Case Report

A Case of Diffuse Large B Cell Lymphoma with Unusual Extranodal Breast, Brain İnvolvement And Autoimmune Hemolytic Anemia: Clinical and Radiological Presentations

Ekstranodal Meme, Beyin Tutulumu ve Otoimmun Hemolitik Anemisi Olan Alışılmadık Bir Diffüz Büyük B Hücreli Lenfoma Olgusu: Klinik ve Radyolojik Prezentasyonlar

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ABSTRACT

Diffuse large B cell lymphoma (DLBCL) is a heterogeneous tumor group consisting of large and transformed B cells that make up 30-40% of all non-Hodgkin lymphomas. Extranodal breast involvement of DLBCL is very rare. We present a case of breast derived DLBCL who presented with coombs positive hemolytic anemia and neurological symptoms. A 54-year-old female patient was admitted to the emergency department with complaints of weakness and palpitations. Hemolytic anemia was considered in the foreground in the patient who did not show atypical cells in the peripheral blood smear. There were an increased fluorodexiglucose uptake detected in the middle and upper quadrant of the left breast in positron emission to-mography–computed tomography. She had impaired consciousness, her speech was dysarth-ric, orientation restricted, muscular strength and sensory examination was natural, and there was no pathological reflex. Cranial magnetic resonance imaging revealed a T2 and FLAIR hyperintense lesion at the pons level, which did not correspond to apparent diffusion coefficient, and had an expansile feature that restricted the diffusion. In the tru-cut biopsy of the breast associated mass, CD20 (+), PAX5 (+), CD3 (-), CD5 (-) large b-cell lymphoma infil-tration was observed. The patient's need for transfusion regressed after a course of R-CHOP and MTX treatment. The patient's neurological symptoms and radiological findings im-proved and regressed completely after one course of therapy. This patient makes a signifi-cant contribution to the literature in terms of referring with neurological symptoms, getting a diagnosis of DLBCL from the breast associated mass during the investigation of autoim-mune hemolytic anemia etiology and treatment preference.

Keywords: Diffuse large B cell lymphoma, extranodal involvement, hemolytic anemia, prognosis

ÖZET

Diffüz büyük B hücreli lenfoma (DBBHL), tüm Hodgkin dışı lenfomaların %30-40'ını oluşturan büyük ve transforme B hücrelerinden oluşan heterojen bir tümör grubudur. DBBHL'nin ekstranodal meme tutulumu oldukça nadirdir. Coombs pozitif hemolitik anemi ve nörolojik semptomlarla başvuran, meme

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kaynaklı bir DBBHL olgusunu sunmaktayız. Elli dört yaşında kadın hasta acil servise halsizlik ve çarpıntı şikayetleri ile başvurdu. Periferik kan yaymasında atipik hücre görülmeyen hastada hemolitik anemi düşünüldü. Pozitron emisyon tomografi-bilgisayarlı tomografide sol meme orta ve üst kadranda florodeksiglikoz tutulumunda artış saptandı. Bilinci bozuk, konuşması dizartrik, oryantasyon kısıtlı, kas kuvveti ve duyu ise muayenesi doğaldı, patolojik refleksi yoktu. Kranial manyetik rezonans görüntülemede pons seviyesinde difüzyonu kısıtlayan ekspansil özellikte T2 ve FLAIR hiperintens lezyon saptandı. Meme ilişkili kitlenin tru-cut biyopsisinde CD20(+), PAX5(+), CD3(-), CD5(-) büyük B hücreli lenfoma infiltrasyonu görüldü. Bir kür R-CHOP ve MTX tedavisi sonrası hastanın transfüzyon ihtiyacı geriledi. Nörolojik semptomları ve radyolojik bulguları bir kür tedaviden sonra tamamen düzeldi. Bu hasta, nörolojik semptomlarla başvurması, otoimmun hemolitik anemi etiyolojisinin araştırılması sırasında meme ilişkili kitleden DBBHL tanısı alması ve tedavi tercihi açısından literatüre önemli bir katkı sağlamaktadır.

