Case Report

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Atypic Primary Ovarian Lymphoma Presenting with Hypercalcemia: A Rare Case Report

Hiperkalsemi ile Başvuran Nadir Bir Atipik Over Lenfoma Olgusu

Ezgi ŞAHİN[1], Faruk KARANDERE[1], Eda KÜÇÜK[1], Emine GÜLTÜRK[2], Şengul Aydın YOLDEMIR[1], Gülçin YEGEN[3]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of of Internal Medicine, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Hematology, İstanbul, Türkiye
[3]Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pathology, İstanbul, Türkiye

ABSTRACT

Here, we present a rare case of primary ovarian lymphoma with bilateral ovarian involvement, which manifested with malignant hypercalcemia. A 39-year-old female patient presented to our hospital with lower abdominal pain. Hypercalcemia, anemia, and thrombocytopenia were observed during the examinations. Abdominal ultrasound revealed a mass lesion thought to be associated with an abscess or malignancy in both adnexal areas, as well as mass lesions in bilateral ovaries, along with paraaortic and paraaortocaval lymphadenomegaly on abdominal computed tomography (CT). In the positron emission tomography CT examination, increased fluorodeoxyglucose uptake (SUV_{max} ranging between 11.5 and 9.5) was observed in the lesions defined on abdominal CT. Bone marrow biopsy performed for thrombocytopenia was found to be compatible with diffuse large B-cell lymphoma (DLBCL). Although this case demonstrates that hypercalcemia can be observed in the course of DLBCL with bilateral ovarian involvement, which is a rare condition, it is also considered significant as it is inconsistent with most of the hypercalcemia mechanisms associated with malignancies described today.

Keywords: Bilateral ovarian lymphoma, hypercalcemia, non-Hodgkin lymphoma

ÖZ

Burada, malign hiperkalsemi ile başvuran bilateral over tutulumu olan nadir bir primer lenfoma olgusunu sunuyoruz. Otuz dokuz yaşında kadın hasta karın ağrısı şikayeti ile hastanemize başvurmuştur. Muayenesinde hiperkalsemi, anemi ve trombositopeni saptanmıştır. Abdominal ultrasonda ve bilgisayarlı tomografide (BT) bilateral adneksiyal alanda apse veya malignite ile ilişkili olabileceği düşünülen kitle lezyon ve paraaortik ve paraaortakaval alanlarda lenfadenomegali saptanmıştır. Pozitron emisyon tomografisi BT'de Batın BT'de tanımlanan lezyonlarda artmış fluorodeoksiglukoz tutulumu (SUV_{maks} 11,5 ile 9,5 arasında değişmekte) gözlendi. Trombositopeni de olması nedeniyle yapılan kemik iliği biyopsisi bulguları diffüz büyük B-hücreli lenfoma (DBBHL) ile uyumlu bulundu. Bu olgu bilateral over tutulumlu DBBHL seyrinde hiperkalseminin görülebileceğini gösterse de bu nadir bir durumdur; aynı zamanda günümüzde tanımlanan çoğu malignite ile ilişkili hiperkalsemi mekanizması ile uyumsuzluk taşıması nedeniyle de önem arz etmektedir.

Anahtar Kelimeler: Bilateral over lenfoması, hiperkalsemi, Hodgkin dışı lenfoma

Address for Correspondence: Faruk Karandere, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
E-mail: farukkarandere@gmail.com **ORCID ID:** orcid.org/0000-0002-7423-0170

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Introduction

Hypercalcemia is a common condition that can occur in 20% to 30% of patients diagnosed as having malignancy. It can manifest in patients with either solid or hematological malignancies. The most common cancers associated with hypercalcemia are breast, kidney and lung cancers, and multiple myeloma (1,2). The release of parathyroid hormone-related peptide and 1.25 dihydroxyvitamin D (calcitriol) in tumor cells, or osteolytic metastases caused by secreted cytokines are three separate major mechanisms implicated in the development of hypercalcemia due to malignancy.

The mechanism of non-Hodgkin lymphoma (NHL)-associated hypercalcemia is currently not clearly understood. In the literature, cases of NHL presenting with severe hypercalcemia are limited.

While ovarian involvement can be observed in the course of diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma among NHLs, bilateral primary ovarian lymphoma is an extremely rare condition. Cases reported in the literature are limited to a few. In this article, we describe a rare case of DLBCL with bilateral ovarian involvement presenting with hypercalcemia.

