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Primary adrenal insufficiency masking as an adrenal B-cell lymphoma

Eric Kuhn,¹ John R Sanchez,² Mohamed KM Shakir,^{1,3} Thanh Duc Hoang ^{1,3}

¹Endocrinology, Walter Reed National Military Medical Center, Bethesda, Maryland, USA

²Pathology, Walter Reed National Military Medical Center, Bethesda, Maryland, USA

³Medicine, Uniformed Services University of the Health Sciences F Edward Hebert School of Medicine, Bethesda, Maryland, USA

Correspondence to
Dr Thanh Duc Hoang;
tdhdthanh@gmail.com

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SUMMARY

We report here a woman in her 70s presenting with adrenal insufficiency secondary to a primary adrenal lymphoma. The patient had a previous history of aphthous ulcers on dexamethasone and was referred to endocrinology with symptoms of fatigue and orthostasis. Subsequent Cosyntropin stimulation showed primary adrenal insufficiency and adrenal CT demonstrated large infiltrative masses. Adrenal biopsy confirmed the diagnosis of primary adrenal lymphoma of the B-cell type. This case demonstrates the importance of including lymphoma in the differential diagnosis of adrenal insufficiency, particularly in the elderly population and in the setting of negative 21-hydroxylase antibody results.

BACKGROUND

Primary adrenal lymphoma (PAL), although very rare with fewer than 200 case reports in the English literature, is increasingly being recognised as a cause of primary adrenal insufficiency, particularly with bilateral disease. PAL represents <1% of non-Hodgkin lymphomas and typical aetiologies include both diffuse large B-cell lymphoma and peripheral T-cell lymphoma.¹ These lymphomas are quite aggressive and associated with a poor prognosis.²

CASE PRESENTATION

A woman in her 70s presented to our endocrinology clinic, referred by her primary care physician for symptoms of adrenal insufficiency. The patient had been complaining of extreme exhaustion for 3–4 weeks, was becoming more forgetful and had exercise intolerance. Her medical history was significant for petit mal seizures treated with phenytoin and phenobarbital as a child (had stopped since college) and recurrent aphthous ulcers. The ulcers began 3 years ago and were being treated with liquid dexamethasone (0.5 mg/5 mL) as frequently as three times a day. A recent cardiology evaluation was positive for orthostatic hypotension. Family history was negative for any neuroendocrine tumours or autoimmune processes. The patient's husband reported her exhaustion as a significant change for the patient as she was previously very active but now grew tired just by reading. She had been an active gardener and would regularly run on the treadmill. Review of symptoms was notable for a 5.4 kg weight loss, dizziness on standing and the need to sleep for 16–18 hours a day. On physical examination, the patient had a blood pressure of 106/62 mm Hg, a heart rate of 82 beats per minute and a respiratory rate of 16 breaths per minute. There was no darkening of the

skin folds, no head or cervical lymphadenopathy. Abdominal examination demonstrated no hepatosplenomegaly and there was no lower extremity oedema. Laboratory test results available at the time demonstrated normal albumin, sodium, potassium, glucose, liver transaminases and slightly increased creatinine of 1.15 mg/dL (normal 0.5–0.9) with a glomerular filtration rate (GFR) of 48.3 mL/min (normal >60). Thyroid function was abnormal with a thyroid-stimulating hormone (TSH) of 5.09 uIU/mL (normal 0.27–4.2) and a free T4 of 1.11 ng/dL (normal 0.93–1.7). Given the patient's symptoms and recent exogenous glucocorticoid use, adrenal insufficiency was considered.

