CASE REPORT

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Primary adrenal non-Hodgkin's lymphoma: Report of two cases

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Primary adrenal lymphoma is very rare. It is characterized by a high incidence of bilateral adrenal involvement of diffuse large B-cell lymphoma. It can be diagnosed with endocrine evaluation, imaging studies and histopathological examination. We present two cases of primary adrenal lymphoma. One is a 74-year-old female patient with right primary adrenal lymphoma and the other is a 62-year-old male patient with bilateral primary adrenal lymphoma associated with normal adrenal function. In both cases, radiological features led to an initial misdiagnosis. The surgical exploration demonstrated masses invading the retroperitoneal space, and the biopsy revealed diffuse large B-cell lymphoma. In conclusion, primary adrenal lymphoma should be kept in mind in the differential diagnosis of adrenal masses. In cases of suspicious primary adrenal lymphoma, percutaneous computerized tomography- or ultrasonography-guided needle biopsy can help to avoid unnecessary surgeries.

Key words: Primary adrenal lymphoma, adrenal mass, non-Hodgkin lymphoma

Primer adrenal non-Hodgkin lenfoma: İki olgu sunumu

Primer adrenal lenfoma oldukça nadirdir. Diffüz büyük B hücreli lenfoma yüksek sıklıkta bilateral adrenal bez tutulumu ile kendini gösterir. Endokrinolojik değerlendirme, görüntüleme yöntemleri ve histopatolojik inceleme ile tanı konulabilir. Burada, primer adrenal lenfoma tanısı konan iki olgu sunulmaktadır. Normal adrenal fonksiyona sahip birisi sağ adrenal tutulumu olan 74 yaşında kadın hasta, diğeri bilateral adrenal tutulumu olan 62 yaşında erkek hasta. Her iki olguda radyolojik bulgular başlangıç aşamasında yanlış tanıya neden oldu. Cerrahi eksplorasyonda retroperitoneal alana invazyon gösteren kitleler görüldü ve biyopside diffüz büyük B hücreli lenfoma saptandı. Sonuç olarak, primer adrenal lenfoma adrenal kitlelerin ayırıcı tanısında akılda tutulmalıdır. Primer adrenal lenfoma şüphesi olan olgularda bilgisayarlı tomografi veya ultrasonografi eşliğinde yapılacak iğne biyopsisi gereksiz bir cerrahiden sakınmamıza yardımcı olabilir.

Anahtar kelimeler: Primer adrenal lenfoma, adrenal kitle, non-Hodgkin lenfoma

INTRODUCTION

Autopsy studies have revealed that 25% of the patients with non-Hodgkin's lymphoma (NHL) have involvement of the adrenal gland during the course of their disease (1,2). However, NHL originating from the endocrine glands accounts for only 3% of extranodal malignant lymphomas and usually appears only in the thyroid gland. Therefore, primary adrenal malignant lymphoma is rare (3). It is difficult to diagnose adrenal lymphoma before surgery due to its nonspecific clinical appearance and imaging findings. Histologically, diffuse large B-cell lymphoma is the most frequent type of primary adrenal lymphomas (PALs) (4). Most patients with PAL have bilateral disease on admission and most of them have adrenal insufficiency subsequent to destruction of more than 90% of adrenal parenchyma by the disease (5). We present two cases of primary adrenal NHL associated with normal adrenal function.

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CASE REPORTS

Case 1

A 62-year-old man was referred to our hospital with a two-week history of progressive anorexia, nausea, vomiting, weight loss, and fatigue. His medical history was unremarkable. There was no palpable mass in the abdomen. His vital signs were all within normal limits: body weight 61 kg, blood pressure 120/70 mmHg, respiratory rate 20/min, pulse rate 74/min, and body temperature 36.8°C. There was no superficial lymphadenopathy or organomegaly. Initial laboratory findings revealed a normal complete blood count, but erythrocyte sedimentation rate was 59 mm/hour (normal range: 0-20 mm/h) and C-reactive protein (CRP) was 41 mg/L (normal range: 0-6 mg/L). A serum biochemistry profile was all within normal limits except lactate dehydrogenase (LDH) of 306 IU/L (100-240). Further findings including serum cortisol level, urine vanillylmandelic acid and serum aldosterone were all within normal range.