Anahtar Kelimeler: Diffüz büyük B hücreli lenfoma, ekstranodal tutulum, hemolitik anemi, prognoz

Introduction

Non-Hodgkin lymphoma (NHL) ranks first among all hematological malignancies. Diffuse large B cell lymphoma (DLBCL) is a heterogeneous tumor group consisting of large and transformed B cells that make up 30-40% of all NHL [1]. Its incidence increases with age, and the median age at diagnosis is 64 years old. It is more common in men and 55% of the patients are male [2, 3]. It can occur de novo or histologically transformed from indolent lymphomas. The disease typically pre-sents as a rapidly growing nodal or extranodal mass associated with systemic symptoms [4].

One of the most common extranodal involvement sites for DLBCL is central nervous system (CNS) involvement. Extra-nodal breast involvement of DLBCL is very rare. It accounts for 0.5% of all NHLs and 2% of extranodal lymphomas [5]. However, even if lymphoma is the most common hematological malignancy affecting the breast, it accounts for only about 0.04% to 0.7% of all breast cancer cases, and this rare involvement appears to be associated with very few lym-phoid tissues in the breast. It is often confused with breast-derived solid malignancies due to both clinical and imaging findings [6].

CNS involvement is seen in one third of NHL patients. Involvement can be considered as leptomeningeal, epidural and intra-parenchymal metastasis. CNS involvement of lymphomas may present in many different clinics. The most common neurological complication of NHL is leptomeningeal disease that develops due to lymphoma infiltration of the leptomeninges. It can manifest with different symptoms and signs such as headache, nausea, communicating hydrocephalus, cranial neuropathy (for example, hearing loss, imbalance, dizziness, dysphagia, and hoarseness), limb weakness, paresthesia and pain. On magnetic resonance imaging (MRI), focal and diffuse leptomeningeal contrast involvement, sub-arachnoid nodule or enlargement of the intradural filum terminale can be seen [7]. Primary CNS lymphomas mostly present with single and all paren-chymal lesions, systemic involvement is not expected due to the blood brain barrier; second-ary CNS lymphomas are mostly characterized by leptomeningeal involvement and multiple parenchymal lesions can be detected [8].

In autoimmune hemolytic anemia (AIHA), autoantibodies are produced in abnormal amounts as a result of hyperfunction of B lymphocytes and complement are absorbed by erythro-cytes. As a result, it is destroyed rapidly after antigen-antibody reaction. While there is no role of any disease in primary AIHA etiology, secondary AIHA causes include lymphoproliferative dis-eases, viruses

such as Ebstein-barr virus, measles or cytomegalovirus, leukemias, thymoma and colon cancers. The incidence of AIHA / NHL is extremely rare [9].

In this case presentation, we present a case of breast derived DLBCL who presented with coombs positive hemolytic anemia and neurological symptoms.

Case Presentation

A 54-year-old female patient was admitted to the emergency department with complaints of weakness, shortness of breath and palpitations. In the systemic examination of the patient, whose medical history was unremarkable, her body temperature was 38.6 C, blood pressure 120/86 mmHg, heart rate 96 / min and respiratory rate was 16 / min. In her neurological exami-nation, she had impaired consciousness, her speech was dysarthric, orientation restricted, muscular strength and sensory examination was natural, and there was no pathological reflex. In the extended biochemical analysis of the patient, hemoglobin was 5.3 gr/dl, leukocyte: 5510/mm^3, neutrophil: 3710/mm^3, thrombo-cyte: 140,000 / mm^3, lactate dehydrogenase (LDH): 1588 IU / L, haptoglobulin: 1 mg / dl (normal range: 30-200 mg / dl), total bilirubin: 1.26 mg /dl, indirect bilirubin: 0.86 mg / dl, and corrected reticulocyte resulted in 5.9%. Direct and indirect coombs tests were resulted as positive; AIHA was considered in the foreground in the patient who did not show atypical cells in the peripheral blood smear. There was no focus for infec-tion that could cause fever, and there was no growth in the blood and urine cultures.

