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Bilateral adrenal masses with adrenal insufficiency: an unusual presentation of hepatocellular carcinoma

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Abstract

Adrenal insufficiency due to adrenal metastasis is rare and may be present only in 6.1% cases even in bilateral adrenal metastasis. The adrenal glands can maintain its cortisol axis until over 90% of adrenal cortex is destroyed. Bilateral large adrenal masses with adrenal insufficiency, though rare, should prompt further evaluation for a metastatic disease. We report a case of bilateral adrenal masses secondary to metastatic hepatocellular carcinoma causing adrenal insufficiency.

Key words: adrenal metastasis, hepatocellular carcinoma, adrenal imaging, adrenal insufficiency

Introduction

The commonest malignant lesions involving the adrenal glands are metastases, and they are the second most common tumours involving the adrenal glands followed by adenomas. A 30% to 70% of incidentally detected adrenal masses with a diagnosis of extra-adrenal malignancy are likely to be metastases.[1] Adrenal metastasis is usually bilateral, but can also be unilateral.[1] The median duration from cancer diagnosis to detection of adrenal metastasis is 2.5 years, though some cases have been reported 22 years later.[1] Detection of isolated adrenal metastasis prior to identification of primary malignancy is uncommon.[1] The commonest primary malignancies that metastasise to the adrenals are lung, breast, melanoma, gastrointestinal tract, pancreas and renal cell carcinoma.[1] Metastasis from hepatocellular carcinoma (HCC) mostly involve the lungs, followed by lymph nodes and bones.[2] Adrenal metastasis in HCC is uncommon, with an incidence of 8.4% in autopsy studies, and 1 to 3.9% in clinical studies.[2] Unilateral adrenal metastasis is unlikely to cause adrenal insufficiency (AI). AI in bilateral adrenal metastasis is also rare, with a prevalence of 6.1%.[3] We present a rare case of bilateral adrenal metastasis from HCC causing AI in a patient who presented with pyrexia of unknown origin.

Case presentation

A 57-year-old man presented with a two-month history of low-grade fever and occasional loose stools. His appetite had been poor and reported a weight loss of 10 kg over a period of one and a half years. He was increasingly fatigued and felt weak. He had received two blood transfusions one month apart at a local hospital 3 months ago, and there were no records of evaluation for a cause of anaemia. He consumed alcohol occasionally, denied intravenous drug abuse and high-risk sexual behaviour. On examination, he was thin built with a body mass index of 19 kg/m^2, pale and had no mucosal hyperpigmentation. His pulse rate was 90 beats per minute and blood pressure was 100/70 mm Hg. Abdomen was slightly distended with no palpable masses. Rest of the clinical examination was normal.

His fasting blood glucose was 80mg/dl, haemoglobin was 7.6 g/dl, with normal white cell and platelet counts. Blood picture showed evidence of iron deficiency anaemia. Erythrocyte sedimentation rate was 70 mm/1st hour and C-reactive protein was 5mg/L (<10 mg/L). Liver functions revealed aspartate aminotransferase (AST) 288 IU/L (8-33 IU/L), alanine aminotransferase (ALT) 80 IU/L (7-55 IU/L), alkaline

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phosphate (ALP) 898 IU/L (44-147 IU/L), and serum albumin 27 g/L (34 to 54 g/L). International normalized ratio (INR) was 1.8 and renal functions were normal. Serum sodium was 135 mmol/l (135-153 mmol/) and serum potassium was 6.0 mmol/l (3.5-5.5 mmol/l).

Ultrasound scan of abdomen showed bilateral suprarenal masses, liver cirrhosis with multiple small hypoechoic liver lesions. Contrast enhanced computed tomography (CECT) of the abdomen showed bilateral adrenal masses; the right measuring 5.7 (coronal) × 4.5 (antero-posterior) × 5.4 (sagittal) cm, with a non-contrast Hounsfield unit (HU) of 40, and the left measuring 2.6 (coronal) × 3.4 (antero-posterior) × 2.3 (sagittal) cm with non-contrast HU of 60. The absolute washout of the adrenal lesions was 66%. There were multiple small liver lesions measuring few millimetres. Specialised endocrine input was sought for further evaluation of the adrenal masses.

