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An unusual cause of bilateral adrenal incidentaloma: a case report of primary adrenal lymphoma

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ABSTRACT

Primary adrenal lymphoma (PAL) is an extremely rare among the causes of adrenal incidentaloma. Most were diagnosed with adrenal insufficiency and B symptoms (unexplained weight loss, night sweats, fever). This article presented a 57-year-old woman who was investigated for bilateral adrenal masses found incidentally on computed tomography (CT). Physical examination and laboratory tests revealed no evidence of adrenal insufficiency or B symptoms. Only 24-hour urinary metanephrine and normetanephrine excretion were increased. Tumour F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) scan showed the greatest dimension was 14 cm in the left adrenal mass and the maximum standardised uptake value (SUV max) was 26.1 (relative to mean SUV in the normal liver parenchyma, which was 2). An adrenal biopsy was performed after taking adequate precautions against the possibility of a catecholamine crisis. Histopathology revealed high-grade B-cell lymphoma. Bone marrow involvement and brain metastasis were not observed. She received the R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen and intrathecal methotrexate therapy as central nervous system prophylaxis. The patient responded well to treatment, and close clinical follow-up continues. PAL should always be considered when a bilateral adrenal mass is detected.

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INTRODUCTION

An adrenal incidentaloma is incidentally detected adrenal lesions during routine imaging without complaints or physical examination findings originating from the adrenal gland.[1] Nonfunctional adrenocortical adenoma, adrenocortical carcinoma, pheochromocytoma, hormone-producing adenoma, metastases, and primary adrenal lymphoma (PAL) are the leading causes of the aetiology. However, PAL is an uncommon cause of adrenal incidentaloma, representing less than 1% of all non-Hodgkin lymphoma (NHL).[2,3] It is an aggressive high-grade lymphoma with a poor prognosis. Both adrenal gland invasion is seen in 70% of the cases.[4] Hepatosplenomegaly, lymphadenopathy, and bone marrow involvement can rarely occur. Patients typically present with adrenal insufficiency and B symptoms (fever, night sweats, and weight loss). Rarely, PAL may be diagnosed incidentally.[5-7] In this report, we present a case of an incidental finding of bilateral PAL.

CASE REPORT

A 57-year-old female with a history of hypertension presented to the emergency department with bilateral flank pain (never before) after a fall. The patient referred to our centre as the contrast-enhanced computed tomography (CT) revealed suspicious lesions in the suprarenal region. She was hemodynamically stable on admission, and her physical examination was unremarkable except for bilateral costovertebral tenderness. She had no palpable lymphadenopathy or splenomegaly. Her initial basic laboratory tests were unremarkable except for anaemia of the chronic disease, mild thrombocytopenia (131 × 103/μL) and hyponatremia (126 mEq/L). ACTH and cortisol tests sent initially for adrenal insufficiency evaluation were within normal range. Hyponatremia was consistent with a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elevated levels of beta-2 microglobulin (3,043 ng/mL) and LDH (512 U/L) were found in laboratory tests. A CT scan with adrenal protocol revealed suprarenal lesions, with the largest measuring 10x4 cm on the left, causing adrenal gland thickening and a prominent soft tissue mass surrounding the glands (Figure 1). A tumour F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) demonstrated intensive FDG uptake in the left supraclavicular-mediastinal-abdominal-mesenteric lymph nodes and bilateral adrenal masses (Figure 2). The greatest dimension was 14 cm in the left adrenal mass, and the maximum standardised uptake value (SUVmax) was 26.1 (relative to the mean SUV in the normal liver parenchyma, which was 2). Before the left adrenal gland biopsy, in the 24-hour urine, metanephrine and normetanephrine levels were measured to exclude pheochromocytoma, which was