The antinuclear antibody test (ANA) and extractable nuclear antigen (ENA) profile (RNP, Sm, SS-A, SS-B, Scl-70, Jo-1, anti-histone, anti-nucleosome) for possible underlying collagen tissue and lympho-proliferative diseases were found to be negative. In thoracic and abdominal computed tomography (CT), the spleen as 137 mm in size, reactive lymphadenopathies in the paraaortic and bilateral inguinal areas, and thickening of the skin and subcutaneous areas in both breast tissues were detected. There were also an increased fluorodexiglucose (FDG) uptake detect-ed in the middle (sudmax: 7.8) and upper quadrant (sudmax: 8.4) of the left breast in positron emission tomography–computed tomography (PET / CT) (Figure 1), and 6 cm heterogeneous contrast enhancement evaluated as breast imaging reporting and data system (BI-RADS) 4A in breast magnetic resonance (MRI) (Figure 2).

A bone marrow biopsy was performed by investigating the etiology of anemia. As a result of biopsy, megakaryocytes without significant clustering and dysplasia were interpreted as hypercellular bone marrow with mild reticulin fiber increase and no blast increase.

Cranial MRI revealed a T2 and FLAIR hyperintense lesion at the pons level, which did not correspond to apparent diffusion coefficient (ADC), and had an expansile feature that restricted the diffusion (Figure 3.A). In addition, a non-contrast appearance was observed, consistent with leptomeningeal thickening (Figure 4.A). Glucose was 78 mg / dL and protein was 18 g/L in the CSF sampling performed on the patient, and no cells were observed in direct examination. CSF flow examination was normal.

In the tru-cut biopsy of the breast associated mass, CD20 (+), PAX5 (+), CD3 (-), CD5 (-) large b-cell lymphoma infiltration was observed (Figure 5a. and 5b) In the second bone marrow biopsy performed for possible infiltration of lymphoma, large b-cell lymphoid infiltration in the interstitial pattern, showing strong CD20 and weak CD5 expression was also revealed (Figure 6). No cytogenetic or molecular features were revealed in the fluorescence in situ

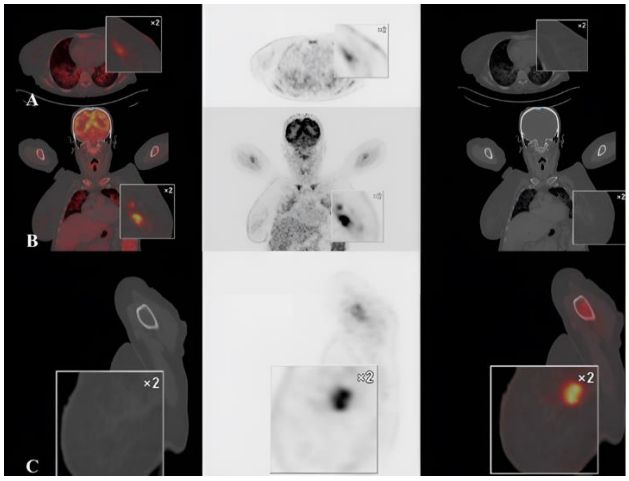

Figure 1.: Positron emission tomography–computed tomography (PET / CT) sections of patient: A. Axial (transverse), B. Coronal, C. Sagittal planes

