

Adrenal Lymphoma: Case Report and Review of Literature

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ABSTRACT

Adrenal lymphoma is a rare diagnosis in subject presenting with bilateral adrenal masses. Adrenal insufficiency is a common complication of this disease. Most cases of primary adrenal lymphoma (PAL) present with adrenal insufficiency and huge bilateral adrenal masses. These are very aggressive tumors with poor prognosis. We, hereby, report two subjects of adrenal lymphoma presenting with bilateral adrenal masses. First case is a 50 years old male presented with features of adrenal insufficiency like anorexia, weight loss, nausea, vomiting, and generalized hyperpigmentation. Routine investigations revealed hyponatremia, normal serum K; serum lactate dehydrogenase was moderately elevated. Primary adrenal insufficiency was confirmed by low basal and cosyntrophin stimulated cortisol. CT abdomen revealed huge bilateral heterogeneous enlargement of adrenal glands. Lymphoma was confirmed by histopathology and immunohistochemistry, diagnosis of PAL was made after further staging. He was treated with Rituximab-CHOP regimen. Second case, 50 years old lady presented with fever, anorexia, weight loss. She had generalized lymphadenopathy. On imaging found to have bilateral adrenal mass, and histopathology from lymph node, breast mass and adrenal mass was suggestive of non-Hodgkin's lymphoma.

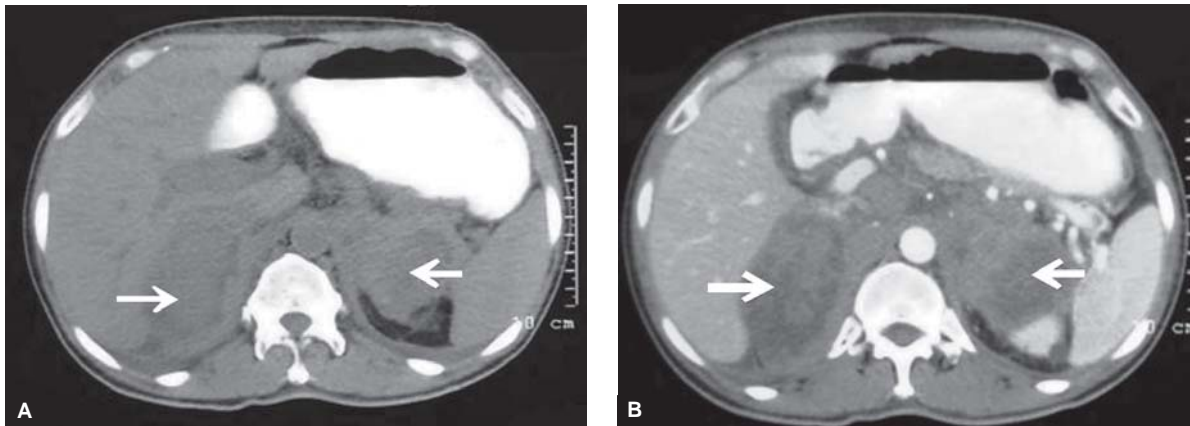
KEYWORDS: Adrenal lymphoma, primary adrenal lymphoma, adrenal insufficiency, bilateral adrenal mass.

CASE 1

A 57-year-old male presented with fever, weight loss, generalized weakness, and moderate to severe abdominal pain for 3 months duration. He had history of anorexia, nausea, vomiting, and generalized hyperpigmentation. He was evaluated in another hospital where ultrasound of abdomen followed by CT abdomen revealed bilateral adrenal masses and was referred to us for further evaluation. On general examination, patient was lean (BMI-17.43 kg/m²), had pulse rate of 86/min and supine blood pressure was 130/80 mm Hg with orthostasis of 14/10 mm Hg. He had generalized hyper pigmentation including oral mucosa and gum pigmentation. He was pale and anicteric with no lymphadenopathy. Examination of the chest, abdomen, and cardiovascular system was unremarkable, and nervous system examination revealed evidence of peripheral neuropathy. Routine investigations revealed normocytic normochromic anemia with normal blood counts and normal

erythrocyte sedimentation rate. Urinalysis, kidney and liver function tests were within normal limit. Serum electrolyte revealed hyponatremia (ranging from 116 mmol/l to 128 mmol/l) and normal serum potassium level. Serum lactate dehydrogenase (LDH) was 1096 U/L (normal 85 to 450 U/L). Serum calcium, and phosphorus were normal. Chest X-ray PA view revealed blunting of cardiophrenic angle. Pleural fluid analysis was done in another hospital prior to referring here, which revealed that fluid was exudative in nature. No malignant cell was seen in pleural fluid analysis. CECT abdomen showed bilateral heterogenous enlargement of adrenal glands (Right adrenal: 10 × 6.4 × 6.2 cm, Left adrenal: 8.6 × 6.4 × 6.2 cm) (Figs 1A and B). There was evidence of necrotic regions within both enlarged adrenals; no calcification was seen. CECT chest did not reveal any mediastinal lymphadenopathy or any parenchymal lesion.

