymphadenopathy with an SUVmax: 21.3 in the mesenteric fat planes, which was interpreted as a metastasis (***Figure 1***). Due to the progressive nature of the patient's disease, a tru-cut biopsy was performed for the diagnosis of lymphadenopathy. A large number of cells with signet ring morphology were observed in the biopsy specimen, and PanCK, CK7, CK20, S100, SMA, vimentin, and calretinin were interpreted as negative by immunohistochemistry. Considering the possibility of a rare SRCL, a lymphoma panel was performed. In the immunohistochemical panel, CD20, PAX5, CD19, Bcl-2 were interpreted as positive and the Ki-67 proliferation index was evaluated as 80% (***Figure 2 A-F***). CD3, CD10, ALK, Cyclin-D1, Bcl-6, MUM-1, CD23, CD21, CD30, Myc were interpreted as negative. CISH performed on the patient was negative for EBER. Based on the morphologic findings, immunohistochemistry, and CISH, the patient was diagnosed with DLBCL. The patient was then referred to in our hematology clinic. Hematology accepted a different primary tumor and initiated the R-CHOP protocol.

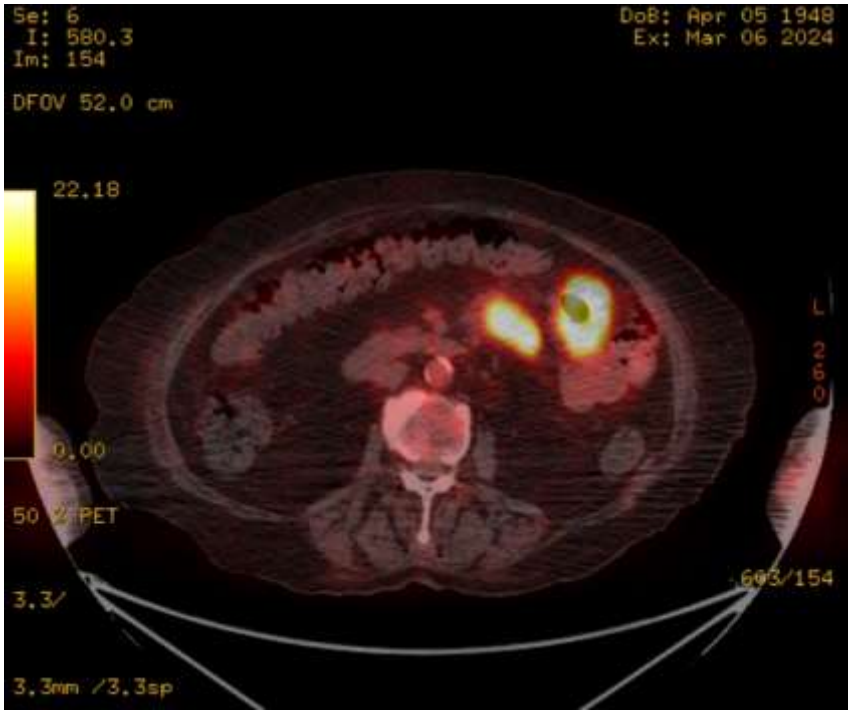

Figure 1. The patient has lymphadenopathies with SUVmax: 21.3 on PET-CT.