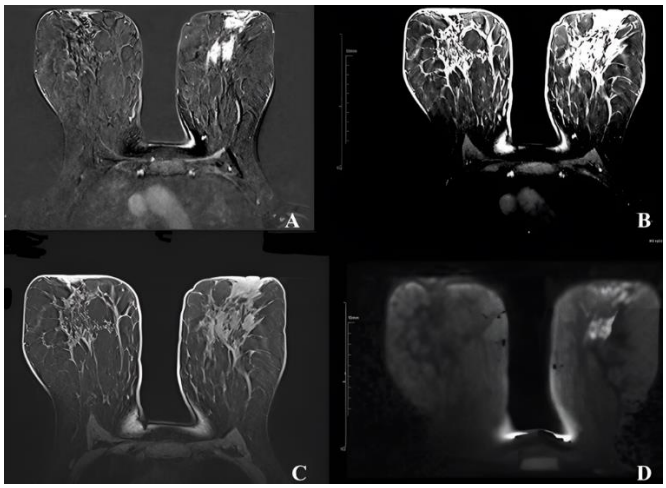

Figure 2.: Magnetic resonance (MRI) sections of breast associated mass: A. T1-weighted dynamic contrast-enhanced, B. Contrast-enhanced T1-weighted fat-suppressed subtraction, C. T1-weighted fat-saturated pre-contrast, D. Diffusion-weighted (DWI)

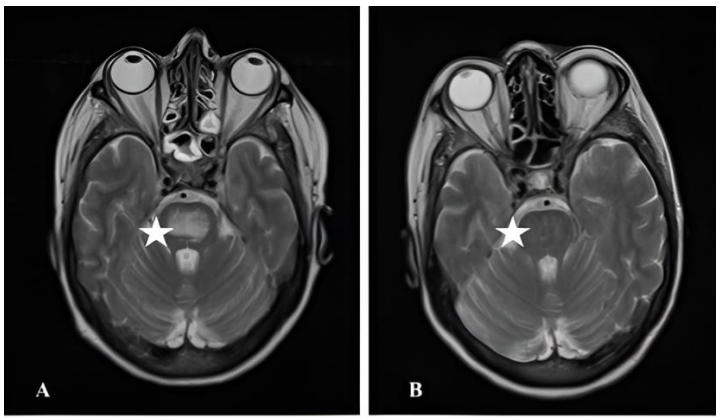

Figure 3: Hyperintense lesion on axial T2W MRI at pontin level. A.: Initial diagnosis, B.: After one course of therapy

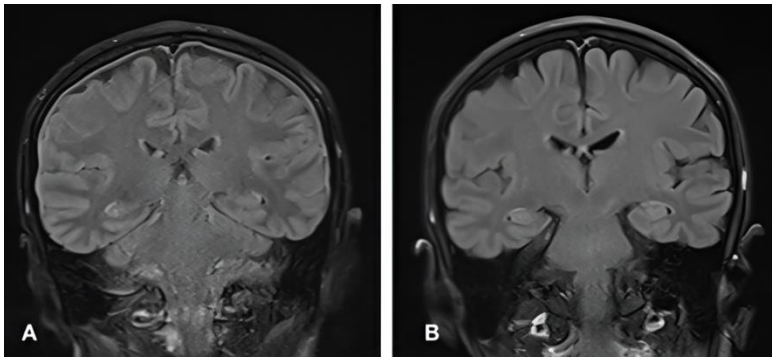

Figure 4: Leptomeningeal thickening on MRI. A.: Initial diagnosis, B.: After one course of therapy

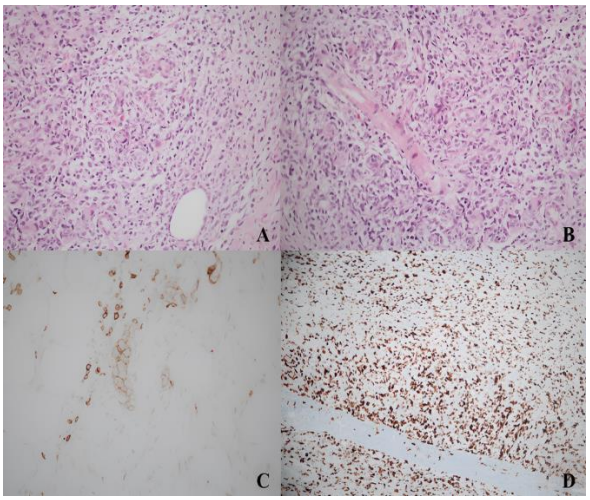

Figure 5a: Tru-cut biopsy sections of the breast associated mass: A. and B. Hematoxylin & eosin staining, C. CD-5 antibody staining, D. KI-67 staining