INVESTIGATIONS

Laboratory tests were ordered to evaluate for adrenal insufficiency including serum ACTH levels, ACTH stimulation test, aldosterone/renin ratio and a CBC was ordered to rule out anaemia. ACTH stimulation test showed a baseline serum ACTH level >700 pg/mL (normal 7.2–63.3) and a peak serum cortisol of 6.4 µg/dL (normal >14), consistent with primary adrenal insufficiency. Patient was started on hydrocortisone 10 mg in the morning and 5 mg in the afternoon with significant improvement. Further investigation revealed a decreased dehydroepiandrosterone (DHEA) sulfate level of 0.945 µg/dL (normal 9.4–246.0) and negative 21-hydroxylase antibodies. Aldosterone/renin activity was <0.3 (normal 0.0–30.0). Repeat ACTH stimulation test performed 3 months later, after holding hydrocortisone for 24 hours, demonstrated continued adrenal insufficiency with peak cortisol of 2.2 µg/dL and ACTH of 240 pg/mL. Adrenal CT showed that the left adrenal bed was infiltrated with a large (6.4×5.6×6.3 cm) hypoenhancing mass crossing the midline to affect the right adrenal ([figure 1](#)). The right adrenal gland was measured at 4.2×1.6×3.7 cm. Core biopsy of the left adrenal mass performed by interventional radiologist revealed a diffuse infiltrate of large B-cells with intermixed tangible body macrophages and mitotic figures. Immunohistochemistry revealed positive staining of CD19, CD20, CD5, bcl-2, bcl-6, MUM1 and PAX5, consistent with diffuse large B-cell lymphoma ([figure 2A,B](#)). Flow cytometry demonstrated a CD5 positive kappa restricted B-cell population without a significant CD4 positive T-cell population, consistent with CLL/SLL or occasional large B-cell lymphomas. Immunohistochemical and molecular markers such as double expression of MYC, BCL2, CD5 expression, lack of CD30 expression, P53 expression, cyclin D2, BCL2



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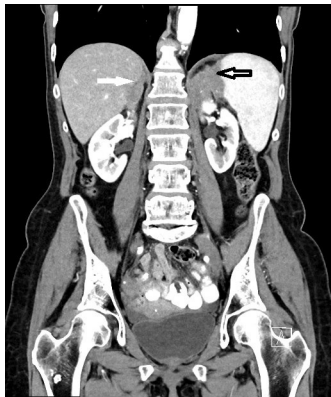


Figure 1 Adrenal CT showing the left adrenal bed infiltrated with a large (6.4×5.6×6.3 cm) hypoenhancing mass and findings suggesting that it may be crossing the midline to affect the right adrenal.

gene rearrangement, etc were performed for prognostication. The patient underwent a PET/CT which showed extension of the adrenal mass into the diaphragmatic crus and F-fluorodeoxyglucose (FDG) uptake concerning for malignancy (figure 3). Hypermetabolic opacities were seen in the right middle lobe of the lung as well which may be demonstrative of metastasis or other inflammatory change as well as uptake in the right thyroid lobe. Ultrasound of the thyroid demonstrated 5 mm right middle lobe and 5 mm left middle lobe cystic thyroid nodules with no concerning features. Further evaluation was performed by haematology/oncology. Quantitative PCR was negative for Epstein-Barr virus DNA and hepatitis virus panel was negative. Beta 2 microglobulin was elevated at 3.5 mg/L (0.0–3.0) and serum lactate dehydrogenase (LDH) was significantly elevated at 541 U/L (135–225). Urate levels were normal at 3.6 mg/dL (2.4–5.7).

DIFFERENTIAL DIAGNOSIS

Having presented with signs and symptoms concerning for adrenal insufficiency, the differential diagnosis for our patient was broad. The autoimmune cause of primary adrenal insufficiency, Addison's disease was excluded with a negative 21-hydroxylase antibody result. Due to the patient's recent use of dexamethasone oral solution with abrupt discontinuation, secondary adrenal insufficiency was considered. However, the patient's ACTH level >700 pg/mL was consistent with primary adrenal insufficiency. Adrenal infiltration is, alternatively, another common cause of adrenal insufficiency with possible aetiologies being metastasis, sarcoidosis, amyloidosis and lymphoma. Infectious causes include tuberculosis, which can present with a mass-like enlargement of the adrenal with preservation of the smooth contours of the gland. However, our patient had not recently

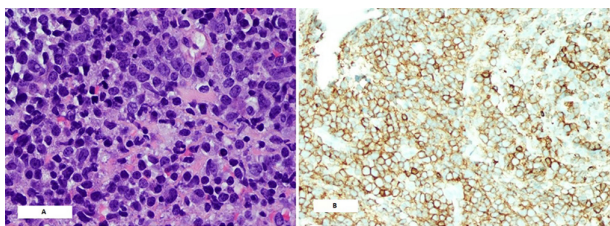


Figure 2 (A B) Immunohistochemistry revealing positive staining of CD19, CD20, CD5, bcl-2, bcl-6, MUM1 and PAX5, consistent with diffuse large B-cell lymphoma.