For further diagnosis, abdominal plain computed tomography (CT) was performed and showed bilateral adrenal massive homogeneous soft tissue masses measuring 9.7 cm x 6.1 cm x 5.3 cm on the right and 11.2 cm x 5.6 cm x 6.1 cm on the left. No other abdominal lesions or lymphadenopathy was detected. Since radiological findings were not suggestive of lymphoma, the patient underwent surgery. The masses in both adrenal glands were found to invade the neighboring organs and vessels on operation and could not be resected. Biopsy was obtained from both adrenal glands. Histopathological examination revealed diffuse proliferation of atypical cells with large hyperchromatic nuclei and narrow eosinophilic cytoplasm. Infiltration extended to the adipose tissue. In the immunohistochemical study, tumor cells were positive for leukocyte common antigene (LCA), CD20, CD79a, and Pax-5, while CD3 and CD30 were negative (Figure 1a, 1b). There was no bone marrow involvement. With the absence of any lymphadenopathy elsewhere or any other site of involvement, the patient was accepted and treated as PAL. Before the therapy began, positron emission tomography (PET)-CT was obtained (Figure 1c). He was administered R-CHOP chemotherapy, including rituximab (375 mg/m^2 intravenous [IV]), cyclophosphamide (750 mg/m^2 IV), doxorubicin (50 mg/m^2 IV), and vincristine (1.4 mg/m^2 IV) on day 1, and prednisolone (100 mg P.O.) on days 1-5 every 3 weeks. PET-CT scan performed after administration of six cycles of R-CHOP chemotherapy showed that the previous adrenal masses had nearly disappeared (Figure 1d).

Computed tomography (CT) of the thorax and the abdomen in the ninth month demonstrated multiple masses in both suprarenal glands, left paraaortic, perirenal, perisplenic, and subdiaphragmatic regions, lungs, and liver. Bone marrow aspiration biopsy showed atypical lymphocyte infiltration. The patient received a total of eight cycles of chemotherapy. Since suprarenal failure occurred, the cortisone dose was increased. The patient died of sepsis in the eleventh month.

Case 2

A 74-year-old woman was referred to our hospital with a three-week history of abdominal pain, anorexia, nausea, vomiting, and fatigue. Abdominal ultrasonography (US) showed right hypoechoic adrenal masses. Upper abdominal magnetic resonance imagine (MRI), performed for further diagnosis, showed right adrenal homogeneous soft tissue mass 7 x 7 x 6 cm in size. There were no other abdominal lesions or lymphadenopathy. The patient had a five-year history of diabetes mellitus and underwent coronary by-pass seven years ago. No palpable mass was found in the abdomen. In the initial laboratory investigations, complete blood count was normal, but erythrocyte sedimentation rate was 50 mm/h (normal range: 0–20 mm/h). A serum biochemistry profile was all within normal limits except LDH of 573 IU/L and albumin of 3.17 g/dl. Further findings including serum cortisol level, urine vanillylmandelic acid and serum aldosterone were all within normal ranges.

The mass in the right suprarenal region was found to invade the vena cava inferior, duodenum, aorta, and liver. It was considered unresectable. Biopsy was obtained. Pathological examination revealed NHL (diffuse B-cell lymphoma with CD20 positivity) (Figure 2a, 2b). Thoracic CT scan did not show any lymph nodes. Bone marrow aspiration biopsy eliminated a secondary lymphoma. Before the therapy began, PET-CT images were obtained (Figure 2c). She received R-CHOP chemotherapy, including rituximab (375 mg/m^2 IV), cyclophosphamide (750 mg/m^2 IV), doxorubicin (50 mg/m^2 IV), and vincristine (1.4 mg/m^2 IV) on day 1, and prednisolone (100 mg P.O.) on days 1-5 every 3 weeks. After six cycles of R-CHOP chemotherapy were completed, there was no evidence of tumor on follow-up fluorodeoxyglucose (FDG)-PET scans (Fi-