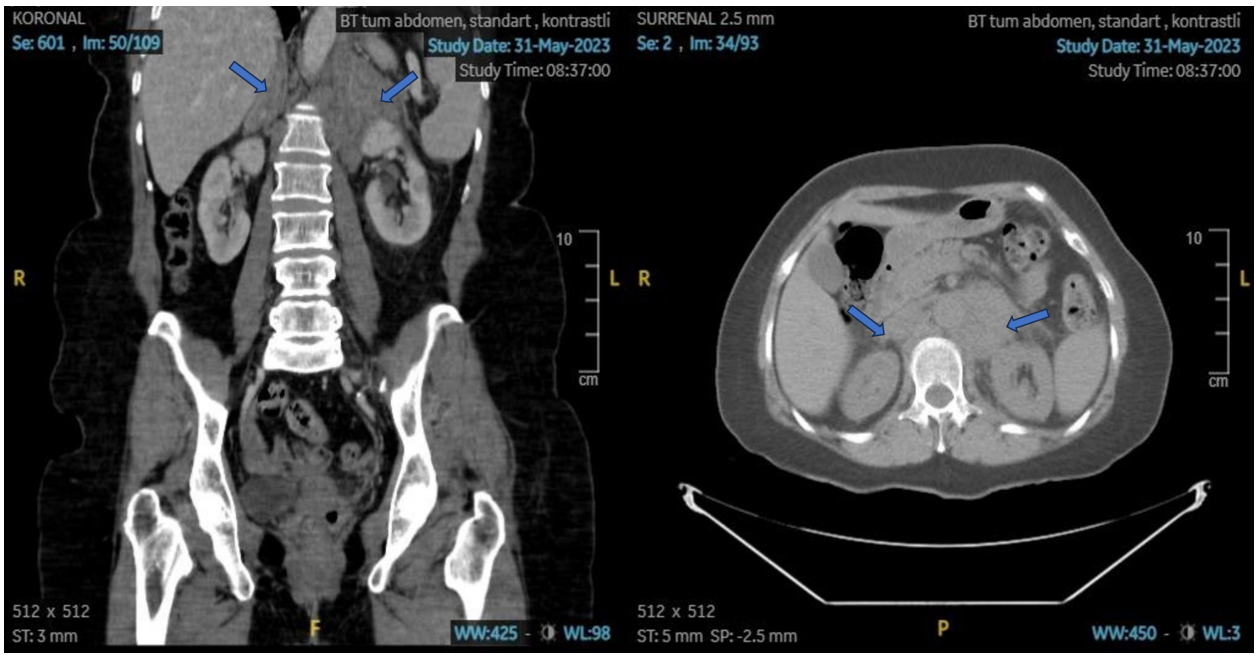

Figure 1. Coronal and axial contrast-enhanced abdominal CT sections showed suprarenal lesions (blue arrow) on the left. The largest was 10x4 cm, causing adrenal gland thickening and a prominent soft tissue lesion surrounding the glands.

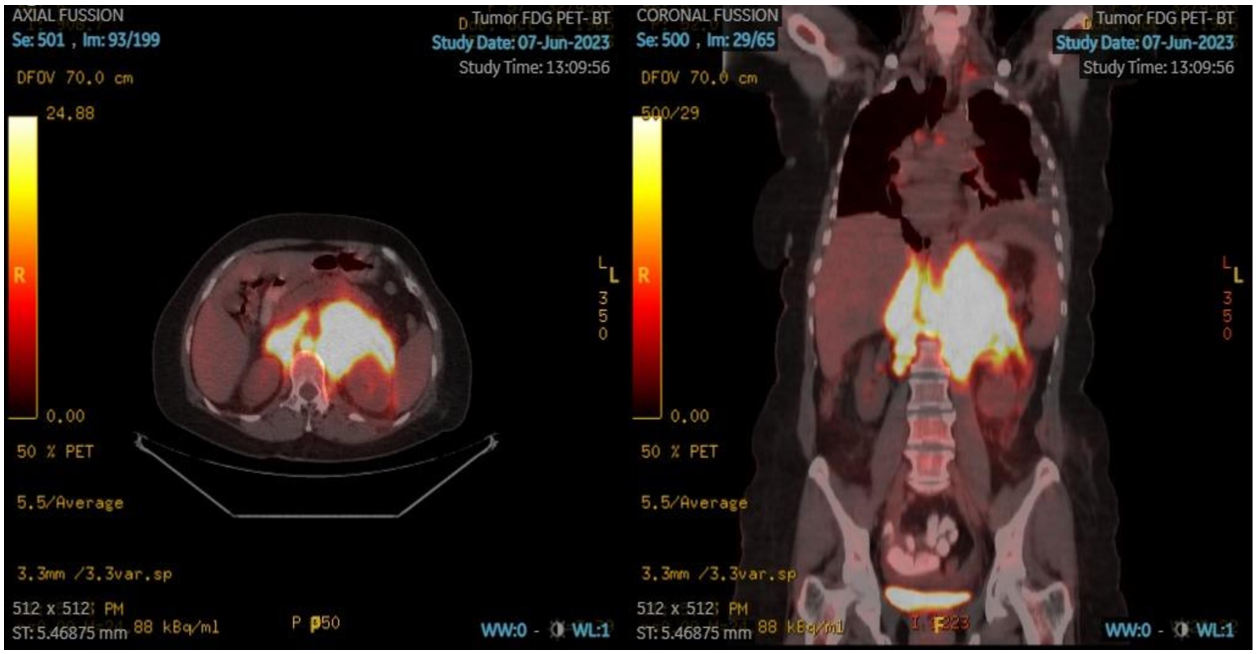

Figure 2. FDG-PET/CT scan showed intense FDG uptake in left supraclavicular-mediastinal-abdominal-mesenteric lymph nodes and bilateral adrenal masses.

found to be significantly increased (metanephrine: 1,432 µg/24-hour, normal range: 164-558 µg/24-hour; normetanephrine 1,426 µg/24-hour, normal range: 128-484 µg/24-hour).