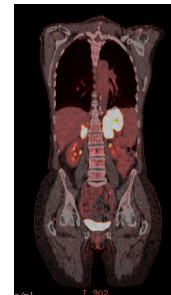


Figure 3 PET/CT showing extension of the adrenal mass into the diaphragmatic crus and FDG uptake concerning for malignancy.

travelled and tuberculous adrenalitis was unlikely in her case. When in an area where tuberculosis is not endemic, bilateral adrenal masses are usually due to secondary metastasis from an extraglandular primary tumour, typically lung, colon or gastric malignancies; however, adrenal biopsy of our patient confirmed a large B-cell lymphoma.

TREATMENT

The patient was placed on hormone replacement therapy with a 10 mg dose of hydrocortisone given in the morning and a 5 mg dose given in the afternoon every day along with fludrocortisone 0.1 mg daily. She reported significant improvement in her symptoms of orthostasis, fatigue and weakness. On treatment, her blood pressures were around 110/65 mm Hg when taken at home. Baseline echocardiography was unremarkable and the lymphoma was subsequently treated with the R-CHOP regimen of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone with significant improvement. Repeat PET scan showed interval resolution of the left adrenal FDG hypermetabolism (figure 4). However, repeat ACTH stimulation test still showed adrenal insufficiency (peak cortisol 1.5 µg/dL).

OUTCOME AND FOLLOW-UP

The patient underwent six cycles of R-CHOP regimen with intrathecal methotrexate prophylactically for occult central nervous system (CNS) involvement with no adverse effects. Follow-up imaging studies showed interval resolution. She was educated about prevention and management of an adrenal crisis in detail.³

She did not develop any adrenal crisis during chemotherapy or during the 15-month follow-up. Currently, she is doing well and continues taking hydrocortisone and fludrocortisone.

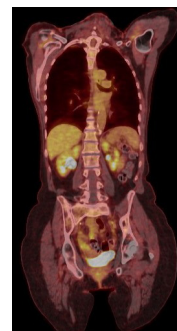


Figure 4 Follow-up PET showing interval resolution of the left adrenal FDG hypermetabolism after 6 months.

DISCUSSION

In Western countries, primary adrenal insufficiency is usually caused by immune mediated processes and is associated with atrophic adrenal glands. Our patient had several features of adrenal insufficiency such as fatigue and orthostatic hypotension on presentation. Because of the advanced age and negative adrenal antibodies, an adrenal CT scan was performed to evaluate for other causes of primary adrenal insufficiency such as infectious diseases, metastatic cancer or lymphoma, adrenal haemorrhage or infarction. The adrenal CT scan showed a left adrenal mass crossing to the midline to affect the right adrenal gland and the core biopsy of the right adrenal mass confirmed diffuse large B-cell lymphoma. Flow cytometry demonstrated a CD5 positive kappa restricted B-cell population without a significant CD4 positive T-cell population, consistent with chronic lymphocytic leukaemia (CLL) or small lymphocytic leukaemia (SLL) or occasional large B-cell lymphoma. A PET/CT scan showed extension of the adrenal mass into the diaphragmatic crus concerning for malignancy. Primary adrenal lymphoma is one of the rare indications for urgent core biopsy of the adrenal gland after excluding pheochromocytoma as done in our patient. In our patient, hyperpigmentation was not noted. Hyperpigmentation is usually evident in most patients with primary adrenal insufficiency and is considered a characteristic physical finding.⁴ The hyperpigmentation is due to increased production of proopiomelanocortin, a prohormone that is cleaved into the biologically active hormones ACTH, Melanocyte-stimulating hormone (MSH) and others. The elevated MSH results in increased melanin synthesis causing hyperpigmentation. The resulting brown hyperpigmentation is generalised but is most conspicuous in areas exposed to light. However, our patient did not have any skin hyperpigmentation and it is possible with the relatively rapid course of the disease there was insufficient time to develop skin hyperpigmentation.