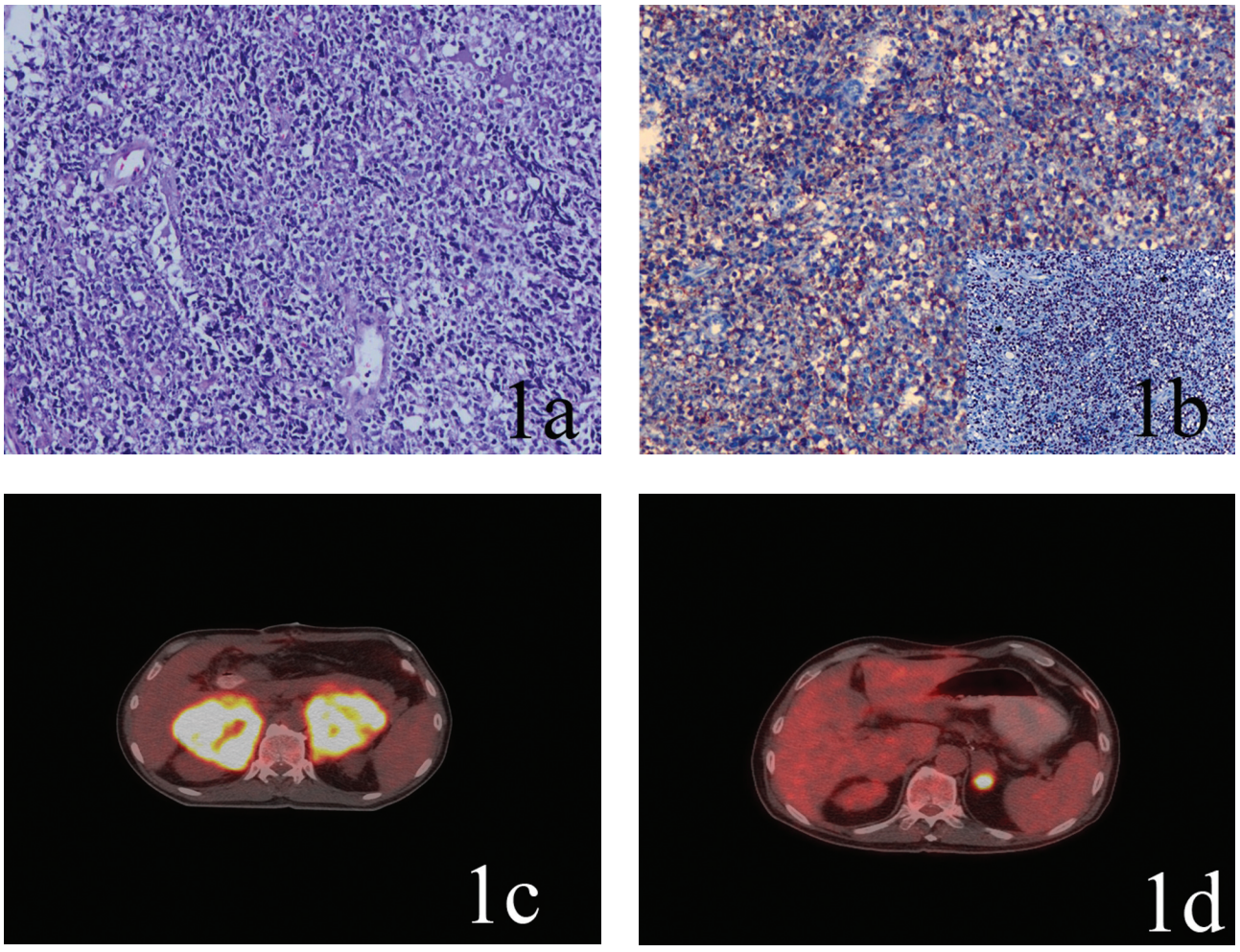

Figure 1a. Diffuse infiltration of large lymphocytes showing small foci of crash artefact (HE x100). **1b.** Immunohistochemical membranous CD20 positivity (main frame) and nuclear Pax-5 positivity (inset) (CD20 x100, Pax-5 x100). **1c.** PET-CT obtained before the chemotherapy began. **1d.** PET-CT obtained after 6 cycles of the chemotherapy were completed.

gure 2d). To date, the patient has been followed regularly in our outpatient clinic for the past 10 months, with no evidence of tumor recurrence.

DISCUSSION

Primary adrenal non-Hodgkin's lymphoma (PAL) is a rare neoplastic disease, and there have been approximately 116 reports about it in the literature so far (4). It has a very poor prognosis, clinical features and radiological/laboratory investigations may not facilitate a firm diagnosis of the disease, and there is no clear treatment protocol. Although features of PAL have not been described well, it usually presents with bilateral, large masses, sometimes accompanied by adrenal insufficiency or hypercalcemia. The disease most frequently affects older men. In fact, the mean age at diagnosis is 68 years and the male-to-female ratio is 2.2:1. Among clinical symptoms of PAL are fever, weight loss, local pain, and symptoms of adrenal insufficiency (6). Immune dysfunction may predispose to PAL in some patients (7). Wang et al. (8), in their review of 55 PAL patients, showed that 8 (15%) had a concurrent or past history of carcinoma, 2 (4%) had human immunodeficiency virus (HIV) infection, and 7 (13%) had concomitant autoimmune disease. They also noted that the most frequent type of PAL is diffuse large B-cell on histological examination (8).

The increase in the use of US, CT and MRI has resulted in a large number of incidentally discovered adrenal masses. Therefore, differentiation of benign from malignant adrenal masses and diagnosis of PAL during its early stages are of importance. Although imaging modalities help in the diagnosis of adrenal masses, making a firm diagnosis