Case Report

A 39-year-old female patient with no known history of chronic disease was admitted to the clinic with complaints of pain in the lower abdomen and groin. She had no family history of malignancy. She did not smoke or drink alcohol. Laboratory tests revealed hypercalcemia, normochromic normocytic anemia, thrombocytopenia, elevated creatinine and increased acute phase reactants. Laboratory findings are summarized in Table 1. In the abdominal ultrasound ultrasonography (USG); bilateral kidney size and parenchymal echogenicity was normal. The uterus was normal, but a densely loculated collection area around the uterus with internal soft tissue echoes measuring approximately 81x65x103 mm filling the entire adnexal lodge was detected. In transvaginal USG, it was stated that there were tuboovarian abscesses or bilateral mass lesions suspicious for malignancy, measuring 97x62 mm in the left ovary and 71x57 mm in the right ovary. In the examinations of tumor markers, carcinoembryonic antigen level was: 3.54 µg/L (normal range <3.8) cancer antigen (CA) 15.3 level:11.4 U/mL (normal range <25) CA125 level:134 U/mL (normal range <35). Abdominal computed tomography (CT) performed without contrast due to acute renal failure revealed lesions suggesting abscess or suspicious lesions in terms of malignancy in both adnexal areas, which were of 8x5 cm on

Table 1. Laboratory results

		Normal range			Normal range
Glucose	98 mg/dL	74-106	Ferritin	**1837 µg/L**	10-120
Creatinine	**2.66 mg/dL**	0.5-1	CRP	**212 mg/L**	0-5
AST	62 mg/dL	0-32	Procalcitonine	0.4 ng/mL	<0.5
ALT	23.7 mg/dL	0-33	Sedimentation	**36 mm/sa**	0-20
ALP	91 mg/dL	35-104	Total protein	6.7 mg/dL	6.4-8.3
GGT	18 mg/dL	0-36	Albumin	3.2 mg/dL	3.9-4.9
LDH	**670 mg/dL**	306	PHT related peptide	2 pmol/L	4.9±0.5
Total bilirubin	0.45 mg/dL	<1.2	Magnesium	2.12 mg/dL	1.6-2.6
Direct bilirubin	0.6 mg/dL	0-0.3	Potassium	4.5 mg/dL	3.5-5.1
PTH	**8.04 pg/mL**	15-65	Sodium	136 mg/dL	136-146
25 OH D vitamin	**3.47 µg/L**	20-80	Phosphorus	**4.9 mg/dL**	2.6-4.5
1.25 OH D vitamin	**<5 pg/mL**	19-73	Calcium	**19 mg/dL**	8.6-10
Hemogram					
Hemoglobin	**8 g/dL**	10.8-14.2	Neutrophils	3.51 10^3/uL	1.63-6.96
Hemotocrit	**24.6%**	35-45	Lymphocytes	**0.49 10^3/uL**	1.09-2.99
MCV	81.7 fl	81-96	Monocytes	0.18 10^3/uL	0.24-0.79
Total leucocytes	4.21 10^3/uL	3.7-10.1	Eosinophiles	0.02 10^3/uL	0.03-0.44
Platelet count	**60 10^3/uL**	155-366			
Coagulation					
PT	16.9 sn	11-16	D-dimer	1.92 µg	0-0.5
aPTT	37 sn	24-36	Fibrinogen	**574 mg/dL**	200-400
INR	**1.25**	0.8-1.2			

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, LDH: Lactate dehydrogenase, OH: Hydroxyvitamin, MCV: Mean corpuscular volume, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, PHT: Parathormone, CRP: C-reaktif protein, PTH: Parathyroid hormone

the right side and 7x5 cm on the left side. Lymph nodes in the paraaortic and paraaortocaval spaces, the largest of which was 19x7.5 mm in size at the paraaortic level were detected. Diffuse heterogeneous increases in density, contamination, free fluid densities and hypodense lesions causing irregularities in the cortex were detected in the perihepatic-perisplenic areas and mesenteric fat tissues in the lower abdominal quadrant. No pathology was detected in thorax CT except bilateral 2 cm pleural effusions. Intensely increased fluorodeoxyglucose (FDG) uptake in the 8.5x6.5 cm diameter lesion filling the right adnexal area and the 7x5 cm lesion observed in the left adnexal area in positron emission tomography (PET) CT taken to evaluate for malignancy due to a dirty appearance in the omentum were detected (SUV_{max}: 11.9 and 13 respectively). Increased FDG uptakes in the upper, middle and lower quadrants of the abdomen at the level of areas of diffuse density increase, mostly diffusely focalized in the mesenteric fatty tissues (SUV_{max}: 6.7), in the right and left anterior diaphragmatic areas in the abdomen in prevertebral, paraaortic and aortacaval areas, in multiple lymph nodes (maximum SUV_{max}: 7.9) in the paracaval areas, bilateral common iliac areas, in places conglomerate, the long axis of the larger one reaching 2.5 cm, in the cranial bones, bilateral