Hormonal evaluation was done for a possible secretory adrenal tumour. The 24-hour urinary metanephrines and chromogranin A was negative excluding the possibility of a catecholamine secreting pheochromocytoma. The androgen profile, serum aldosterone and renin levels were normal (Table 1). Overnight dexamethasone suppression test (ODST) was non-suppressed when repeated twice; the values being 95 nmol/L and 68.6 nmol/L. Serum adrenocorticotrophic hormone (ACTH) was elevated at 202 pg/ml (10-50 pg/ml). At this point, an ACTH secreting pheochromocytoma was suspected, but this was soon excluded by the low dose dexamethasone suppression test (LDDST) and extended dexamethasone suppression test (EDST) being suppressed. The cortisol day curve showed a low cortisol burden, with a 9 am cortisol of 248 nmol/l. The cosyntropin test showed a failed response confirming adrenal insufficiency (AI). (Table 2).

Table 1. Hormonal evaluation for secretory adrenal tumour

24 hour urinary metanephrines	0.06 mg/24 hours (<1 mg/ 24 hours)
Chromogranin A	66.53 µg/L (<100 µg/L)
ODST	95 nmol/L → 68.6 nmol/L (non-suppressed when repeated twice)
Plasma aldosterone	8.72 ng/dl (3-16 ng/dl)
Plasma renin	2.89 mU/L (3.11-41.2 mU/L)
Aldosterone renin ratio (ARR)	3 ng/dl/mU/L (<3.7 ng/dl/mU/L)
Dihydroepiandrostenidione sulphate (DHEAS)	150 µg/dL (26 to 200 µg/dL)
Testosterone	4.8 nmol/L (2.49-21.6 nmol/L)

Table 2. Hormonal evaluation of the cortisol axis

ODST	95 nmol/L → 68.6 nmol/L (non-suppressed when repeated twice)
LDDST	20.2 nmol/L (<50 nmol/L)
ACTH	202 pg/ml (10-50 pg/ml)
EDST	Day 0-323 nmol/l Day 2-16.1 nmol/l Day 4-23.8 nmol/l
Cortisol day curve	9 am-268 nmol/l 11 am-279 nmol/l 1 pm-220 nmol/l 3 pm-268 nmol/l 5 pm-245 nmol/l
Cosyntrophin test for cortisol	9.00 am-240 nmol/l 9.30 am-292 nmol/l 10.00 am-324 nmol/l

CECT of the whole body with CT adrenal protocol was performed to further evaluate the adrenal masses and look for the primary site of malignancy, and this was 2 months after the initial CT. Bilateral adrenal masses had increased in size, with the right measuring 10 (coronal) × 9 (antero-posterior) cm, with an absolute contrast wash-out of 63%, and the left measuring 3.5 (coronal) × 4.5 (antero-posterior) cm, with an absolute contrast wash-out of 72%. The non-contrast HU was 48 in both lesions (Figure 1). Cirrhotic liver was noted with multiple focal liver lesions in all segments in both lobes of the liver, ranging from 2mm to 30mm in size (Figure 2). Some lesions showed arterial phase enhancement with washout in portal venous and delayed phases. Multiple enlarged porta-hepatis and para-aortic lymph nodes were noted.

The possibility of HCC with adrenal metastasis, malignancy of unknown primary with hepatic and adrenal metastasis, or primary adrenal lymphoma with liver metastasis were considered and CT guided biopsy of the right adrenal gland was carried out. The histology of adrenal biopsy showed well vascularized tumour with prominent acinar pattern, cytologic atypia, mitotic activity, vascular invasion, absence of Kupffer cells and the loss of the reticulin network. Immunohistochemistry (IHC) was strongly positive for PCK and HepPar1, strongly consistent with HCC. Staining for synaptophysin, chromogranin, Melan A, S100, CD10, Calretinin, CK7, CK20, TTR-1, PSA, CA19-9 were negative. Staining for ACTH was negative (Figure 3). Hepatitis B, C and retroviral serology were negative, and Alpha-feto protein level was 1000 ng/ml.