Alpha-blocker therapy (doxazosin 2 mg/day) was initiated for blood pressure control. Biopsy of the left adrenal mass under image guidance revealed a diagnosis of diffuse large B cell lymphoma with non-germinal centre B cell phenotype. Immunohistochemical stains were strongly positive for CD20, Bcl-2 and MUM-1, with faint positivity for Bcl-6, and negative for CD10, CD5, and cyclin D1. Ki67 stain showed a proliferative index of %90. MYC staining was not available in the immunohistochemical examination.

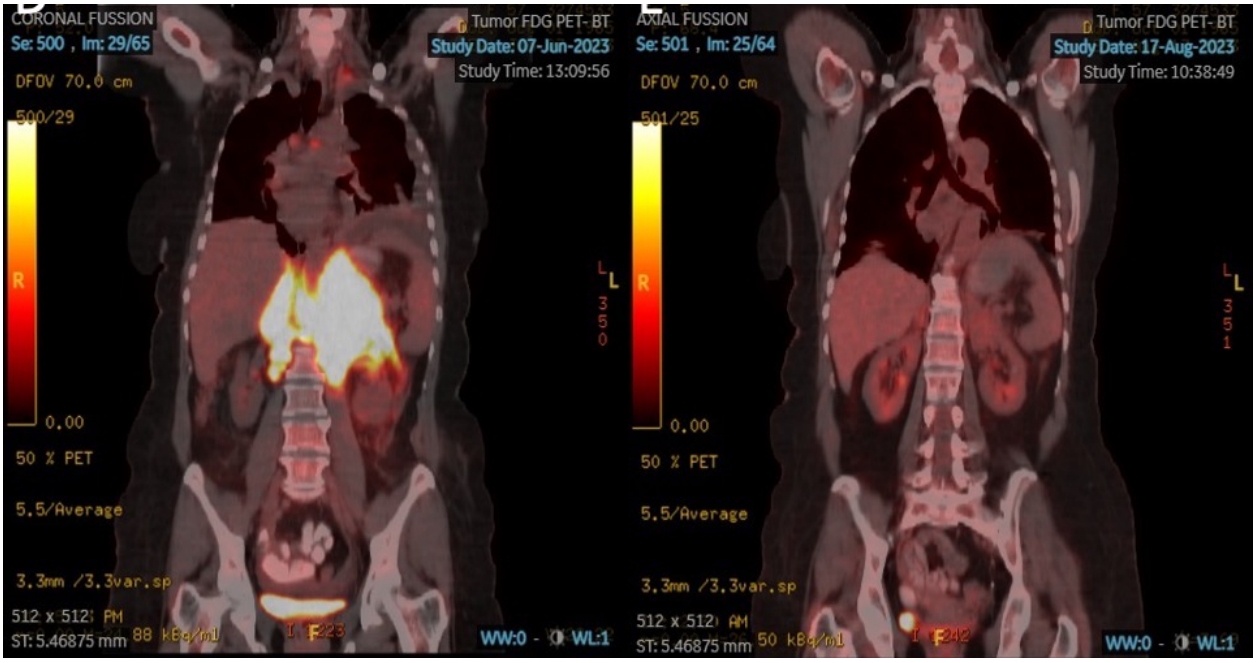

Figure 3. FDG-PET/CT scan in the third month of treatment showed a complete metabolic response.

Bone marrow aspiration and biopsy revealed no bone marrow invasion. No brain metastases were detected on cranial imaging. Her Eastern Cooperative Oncology Group (ECOG) performance status was Grade 2 at diagnosis. She was in the high-risk group by the International Prognostic Index (IPI). According to the Ann Arbor staging system, it was determined as stage 4. The patient received three cycles of R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) regimen, and intrathecal methotrexate therapy was included as central nervous system prophylaxis. PET-CT showed a complete metabolic response at the three months of treatment control (Figure 3). R-CHOP (rituximab, prednisone, vincristine, cyclophosphamide, and doxorubicin) chemotherapy treatment continued, and the patient was under close clinical follow-up.