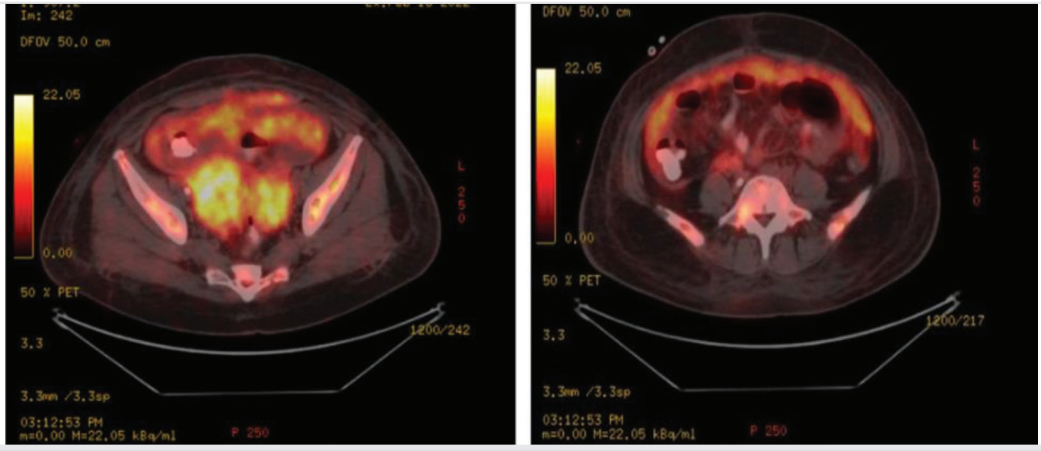

Figure 1. PET-CT images of bilateral ovaries and anterior abdomen-omentum

PET-CT: Positron emission tomography-computed tomography

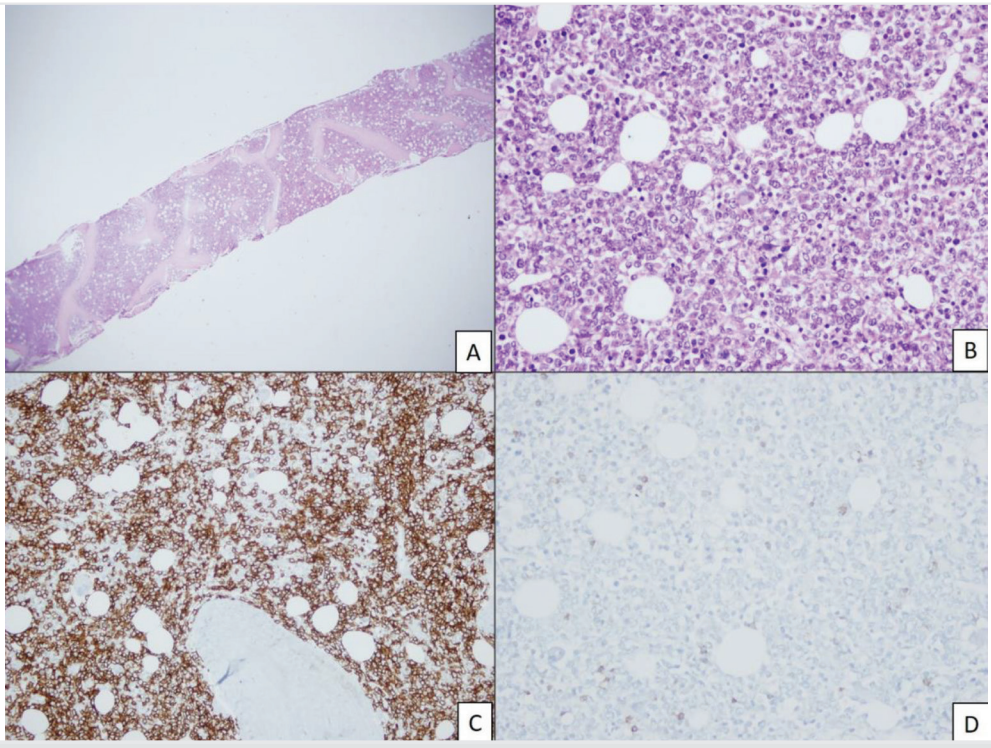

Figure 2. Hypercellular bone marrow biopsy (A, H&E, 2X magnification), revealed diffuse infiltration of neoplastic lymphoid cells (B, H&E, 40X magnification), which were positive for CD20 (C, 20X magnification), and negative for CD3 (D, 20X magnification)