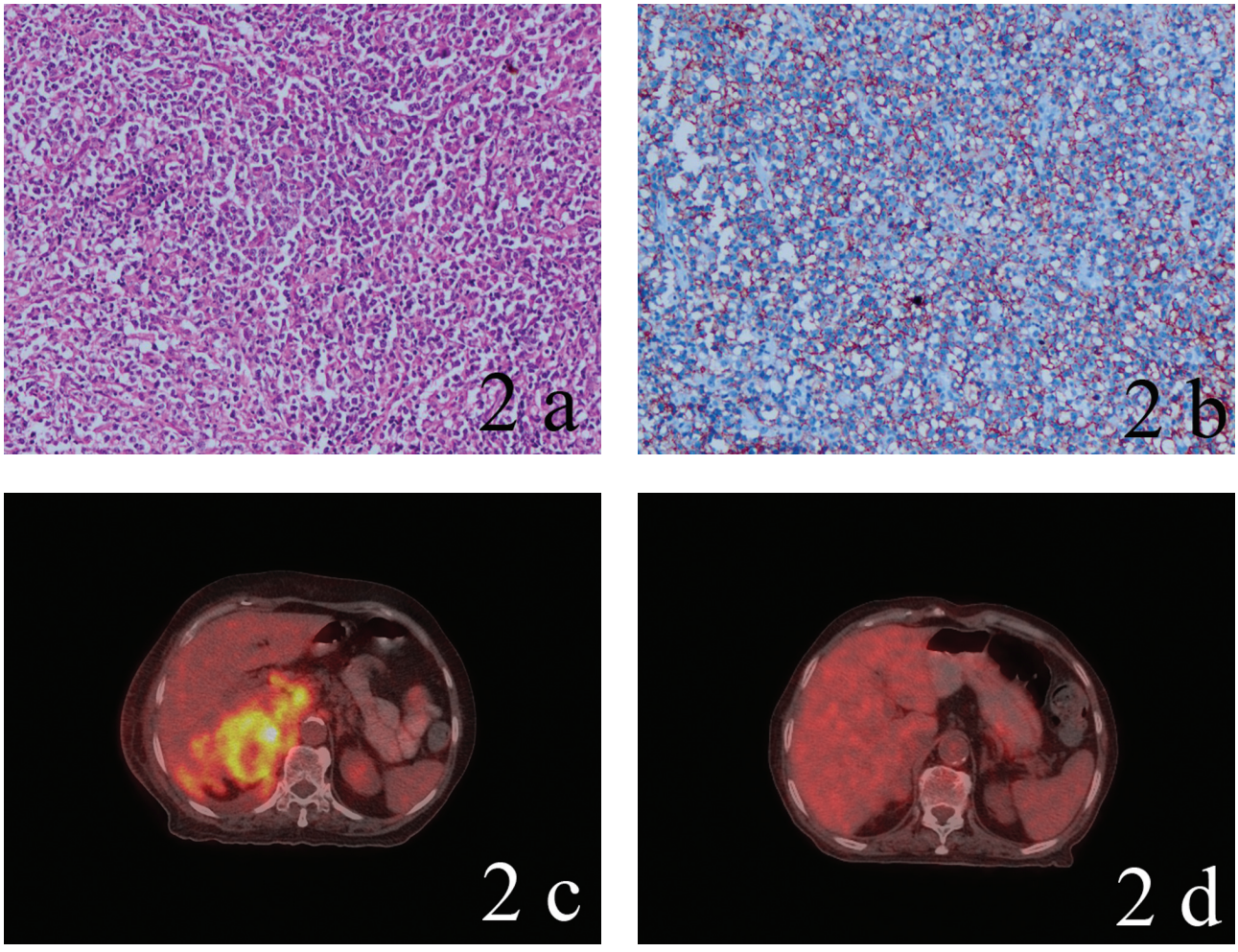

Figure 2a. Atypical lymphocytes with large nuclei and scant eosinophilic cytoplasm (HE x100). **2b**. Immunohistochemical membranous CD20 positivity (CD20 x100). **2c**. PET-CT obtained before the chemotherapy began. **2d**. After 6 cycles of the chemotherapy were completed, there was no evidence of tumor on follow-up FDG-PET scans.

is difficult due to nonspecific findings, especially when there is unilateral involvement. Only pathological examination confirms the diagnosis of PAL. Ultrasound- or CT-guided core biopsy or surgical biopsy through laparoscopy or laparotomy is necessary to make a definitive histopathological diagnosis. In the event of suspected PAL, Tru-cut biopsy or fine needle biopsy can obviate unnecessary surgery for biopsy.

Adrenal insufficiency can be due to infiltration of malignant cells into the adrenal glands. Approximately 90% of the adrenal cortex is supposed to be destructed for adrenal insufficiency to become apparent. Therefore, not all cases of neoplasms involving the adrenal glands result in adrenal insufficiency (9). Adrenal insufficiency crisis causes severe life-threatening consequences. Therefore, immediate hormone replacement therapy must be given when primary adrenal insufficiency is suspected. Although adrenal insufficiency may not appear at the beginning, it may develop in later stages, and surgeons should be alert for acute adrenal insufficiency. In the presented Case 1, there was no sign of adrenal insufficiency initially in the adrenal function test, but over the course of the treatment the patient developed marked general weakness and lethargy, and the laboratory study showed hyponatremia (to 126 mEq/L) and hyperkalemia (to 5.9 mEq/L). We thought that these manifestations were likely due to adrenal insufficiency, and they were rapidly corrected with continuous small doses of prednisolone.

It has been reported in the literature that advanced age, primary adrenal insufficiency as an initial sign, tumor size, LDH level, and involvement of other organs can be poor prognostic indicators (10).