The basal serum cortisol was less than 3 ug/dl (normal range 5 to 20 ug/dl), and stimulated cortisol was less than 5 ug/dl (reference normal value > 20 ug/dl). Thyroid hormonal



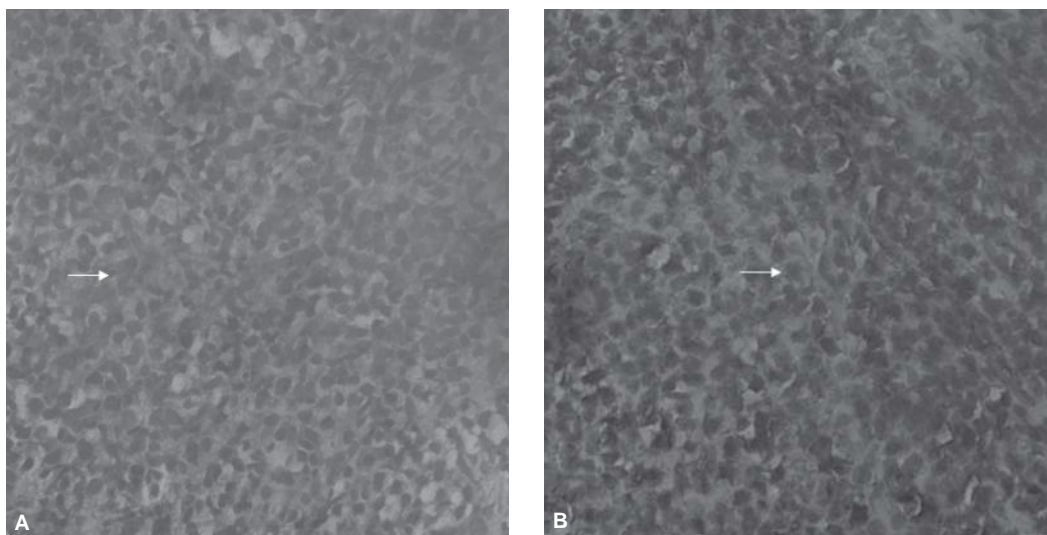
Figs 1A and B: CECT abdomen (A) plain and (B) with contrast showing large heterogeneous adrenal masses with evidence of necrosis but without calcification

profile was within normal limit. Serum ACTH estimation was not done. In presence of hyperpigmentation, and bilateral adrenal mass with hypocortisolism primary adrenal insufficiency was the most likely diagnosis. He was treated with replacement dose of prednisolone (7.5 mg/day) and fludrocortisone (0.1 mg/day). He was also treated with analgesics for severe abdominal pain, and later opioid analgesics were added. When he did not respond to these medications, he was subjected to celiac plexus block by 80 mg depomedrol. His abdominal pain subsided, but he was not completely relieved of pain. His blood sugars were managed with insulin, and he maintained fair glycemic control.

Fine needle cytology from adrenal mass was inconclusive. So CT-guided biopsy of adrenal mass was done. Smears and cultures were negative for fungal, bacterial

Table 1: Biopsy of adrenal mass	
Fungal smear	No fungal element
Fungal culture	Negative
Bacterial smear	Pus cells
Bacterial culture	Sterile
Mycobacterium	AFB-Negative
Cytopathology	Histopathology: sheets of atypical cells displaying round to oval small to med sized nuclei, S/O- <i>Non-Hodgkin's B cell lymphoma</i>
Immuno-histochemistry	Positive for CD20 and CD 45, and negative for cytokeratin and CD3

elements as well as for mycobacterium (Table 1). Histo-pathologic examination revealed sheets of monomorphous atypical cells displaying round to oval small to medium sized



Figs 2A and B: (A) Histopathology (H and E) of adrenal mass revealed sheets of monomorphous atypical cells (B)Immunohistochemistry showed tumor cells expressing CD45 and CD20

nuclei with scanty cytoplasm suggestive of non-Hodgkin's lymphoma (Fig. 2A). Immunohistochemistry showed tumor cells expressed common leukocyte antigen (CD45) and CD20, markers of B lymphocytes (Fig. 2B). Tumor cells were negative for CD3 and cytokeratin. Bone marrow aspiration cytology and biopsy done for staging did not reveal any lymphomatous infiltration of marrow. So the final diagnosis of primary adrenal lymphoma was made.

He was referred to hematology department where he was managed with combination chemotherapy (Rituximab-CHOP regimen). He received 8 cycles of this regimen. At last follow-up after 6 months of diagnosis and treatment he was doing well with gain in weight, general feeling of well-being, and significant reduction in hyper pigmentation and was completely pain free.