It is interesting to note that primary adrenal insufficiency occurs more commonly in primary adrenal lymphoma compared with other non-lymphomatous metastatic cancer affecting both adrenal glands, although the exact underlying pathogenesis of this is not clear. Furthermore, Rashidi and Fisher reported that 20% of cases of primary adrenal lymphoma associated with adrenal insufficiency occurred with unilateral disease and these authors suggested that tumour size appeared to have little correlation in causing adrenal insufficiency.⁵ Rashidi and Fisher also showed a correlation between the presence of hyperpigmentation and the occurrence of adrenal insufficiency which is most commonly seen in older patients and those with bilateral adrenal disease. These authors further suggested that a cytokine-related paracrine effect on the adrenal biochemical microenvironment may be involved in contrast to direct tissue infiltration and destruction by lymphoma. More recently, Majidi *et al* conducted a retrospective analysis of 81 patients showing that 23% of patients had isolated adrenal involvement while 77% had extra-adrenal involvement.⁶ The common clinical manifestations were B symptoms, such as fever, night sweats, unintentional weight loss of more than 10% body weight over 6 months, painless swelling in one or more lymph nodes, persistent fatigue, loss of appetite, cough or chest, stomach pain, bloating, itchy skin, splenomegaly, hepatomegaly and rashes. Our patient reported fatigue, back pain, weight loss, but no significant abdominal pain or hyperpigmentation. Majidi *et al* finally concluded that there is significant heterogeneity in the manifestation of primary adrenal lymphoma.⁷

Primary adrenal lymphoma has been characterised as either unilateral or bilateral lymphoma in a patient without a medical history of lymphoma elsewhere and with the adrenals being the predominantly involved organ.⁷ About 70% of cases of primary adrenal lymphoma are bilateral. With unilateral involvement, PAL can present with insufficiency, weight loss, night sweats and fever. However, insufficiency is more typical of bilateral gland involvement.⁷⁻⁹ PAL has a male to female predominance of 2:1 and typically occurs in the elderly, with a median age of 68 years.^{10 11} Diffuse large B-cell is the most common type of lymphoma in the United States (30% of cases) and also constitutes the majority of primary adrenal lymphomas. This is an aggressive lymphoma that can be further delineated into multiple subtypes. Notably, absent germinal centres and Bcl2 positivity are the common pathological findings in these tumours, as was the case with our patient. Forty percent of DLBCL cases start as extranodal disease and these arise most commonly in the gastrointestinal tract. They can, however, occur in any organ. Besides diffuse large B-cell lymphoma, the most common type is peripheral T-cell lymphoma, accounting for 7% of primary adrenal lymphoma.

Treatment for primary adrenal lymphoma is typically with the R-CHOP chemotherapy regimen (rituximab, cyclophosphamide, hydroxyl doxorubicin, oncovin and prednisolone).^{12 13} This regimen was shown to be superior to previous regimens which did not include rituximab, improving overall survival by 20%. An alternate regimen is DA-EPOCH-R (etoposide, prednisone, oncovin (vincristine), cyclophosphamide, hydroxydaunorubicin (doxorubicin), rituximab), which has been shown to have certain benefits when compared with R-CHOP. In early studies, this regimen resulted in a 12-month progression free survival (PFS) rate of 85%.¹⁴ Recently, in post hoc analysis of a phase III trial, there was increased progression free survival scores in those groups with the International Prognostic Index (IPI) III-V when compared with R-CHOP.¹⁵ However, our patient was treated with R-CHOP regimen and responded well to the treatment.

Learning points

- ▶ Primary adrenal insufficiency without 21-hydroxylase antibodies should prompt imaging to evaluate presence of infiltrating masses.
- ▶ Adrenal insufficiency occurs more commonly in primary adrenal lymphoma compared with other non-lymphomatous metastatic cancer affecting the adrenal glands.
- ▶ When the aetiology of adrenal enlargement is unknown, bilateral adrenal masses require prompt tissue biopsy after excluding pheochromocytoma.
- ▶ Clinical presentation of primary adrenal lymphoma may vary depending on the presence of unilateral or bilateral disease.
- ▶ During chemotherapy, these patients need to be closely monitored for adrenal crisis and appropriate intervention be instituted if adrenal crisis is suspected.

Twitter Thanh Duc Hoang @tdhdthanh

Contributors EK: drafted the manuscript. JRS: provided the histology slides and interpretation. MKMS: reviewed and edited the manuscript. TDH: mentored, reviewed, edited and finalised the manuscript.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iD

Thanh Duc Hoang <http://orcid.org/0000-0001-7437-5604>

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