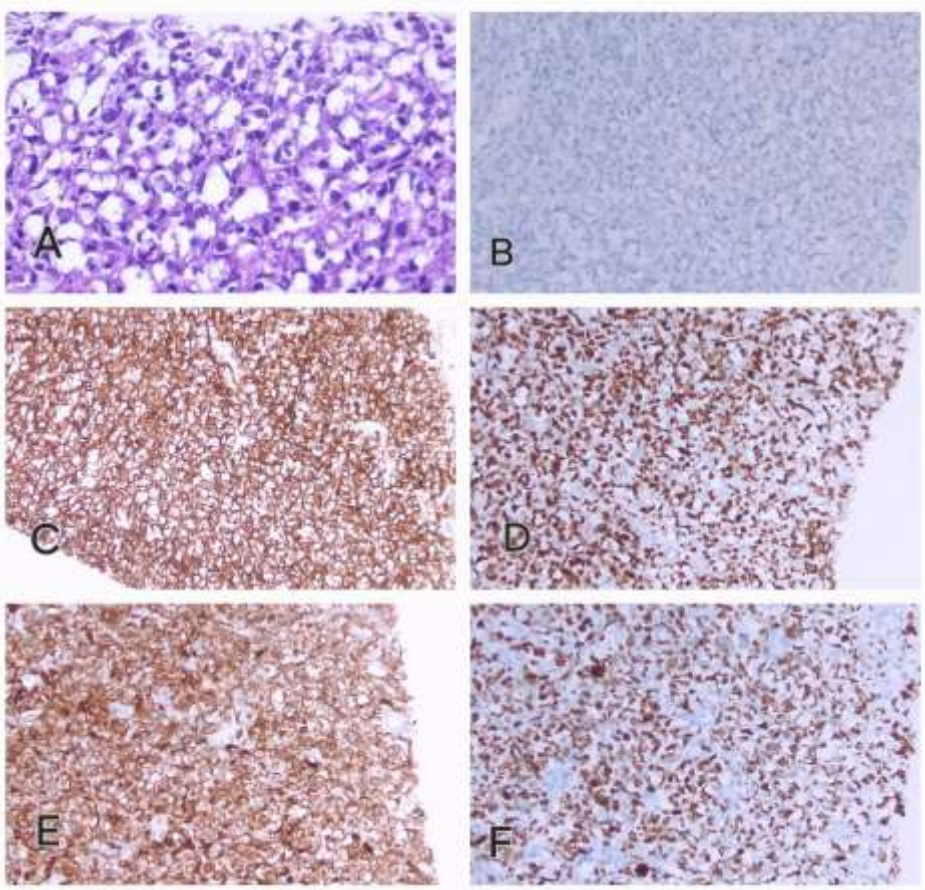

Figure 2 A= High magnification (H&E, ×200) of cells with signet ring cell morphology., B= PanCK-negative in tumor cells (x100), C= CD20 positive in signet ring cells (x100), D= PAX-5 positive in tumor cells (x100), E= Bcl-2 positive in cells with the morphology of a signet ring (x100), F= Ki-67 proliferation index is about 80% (x100).

DISCUSSION

Signet ring cell morphology can be seen in many types of cancer. Although adenocarcinoma is the first to come to mind for malignant lesions of the cell group with this morphology, lymphomas may rarely have this cell morphology and this possibility should be considered.

SRCL has been reported in most cases to belong to the subtypes of non-Hodgkin lymphoma. Diagnoses to date have included follicular lymphoma, but also small lymphocytic lymphoma(14), lymphoplasmacytic lymphoma, MALT-associated marginal zone lymphoma, diffuse large B-cell lymphoma, T-cell lymphoma(15,16), anaplastic large cell lymphoma(17), and plasma cell myeloma(10,11). Signet ring cell lymphoma most commonly arises from the lymph nodes, but there are also cases from extranodal sites such as skin (18), gastrointestinal tract(19), salivary gland, breast(12), central nervous system(20), thyroid(21), and bone marrow(22).

In our case, PanCK negativity showed that the neoplastic cells were not epithelial origin. Immunohistochemical studies for CK7, CK20, S100, SMA, vimentin, and calretinin were performed to exclude other diseases with signet ring cell morphology in the differential diagnosis. When these were negative, immunohistochemical panels for lymphoid cells were ordered, considering that the neoplastic cells could be lymphoid origin. CD3 negativity and CD20 positivity suggested that the neoplastic cells were B cell origin. No Reed-Sternberg cells in the tumor and MUM-1 or CD30 negativity excluded the possibility of Hodgkin lymphoma.The high Ki-67 proliferation index suggested a high-grade lymphoma. Diffuse infiltration of neoplastic cells and negativity for follicular dendritic cell markers such as CD21 and CD23 excluded posibilty of follicular lymphoma. Cyclin-D1 and Sox11 negativity ruled out mantle cell lymphoma. The diffuse infiltration pattern in neoplastic cells, high Ki-67 proliferation index, negativity of EBV and follicular dendritic cell markers, rapid clinic progression were consistent with DLBCL. ALK and Myc were found to be negative.