Since PAL is a rare entity, therapeutic regimens have not been defined in detail, and most patients are treated with regimens similar to those used for other types of lymphoma. Among the treatment alternatives used are surgery, combination chemotherapy and radiation. PAL is usually lethal and early death may occur during chemotherapy. There have been a few cases of complete and partial remissions with a longer mean duration of survival (5,6). The cases presented here received rituximab-CHOP chemotherapy, which was used to treat PAL by Kim et al. (11). Case 1 showed almost complete remission following the sixth cycle. However, the disease showed an invasive involvement in the ninth month. The patient died of sepsis after receiving the eighth cycle of chemotherapy in the eleventh month. Case 2 showed complete remission following six cycles of chemotherapy. Follow-up PET-CT did not indicate any involvement. The disease progression differed between these two cases despite their having received the same chemotherapy. Based on only two cases, it can be difficult to make comments. However, it seems that cases of unilateral adrenal lymphoma may have longer survival. Poor prognosis in the case of bilateral adrenal lymphoma can be attributed to adrenal insufficiency.

Positron emission tomography (PET)-CT has been widely employed in recent years. CT and MRI are different from FDG-PET in that the latter is based on increased glucose metabolism in malignant lesions. PET-CT offers a powerful combination of functional and attenuation information to reveal characteristics of adrenal lesions (12).

In conclusion, PAL should be kept in mind in the differential diagnosis of patients presenting with unilateral or bilateral huge adrenal malignant masses without nodal involvement in the absence of other malignancies. In addition, fine needle biopsy may help to avoid unnecessary surgery. Surgeons should be cautious regarding adrenal insufficiency crisis, which is likely to arise in the follow-up period.

REFERENCES

1. Rosenberg SA, Diamond HD, Jaslowitz B, Craver LF. Lymphosarcoma: a review of 1269 cases. Medicine (Baltimore) 1961; 40: 31-84.
2. Salvatore JR, Ross RS. Primary bilateral adrenal lymphoma. Leuk Lymphoma 1999; 34: 111-7.
3. Freeman C, Berg JW, Culter SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972; 29: 252-60.
4. Ozimek A, Diebold J, Linke R, et al. Bilateral primary adrenal non-Hodgkin's lymphoma and primary adrenocortical carcinoma – review of the literature. Preoperative differentiation of adrenal tumors. Endocr J 2008, 55: 625-38.
5. Mantzios G, Tsirigotis P, Veliou F, et al. Primary adrenal lymphoma presenting as Addison's disease: case report and review of the literature. Ann Hematol 2004; 83: 460-3. Epub 2004 Jan 17.
6. Kumar R, Xiu Y, Mavi A, et al. FDG-PET imaging in primary bilateral adrenal lymphoma: a case report and review of the literature. Clin Nucl Med 2005; 30: 222-30.
7. Grigg AP, Connors JM. Primary adrenal lymphoma. Clin Lymphoma 2003; 4: 154-60.
8. Wang J, Sun NC, Renslo R, et al. Clinically silent primary adrenal lymphoma: a case report and review of the literature. Am J Hematol 1998; 58: 130-6.
9. Kuwahara K, Fukata J, Kamio M, et al. Angiotropic large cell lymphoma which infiltrated to the adrenal glands presenting as reversible adrenal insufficiency. Intern Med 1998; 37: 73-6.
10. Zhang LJ, Yang GF, Shen W, Qi J. Imaging of primary adrenal lymphoma: case report and literature review. Acta Radiol 2006; 47: 993-7.
11. Kim KM, Yoon DH, Lee SG, et al. A case of primary adrenal diffuse large B-cell lymphoma achieving complete remission with rituximab-CHOP chemotherapy. J Korean Med Sci 2009; 24: 525-8.
12. Xiu Y, Mavi A, El-Haddad G, et al. FDG-PET imaging in primary bilateral adrenal lymphoma: a case report and review of the literature. Clin Nucl Med 2005; 30: 222-30.