DISCUSSION

Although there is no consensus, adrenal incidentaloma is described as an adrenal mass greater than 1 cm in diameter detected during imaging for reasons other than suspected adrenal disease. The differential diagnosis for adrenal incidentaloma includes non-secreting adenomas, subclinical cortisolic adenomas, pheochromocytoma, adrenal carcinomas and metastases. Occasionally, PAL may also be an incidental diagnosis on imaging.[5-7] PAL is an exceptionally rare and aggressive form of NHL originating in the adrenal glands. It represents fewer than 1% of all NHL, with approximately 200 cases documented in the literature.[7,8] The exact aetiology of primary adrenal lymphoma remains largely unknown, but it is believed to arise from B-cell lymphocytes within the adrenal glands. Some studies demonstrated that Ebstein-Barr virus (EBV) can be a possible causative agent.[9] Immunocompromised states, such as human immunodeficiency virus (HIV) infection, immunosuppressive therapy, or autoimmune diseases, may increase the risk of developing this malignancy.[10] Genetic defects in p53 and c-kit have also been implicated in the aetiology of the disease.[7]

Primary adrenal lymphoma predominantly affects males with a median age of diagnosis around 60-70 years. Bilateral adrenal gland invasion is seen in the most of the cases.[7] Patients typically present with B symptoms, abdominal pain, back pain, and adrenal insufficiency (AI), while 1% of cases are found incidentally.[5-7] Although 60 to 70% of patients present with AI regardless of the tumour size and involvement,11 our patient did not have any AI-related symptoms and were completely asymptomatic except for flank pain, which was developed after a fall. Some studies suggested that bilateral lesions and older age are factors significantly related to AI in PAL cases. However, the exact cause remains unclear.[7] In addition, regarding differential diagnosis, adrenocortical adenomas and carcinomas are usually unilateral, whereas pheochromocytoma and PAL are usually bilateral. Therefore, the differentiation of pheochromocytoma and PAL is very significant.

An adrenal gland biopsy should be done for definitive diagnosis. Before biopsy, urine catecholamine levels should be measured to rule out pheochromocytoma. If these levels are elevated, alpha-blocker therapy should be initiated to prevent a hypertensive crisis. Diffuse large B-cell lymphoma (DLBCL) is the more prevalent form of PAL, representing over 70% of cases.[7,12] DLBCL can be further classified into two subtypes: germinal centre B cell (GCB) or non-germinal centre B cell (non-GCB). Non-GCB subtype is associated with a worse prognosis.[7,8]

The treatment of primary adrenal lymphoma is challenging, primarily due to its aggressive nature and the lack of standardised therapeutic guidelines. The rarity of the disease limits the availability of large-scale clinical trials, resulting in no universally accepted treatment approach. Treatment options include chemotherapy, radiotherapy, and adrenalectomy. Several studies have demonstrated that adrenalectomy has no benefit to survival.[12-14] Chemotherapy with R-CHOP remains the most used treatment approach for PAL. A retrospective study of 50 primary adrenal lymphoma patients reported that patients treated with the R-CHOP regimen had better overall survival (OS) rates than patients who underwent surgery and received supportive treatment only (84.2% vs 41.7%).10 Another study has shown that patients who received R-CHOP therapy had increased 2-year OS rates compared to patients treated with traditional CHOP regimens (57% vs 38%, $p < 0.001$).[15] Additionally, central nervous system involvement significantly decreases survival in DLBCL cases.[16] Therefore, in our case, methotrexate was administered as intrathecal prophylaxis in addition to standard chemotherapy. However, a recent meta-analysis showed that intravenous or intrathecal CNS prophylaxis did not significantly reduce the recurrence rate in patients at high

risk of CNS.[17]

Primary adrenal lymphoma has a poor prognosis, primarily due to the advanced stage of disease at diagnosis and the aggressive behaviour of the tumour. While earlier studies reported 2-year OS rates of PAL to be 20%, recent studies have demonstrated 2-year OS rates of PAL ranging between 68 and 72.5%.7,10,12 In another study, the estimated 5-year PAL OS rate was less than 20%.18 Our patients were in the high-risk group according to IPI score. Multiple extranodal involvement is a prognostic factor for IPI score. Recent validation studies have also proven this.19 Several factors have been identified as poor prognostic indicators in PAL cases. These include older age, bilateral involvement of the adrenal glands, larger tumour size, high serum lactate dehydrogenase levels, AI, nongerminal centre B-cell-like classification, and a high Ki-67 proliferation index.[2,12,20] All poor prognostic factors were present in our case except AI.

Conflict of Interest

None declared.

Patient consent

Written informed consent for publication of their details was obtained from the patient.

Authors' Contribution

Conception and design: M.T, N.N.G; analysis and interpretation of the data: M.T, N.N.G, M.I.E; drafting of the article: M.T, N.N.G; Critical revision of the article for important intellectual content: U.Y.M, O.A.U; Final approval of the article: M.T, N.N.G, M.I.E, O.A.U.

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