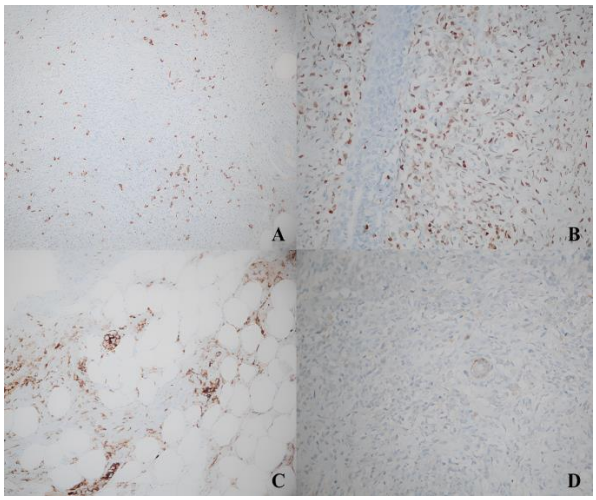

Figure 5b: Tru-cut biopsy sections of the breast associated mass: A. CD-3 staining, B. MUM-1 staining, C. CD-20 staining, D. CD-10 staining

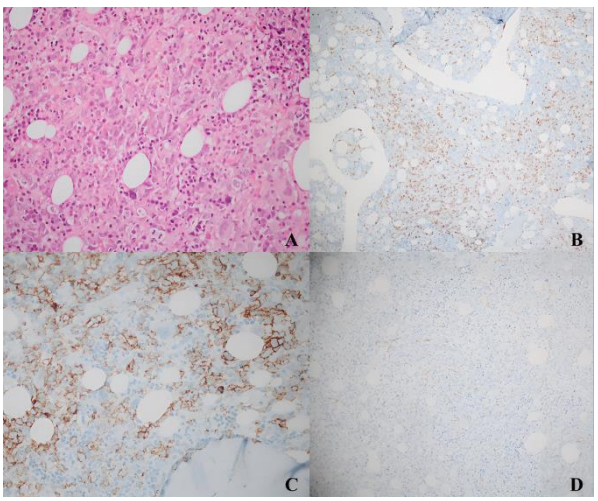

Figure 6: Bone marrow biopsy sections: A. Hematoxylin & eosin staining, B. MUM-1 staining, C. CD-20 staining, D. CD-34 staining

hybridization (FISH) analysis performed on both biopsy specimen and bone marrow samples.

Neurological clinical findings of the patient were considered as a result of neurological involvement of DLBCL. Methylprednisolone at a dose of 1 mg/kg was initiated due to hemolytic anemia and a treatment plan was made such as follows: Rituximab 375 mg/ m^2, cyclophosphamide 750 mg/m2, adriamycin 50 mg/m^2, vincristine 1,4 mg/m^2, prednisolone 100 mg (R-CHOP) every 21 days and on the 14th day, methotrexate (MTX) 3 gr/m^2, every 21 days. The patient's need for transfusion regressed after a course of R-CHOP and MTX treatment. The patient's neurological symptoms and radiological findings improved and regressed completely after one course of therapy (Figure 3.B., Figure 4.B.).

Discussion

Our case contributes significantly to the literature with its three features: AIHA, DLBCL diagnosed by a biopsy from breast associated mass, and CNS involvement associated or parane-oplastic neurological symptoms.