There are less than 100 cases of lymphoma with signet ring cell morphology in the literature, and very few of these cases are DLBCL. The characteristics of lymphoma cases in the literature are summarized in the table (***Table 1***).

Table 1. Signet Ring Cell Lymphoma - List of case reports and case series. DLBCL=Diffuse Large B-Cell Lymphoma, LN=Lymph Node.

Reference	Number of cases	Diagnosis	Anatomic Location
Kim et al.[7]	7 cases	Follicular Lymphoma	2 Mesenteric LN, 1 Submaxillary LN, 1 Post Auricular LN, 1 Supraclavicular LN, 1 Inguinal LN
Van den Tweel et al.[23]	3 cases	Follicular Lymphoma	1 Mesenteric LN, 1 Cervical LN, 1 Pelvic LN
Moir et al.[24]	1 case	Follicular Lymphoma	Inguinal LN
Iossifides et al.[25]	1 case	Follicular Lymphoma	Supraclavicular LN
Harris et al.[26]	1 case	Follicular Lymphoma	Femoral LN
Pileri et al.[27]	1 case	Follicular Lymphoma	Axillary LN
Spagnolo et al.[28]	3 cases	Follicular Lymphoma	
Navas-Palacios[29]	3 cases	Follicular Lymphoma	1 Retroperitoneal LN, 1 Submandibular LN, 1 Supraclavicular LN
Vernon et al.[30]	1 case	Lymphocytic Lymphoma	Pelvic mass
Silberman et al.[31]	1 case	Follicular Lymphoma	Cervical LN
Allevato et al.[21]	1 case	Follicular Lymphoma	Thyroid
Weiss et al.[32]	2 cases	T-cell Lymphoma	Skin
Grogan et al.[33]	1 case	T-cell Lymphoma	Skin
Hanna et al.[34]	1 case	Follicular Lymphoma	Skin
Manivel-Rodriguez et al.[35]	1 case	B-cell Lymphoma (Not specified)	Cervical LN
Lee et al.[36]	1 case	Burkitt's-like Lymphoma	Cervical LN
Uccini et al.[37]	1 case	Follicular Lymphoma	Axillary LN
Pappas et al.[20]	1 case	Not specified	Brain
Cross et al.[15]	1 case	T-cell Lymphoma	Skin
Bellas et al.[16]	1 case	T-cell Lymphoma	Inguinal LN
Vaillant et al.[38]	1 case	T-cell Lymphoma	Skin
Talbot et al.[39]	1 case	DLBCL	Bone marrow
Mc Cluggage et al.[22]	1 case	High Grade Centroblastic Lymphoma	Bone marrow
Yu et al.[40]	1 case	DLBCL with Follicular Lymphoma	Mesenteric Mass
Zamboni et al.[3]	26 cases	MALT Lymphoma	Gastric associated Lymphoid Tissue
Fallini et al.[17]	1 case	ALCL	Supraclavicular LN
Cangiarella et al.[41]	1 case	Follicular Lymphoma	Paraaortic Mass
Ramnani et al.[14]	1 case	CLL/SLL	Axillary LN
Jaeger et al.[42]	1 case	DLBCL	Mandible
Chim et al.[43]	1 case	Follicular Lymphoma	Bone Marrow
Moran et al.[18]	3 cases	Cutaneous B Cell Lymphoma	Skin
Masir et al.[44]	1 case	Follicular Lymphoma	Inguinal LN
Nakamura et al.[45]	1 case	Immunoblastic Post Germinal Center	Cervical LN
Nagasaki et al.[46]	1 case	Follicular Lymphoma	Cervical LN
Coffing and Lim[47]	1 case	Follicular Lymphoma	Cervical LN
Sarro et al.[48]	1 case	Follicular Lymphoma	Uterine
Basir et al.[19]	1 case	Follicular Lymphoma	Small Bowel
Wu et al.[49]	3 cases	Follicular Lymphoma	1 Inguinal LN, 1 Mesenteric LN, 1 Peripancreatic Mass
Krause et al.[50]	2 cases	Follicular Lymphoma	1 Inguinal LN, 1 Mesenteric LN
Wang et al.[51]	7 cases	5 Follicular Lymphomas,	1 Mesenteric LN,