H&E: Hematoxylin and eosin, CD20: Cluster of differentiation 20, CD3: Cluster of differentiation 3

humerus, sternum, bilateral scapulas and clavicles, vertebral colon, ribs, and pelvic bones at the level of extensive lesion areas, mostly lytic, in multiple foci G involvements (maximum SUV_{max}: 9.5) were detected (Figure 1). No pathological findings were observed in gastroscopy and colonoscopy which was performed to screen for gastrointestinal system malignancies. The patient's general condition was poor due to high creatinine level and hypercalcemia. Since she also had bilateral ovarian involvement, needle biopsy was postponed because of the thought that it might cause new implantation. Due to the thrombocytopenia at peripheral blood and bone involvement at PET-CT, bone marrow biopsy was performed. Atypical cells were not observed. Due to the thrombocytopenia and bone involvement at PET-CT, bone marrow biopsy was performed. In the H&E stained sections of the bone marrow, diffuse infiltration characterized by large to medium-sized cells with vesicular nuclei and prominent nucleoli was observed. Immunohistochemically neoplastic cells were cluster of differentiation (CD)20 (+), CD3 (-), CD5 (-), CD30 (-), CD10 (-), BCL-6 (-), multiple myeloma oncogene 1 (-), BCL-2 weak (+), epstein-barr virus-latent membrane protein (EBV-LMP) (-), CD38 (-), c-myc (-), terminal deoxynucleotidyl transferase (TdT) (-), cyclinD-1 (-). Ki-67 proliferation index was evaluated as 60%. The findings were found to be consistent with DLBCL (Figure 2).

Acute renal failure was thought to be due to prerenal renal failure secondary to vasoconstriction and postrenal renal failure due to compression. Despite intensive intravenous (IV) hydration and IV furosemide 40 mg twice a day, the patient's hypercalcemia did not regress. She underwent hemodialysis 6 times due to persistence of hypercalcemia findings. Subsequently, IV 4 mg zoledronic acid was administered once. With the diagnosis of DLBCL with bilateral ovarian, omental and diffuse paraaortic lymph node involvement, the patient was started on rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Under these treatments, the initial calcium level decreased from 19 mg/dL to 10.5. After one cure of standard-dose R-CHOP treatment, the patient developed high fever and shortness of breath during the cytopenia period, and died due to coronavirus disease 2019 pneumonia and sepsis forty days after the initial diagnosis.

Discussion

Primary ovarian lymphoma is one of the rare malignancies of the ovary, constituting 0.5% of NHL and 1.5% of ovarian malignancies (3,4). It is generally thought as a manifestation of systemic disease, most commonly associated with DLBCL and Burkitt lymphoma (5). In our case, similar to the literature, DLBCL was detected as the histological subtype of NHL.

Hypercalcemia is a common condition that can occur in 20% to 30% of patients with malignancy. Hypercalcemia as a paraneoplastic finding has been associated with many malignancies; however, hypercalcemia observed in the context of ovarian cancer is a rare condition. Only a few cases were reported in the literature, so its incidence is not clearly known (1,6,7). In most of these few reported cases, the histologic type was clear cell adenocarcinoma. NHL was detected in one case, where calcitriol levels were found to be high, and hypercalcemia was correlated with it (8-10).

The mechanism of hypercalcemia in NHLs has not been fully elucidated. In one study, calcitriol levels were found to be high in all patients with HL presenting with hypercalcemia and in one-third of patients with NHL. In similar studies, it has been reported that there may be a relationship between hypercalcemia and parathormone associated peptide (PTHrP) levels in some individuals with HL and NHL (11-15). When all these studies are evaluated together, it can be said that hypercalcemia observed in the context of NHL may be associated with an increase in calcitriol or PTHrP. However, in a study by Shallis et al. (15). involving patients with NHL, no relationship was found between calcitriol and PTHrP levels and hypercalcemia. It was reported that hypercalcemia was observed in individuals with aggressive disease, and it was suggested that there might be an association between disease activity and hypercalcemia. In our case, despite the severe hypercalcemia observed, similar to the findings of that study, calcitriol and PTHrP levels were low.

Conclusion

We aimed to contribute to the literature by reporting this rare and interesting DLBCL case, notable for both bilateral ovarian involvement and its presentation with severe hypercalcemia.

Ethics

Informed Consent: Patient consent obtained.

Footnotes

Authorship Contributions

Concept: E.Ş., Ş.A.Y., Design: E.Ş., Ş.A.Y., Data Collection or Processing: E.Ş., F.K., E.K., G.Y., Analysis or Interpretation: E.Ş., F.K., E.G., G.Y., Literature Search: F.K., E.G., Writing: E.Ş., F.K., E.K., E.G., Ş.A.Y., G.Y.

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