CASE 2

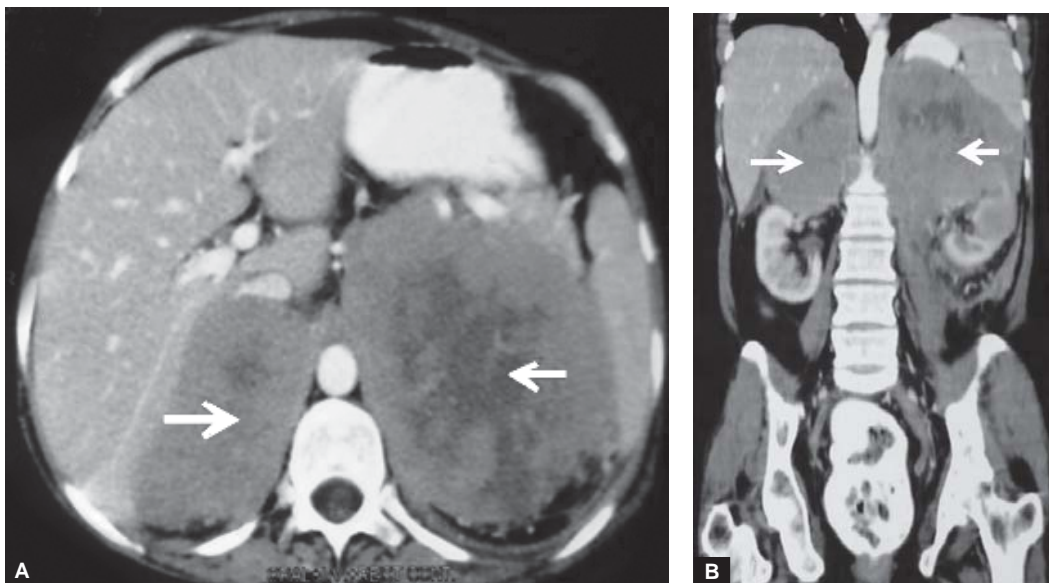
A 50-year-old lady presented with fever, weakness, decreased appetite, weight loss, and night sweats for 2 months duration. She had history of decreased appetite, nausea, occasional vomiting. She did not have hyper pigmentation. On clinical examination she was found to have pallor, axillary and posterior cervical lymphadenopathy. She also had a 3 × 3 cm hard, mobile, nontender breast nodule in right upper quadrant. Systemic examination was essentially normal. Her Hb was 8.4 gm/dl, with normal leucocyte counts and ESR. Serum electrolytes were within normal limits. Serum lactate dehydrogenase (LDH) was 1200 U/L. USG abdomen revealed bilateral adrenal mass and subsequent CECT abdomen revealed enlarged left adrenal (11.1 × 11 × 14.5 cm)

with irregular nonenhancing areas, extending into the left paravertebral region upto the lower pole of left kidney (Figs 3A and B). Left renal vein and artery were encased by the mass. Right adrenal was also found to be enlarged (10 × 7.5 × 6 cm). There were few mildly enlarged mesenteric and retrocaval lymphnodes. Short adrenocorticotrophic hormone stimulation test did not reveal adrenal insufficiency with a baseline cortisol concentration of 502 nmol/l and 1 hour stimulated value of 608 nmol/l. CECT-guided biopsy from adrenal mass and cytopathology from breast nodule and right axillary lymphnode revealed atypical lymphoid cells with nucleoli and coarse chromatin; suggestive of non-Hodgkin's lymphoma. Final diagnosis of disseminated non-Hodgkin's lymphoma with bilateral adrenal mass was made.

On 3rd day of hospitalization she developed hypotension and dyspnea. She desaturated and was put on ventilatory support. She was started on vasopressors and stress dose hydrocortisone infusion. However, she subsequently succumbed to multiple organ failure resulting from tumor lysis syndrome.

DISCUSSION

When adrenal masses occur bilaterally, the most likely diagnoses are metastatic disease, congenital adrenal hyperplasia, bilateral cortical adenomas, and disseminated infections like tuberculosis, histoplasmosis, and cryptococcosis.¹ Malignant tumors have a predilection for metastasizing to the adrenal glands; this is especially true of carcinomas of the breast, lung, and gastrointestinal tract and malignant melanoma. Clinically apparent adrenal insuffi-



Figs 3A and B: CECT abdomen (A) and (B) with contrast showing large heterogeneous adrenal masses with evidence of necrosis

ciency is rare in patients with adrenal metastases since about 90% of the adrenal gland must be destroyed before adrenal insufficiency is detectable.² However, a prospective study by Redman et al showed that 33% of patients with radiologic evidence of bilateral adrenal metastasis had adrenal insufficiency as demonstrated by the cosyntropin stimulation test.³