The incidence of AIHA and NHL is extremely rare. In a study by Ji-cheng Zhou et al., a total of 2204 NHL patients and 204 AIHA patients were screened between 2009 and 2018. AIHA and NHL association was observed in 20 of them. AIHA was detected in 0.91% of NHL patients, while NHL was detected in 9.8% of AIHA patients. Fourteen of the cases were male, 6 were fe-male and, the median age was 60 years old. All patients were stage 3-4 NHL. Lymphoma subtype with the highest incidence of AIHA was angioimmunoblastic t-cell lymphoma (AITL) with 7.31%, while marginal zone b-cell lymphoma was 6.25%, B cell lymphoma 4.25%, chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL / SLL) 2.5% and mantle cell lymphoma 2.3% [9]. In another study, an AIHA serie was reported in patients diagnosed with splenic marginal zone lymphoma [10]. A total of 13 patients were complicated with AIHA in total and all patients died during follow-up. Patients with AIHA were found to have significantly ($p < 0.001$) shorter survival than those without AIHA [10]. In a study from 2000, a total of 16 patients with a diagnosis of NHL were found to be complicated with AIHA [11]. The treatment response for NHL was found to be significantly lower in this group, patients with NHL who did not develop AIHA had longer overall and median survival compared to the NHL/AIHA subgroup [11]. In another French multicenter retrospective cohort, all autoimmune manifestations were revealed in patients diagnosed with lymphoma and they were defined frequently together with CLL and DLBCL, while AIHA was the most common cause of autoimmune cytopenias [12]. The presence of autoimmune phenomena was associated with lower survival compared to non-autoimmune feature group when examining entire cohort. In general, it has been shown that the presence of AIHA or any autoimmune phe-nomenon has negative effects on treatment response and survival in patients diagnosed with lym-phoma. Although AIHA/ NHL coexisting is a rare condition, AIHA was detected as the first sign of the disease in our NHL patient.

Clinically, primary breast lymphomas manifest as painless palpable masses. Its distinction from other carcinomas is not clear radiologically. More than 95% of the primary breast lymphoma cases are B cell non hodgkin lymphomas, and 60% to 85% of them are DLBCL. Follicular lym-phoma, mucosa-associated lymphoma or marginal zone lymphoma are seen less common. Since these lymphomas are rare, there is no common approach to treatment. However, current treat-ments such as chemotherapy, immunotherapy and radiotherapy provide well designed disease con-trol in these patients. Average life

expectancy in 80% of the patients is 5 years [13].

It is difficult to differentiate breast lymphomas from benign and malignant breast diseases radiologically and clinically. However, differentiation of breast lymphomas from other malignan-cies (such as invasive breast cancer, inflammatory breast cancer or metastasis) is very important in terms of treatment preference. It is very important to know whether there is a systemic in-volvement. If the patient has systemic lymphoma, the risk of lymphoma involvement of breast increases.6 There was no finding in favor of systemic involvement in the different imaging results of our patient; the presence of only breast involvement was the most important clinical challenge.

Although DLBCL and neurological involvement has been widely reported, it is a difficult condition to diagnose. It often occurs as leptomeningeal involvement, intracranial and spinal me-tastasis, lymphomatosis cerebri and peripheral nervous system involvement causes different radi-ological appearances associated with these conditions.[7] Abe et al. evaluated cranial MRIs of 33 patients with intravascular DLBCL and found hyperintense lesions in the pons as the most com-mon finding (n = 19 (57.6%); leptomeningeal thickening was observed in 12.1% of cases [14]. Kawata et al. presented also a DLBCL case with central pontine myelinosis [15]. In our case, a lesion in pons and leptomeningeal thickening were observed together. However, flow cytometry and pathology of the patient's CSF sampling did not show any findings compatible with the DLBCL involvement. Also, sodium values measured in terms of central pontine myelinosis were normal during the clinical follow-up. High-dose systemic methotrexate ($3mg/m^2$) treatment was also administered, considering intracranial involvement, since it could not be differentiated in terms of etiology. Additionally, in our patient, the fact that a score that could objectively doc-ument the patient's neurological status before and after treatment was not recorded was an important limitation point.

As a result, our patient makes a significant contribution to the literature in terms of refer-ring with neurological symptoms, getting a diagnosis of DLBCL from the breast associated mass during the investigation of AIHA etiology and treatment preference. Detailed screening of differ-ent organs and systems is of great importance in DLBCL cases where bone marrow biopsy is nor-mal and difficult to diagnose in the early period.

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