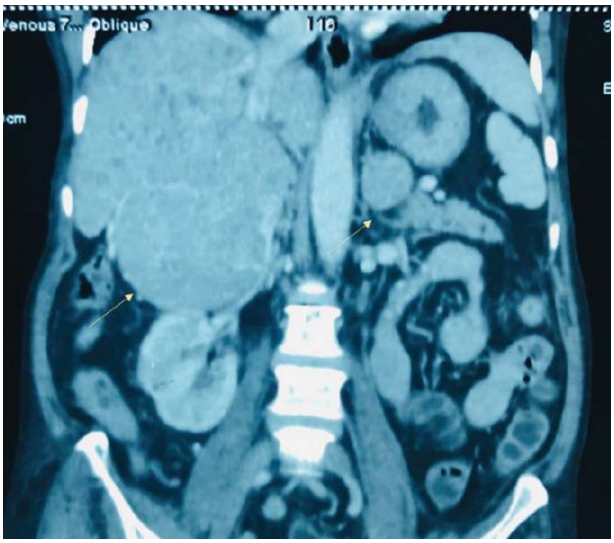


Figure 1. CECT showing bilateral adrenal masses, the right measuring 10cm × 9cm with a washout of 63%, and the left measuring 3.5cm × 4.5cm with a washout of 72%.

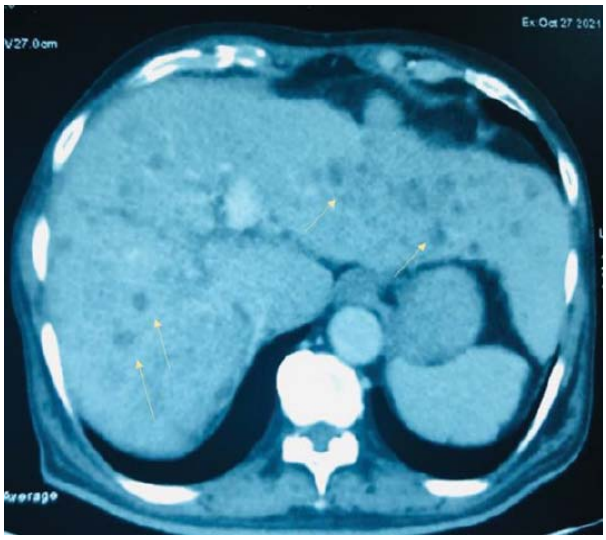
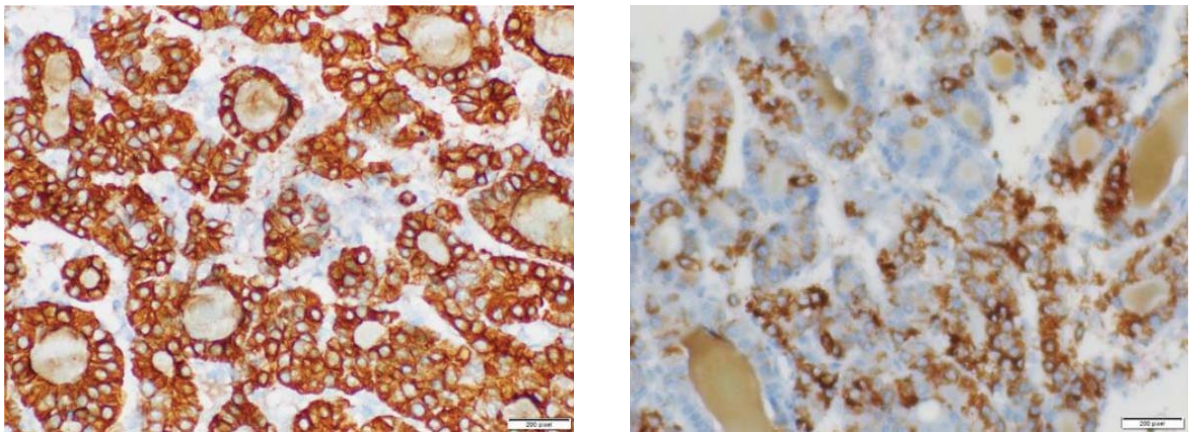


Figure 2. CECT abdomen showing the cirrhotic liver with multiple focal lesions.



(a) **(b)**

Figure 3. Right adrenal biopsy for histology and immunohistochemistry expressed PCK (a) and HepPar1 (b) consistent with hepatocellular carcinoma.

He was started on physiological replacement doses of oral hydrocortisone with the improvement of fatigue and weakness. Chemotherapy was commenced with intra-venous gemcitabine 1125mg on day 1, day 8 and day 15 with the plan of repeating up to 6 cycles every 28 days, followed by sorafenib 400 mg daily. Banding for oesophageal varices was done to prevent further occult bleeding. Two months later he developed left hemiplegia with a reduced level of consciousness. CT brain showed cerebral metastasis. Within a few days, he succumbed to multiorgan failure due to disseminated malignancy.