Lymphoma disseminating to both the adrenals is a common cause of bilateral masses. Adrenals are involved in 24% of cases with disseminated non-Hodgkin's lymphoma in an autopsy study (Rosenberg, et al. 1961),⁴ and occurs in 4% of cases as assessed by computed tomography.⁵ Adrenal insufficiency was reported only in four cases with adrenal involvement in a series of 127 patients with non-Hodgkin's lymphoma.⁶

Lymphoma arising in, and confined to, the adrenal glands is unusual and is termed primary adrenal lymphoma (PAL). The adrenal gland in man contains no lymphoid tissue, and the follicle center cell origin of this lymphoma suggests the tumor may have arisen on a background of previous autoimmune adrenalitis, consistent with the finding of profound adrenal insufficiency.⁷

Primary adrenal lymphoma is exceedingly rare clinical entity.⁸ So far about 100 cases have been reported in both Western and Eastern countries over the past 4 decades.⁹ Mantazios et al reviewed clinicopathological features of 84 cases. According to their findings, PAL shows a predilection for older males with a male-to-female ratio of 2:1. The mean age of presentation was 65 years. Most patients presented with symptoms and signs of adrenal insufficiency. More than two-thirds of all patients had significant bilateral enlargement of the adrenal glands, however, cases with unilateral slightly enlarged adrenal glands have also been reported.⁸

In a review of 55 cases by Wang et al, authors observed that majority of the reported cases (40/55) are bilateral, among which about 50% (20/40) manifest adrenocortical insufficiency even when the neoplasms are small.¹⁰ In patients with apparent adrenal insufficiency due to PAL, more than 90% of the adrenal cortex has already been destroyed. Therefore, clinically apparent adrenal insufficiency is a late feature of PAL, often accompanied by symptoms of advanced malignancy.¹¹

Primary adrenal lymphoma can be confused with metastatic carcinoma. Ultrasound, CT scans, and magnetic resonance imaging (MRI) are useful for the detection of adrenal gland enlargement. On CT and MRI, PALs tend to appear as complex masses with variable density; but a few

cases also show a homogeneous density¹⁴ and lesions with cystic appearance due to necrosis have been documented as well. Masses are low-signal intensity on T1-weighted MR images and high-signal intensity on T2-weighted images,¹⁵ with occasional areas of mixed signal. Several imaging features have been suggested as a means to differentiate adrenal malignancy and benign pathologies. PAL has been described to have a predilection for necrosis. Hemorrhage and calcification are also common.¹⁶ Nevertheless, there is no pathognomonic appearance on CT, MRI, or US to indicate lymphomatous involvement of adrenal glands and one cannot distinguish primary from metastatic lesions.¹⁷

The definite histopathological diagnosis is possible after CT-guided needle biopsy or surgical biopsy through laparoscopy or laparotomy. Most PALs are of B-cell lineage. More than 80% of those are diffuse large-cell lymphomas (DLBCL).^{10,12,13} In our case, the cells were positive for CD20 B-cell antigen and the CD45 leukocyte-common antigen.

The prognosis of PAL is poor. More than 90% of patients die within 1 year after the initial diagnosis.⁹ Advanced age, large tumor size, and adrenal insufficiency at the time of presentation and elevated LDH levels have been suggested as poor prognostic factors.¹⁸

Treatment of primary adrenal lymphoma is not satisfactory. Different modalities were used for the treatment of these patients such as bilateral adrenalectomy, multi agent chemotherapy, radiotherapy or a combination of them. CHOP chemotherapy is the standard first line treatment for diffuse large B-cell lymphoma. However, advanced patient age is a negative prognostic factor and the clinical experience with CHOP chemotherapy in DLBCL remains limited due to the rarity of the pathology. The addition of rituximab to CHOP (R-CHOP) has been recently shown to improve the outcome in elderly patients.¹⁹ Our patient with primary adrenal lymphoma who was treated with R-CHOP regimen was doing well till last follow-up. A new formulation of doxorubicin, pegylated liposomal doxorubicin has a reduced risk of toxicity (myelosuppression, gastrointestinal toxicity and cardiotoxicity) and may also have enhanced antitumor activity, due to its pharmacokinetic profile.²⁰

CONCLUSION

Primary adrenal lymphoma is a rare clinical entity and may present with adrenal insufficiency in 50% of cases. Adrenal insufficiency due to adrenal involvement in widespread non-Hodgkin's lymphoma is rare. Bilateral enlargement of

adrenal glands should raise the suspicion of lymphoma, especially in patients with clinical or laboratory features of adrenal insufficiency. Surgical treatment is now passé and standard CHOP is the first line treatment. However, prognosis remains poor.

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