		1 DLBCL Follicular Center Cell Origin, 1 B-cell Lymphoma with Plasmocytoid features low grade.	2 Retroperitoneal LN, 1 11th Vertebra, 1 Inguinal LN, 1 Lung, Hilar Mass 1 Inferior Auricular Mass
Bogusz et al.[52]	1 case	DLBCL with Follicular Lymphoma origin	Femoral LN
Mulay et al.[53]	1 case	DLBCL	Orbital Mass
Venkateshwar et al.[54]	1 case	B-cell Lymphoma (Not Specified)	Gastric Tissue
Murakami et al.[55]	1 case	MALT Lymphoma	Omentum
Machado et al.[56]	1 case	DLBCL with Marginal Zone Lymphoma	Supraclavicular LN
Sakai et al.[13]	1 case	DLBCL	Gastric Tissue
Dardick et al.[57]	1 case	DLBCL	Tonsil
Zhang et al.[12]	7 cases	4 Follicular Lymphomas, 1 Germinal Center DLBCL, 1 DLBCL with Follicular Lymphoma, 1 DLBCL with Marginal Zone Lymphoma	1 Submandibular LN, 2 Not location specified LNs, 1 Thigh Mass, 1 Breast, 1 Parotid LN, 1 Tonsil
Gore et al.[58]	1 case	Follicular Lymphoma	Cervical LN
Patel et al.[59]	1 case	Germinal Center DLBCL with minor Follicular Lymphoma	Inguinal LN
Mishra et al.[60]	1 case	Follicular Lymphoma	Presacral mass
Younes et al.[61]	1 case	Non-Germinal Center DLBCL	Thigh/Groin Mass
Zhang and Min et al.[62]	1 case	DLBCL	Breast

In these case series, a history of colon adenocarcinoma (21), early-stage gastric adenocarcinoma (55), skin cancer (subtype not specified) (40), renal failure (no history of renal transplantation) (13, 44), and of immunosuppression (one under steroid treatment, two HIV-positive patients) (22, 36, 54) were previously reported. We consider our case may develop with the effect of immunosuppression secondary to transplantation.

Post-transplant lymphoproliferative disorders (PTLDs) are lymphoid or plasmacytic proliferations that develop as a result of immunosuppression in a solid organ or stem cell allograft recipient(63). PTLDs are further categorized by the lymphoma they resemble, such as monomorphic and classical types of Hodgkin's lymphoma, as seen in non-immunosuppressed patients. EBV-negative PTLDs are more common in adults, present with transplantation, and are more likely to be monomorphic than EBV-positive cases. The etiology of EBV-negative PTLDs is unknown. Some may be due to EBV that is no longer detectable, some to other unknown viruses, and some to the transplant itself.

Monomorphic PTLDs are post-transplant lymphoproliferative disorders recognized in immunocompetent hosts that meet the criteria for either B-cell or T/NK-cell neoplasms. Monomorphic B-cell PTLDs are B-lymphocytic or plasmacytic proliferations with monoclonal transformation that meet the criteria for DLBCL or, less commonly, Burkitt lymphoma or plasma cell neoplasm. The clinical picture of these cases is generally similar to that of the lymphomas or plasma cell neoplasms. On microscopic examination, monomorphic B-PTLDs often fulfill the traditional criteria for diffuse large B-cell lymphoma. EBV-negative cases are more likely to have a germinal center-type phenotype. Consistent with phenotypic findings, EBV+ PTLDs are of the activated B-cell type, but 45% of EBV-negative cases are of the germinal center type. Furthermore, EBV-negative monomorphic PTLDs often lack expression of the cyclin-dependent kinase inhibitor CDKN2A (p16INK4a). In our case, the patient was a transplant recipient and immunosuppressed. The patient has monomorphic cells and is classified as EBV-negative PTLD based on negative EBER studies and a diagnosis of DLBCL in the B-cell population.

As a result, in small biopsies, the possibility of lymphoma should be considered in panCK-negative tumors with signet ring cell morphology.

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