Discussion

This patient presented with a long-standing fever and was found to have an underlying malignancy. Neoplasms associated with fever are Castleman disease, Hodgkin and non-Hodgkin lymphoma, renal cell carcinoma (RCC), HCC, leukaemia, glioblastoma multiforme, ovarian cancer, and atrial myxoma.[4] The mechanism of neoplastic fever is due to the release of pyrogenic cytokines which act on the hypothalamus, causing a change in thermostatic set point.[4]

Our patient had clinical features suggestive of AI; fatigue, low normal blood pressure and hyperkalaemia. His symptoms improved with oral hydrocortisone replacement. AI was confirmed by failed response to the cosyntropin test. Unilateral adrenal metastasis does not generally cause AI and is reported in only 6.1% of bilateral adrenal metastasis.[3] Even bulky bilateral adrenal metastasis can maintain an adequate cortisol axis as adrenal glands have the ability to maintain their' function until >90% of the adrenal cortex is destroyed.[3] Malignancy can cause "stress" on the adrenal glands which may further blunt the cortisol response.[5] Further, severe weight loss can reduce plasma corticosteroid-binding globulin, and if this is not met with an increase in cortisol secretion, it may lower measured total plasma cortisol.[6] A combination of all these factors may have caused AI in this patient with bilateral adrenal metastasis.

Hounsfield unit (HU) is a relative quantitative measurement of radio density used in radiology when interpreting CT images. Water is arbitrarily defined as "0 HU". Tissues denser than water have positive (+) HU values and appear whiter on CT, and tissues less dense than water have negative (-) HU values and appear darker on CT. Therefore, lipid-dense tissue has a lower HU value. A non-contrast HU of > 10, as in our patient, can be seen in adrenal metastasis, primary adrenal malignancy like adrenocortical carcinoma (ACC), pheochromocytoma, and primary adrenal lymphoma. Benign tumours are generally lipid dense and therefore have a non-contrast HU <10, but 30% of benign adenomas are lipid poor and can have non-contrast HU of >10.[7] A malignant adrenal lesion usually enhances rapidly on CECT, and has a slower washout of contrast medium. Therefore, a relative washout of >40% or an absolute washout of >60% is suggestive of a benign lesion.[7] However, one-third of pheochromocytomas and metastasis from hyper-vascular malignancies like RCC and HCC can rarely have an increased washout >60% as observed in this patient.[8] It has been reported that 33% of hyper-vascular HCCs have increased contrast washout.[9] Absolute contrast washout of >60% has a sensitivity of 75.5% and specificity of 80% in differentiating a benign adrenal lesion from a malignant lesion excluding pheochromocytoma.[8] Therefore, the combination of a HU >10 with washout >60% supported the prior suspicion of pheochromocytoma or HCC. Furthermore, based on the HU value and contrast washout, the less likely possibility of bilateral pheochromocytoma with liver metastasis warranted exclusion. The 24-hour urinary metanephrines have a sensitivity of 97-100%, and chromogranin A has a sensitivity of 83% in detecting pheochromocytoma, and neither of these were elevated in this patient.[13] However, 15-20% of pheochromocytoma patients may have normal basal plasma and urinary catecholamine levels, termed as "non-functional" or "silent" pheochromocytomas.[11] This can be due to possible elevations in catecholamines only during paroxysms, or due to secretion of vasoactive peptides instead of catecholamines.[11] There are rare cases of ACTH-secreting pheochromocytoma in the absence of detectable catecholamine secretion.[12] However in this patient, the possibility of ACTH secreting pheochromocytoma was unlikely considering he had no cushingoid appearance, had hyperkalaemia instead of hypokalaemia, and he had no biochemical diagnosis of Cushing disease. Adrenal biopsy clearly excluded pheochromocytoma and negative IHC staining for ACTH thereby excluding adrenals as to be the source of ACTH secretion. Non-suppressed ODST in this patient was considered a false positive possibly due to poor absorption of dexamethasone by the diarrhoea or secondary to gut oedema in cirrhosis.[13]

Metastatic spread to the adrenals is mainly haematogenous, though lymphomatous spread and local invasion can also occur. Haematogenous spread to the adrenals occurs via the sinusoidal blood supply.[1] HCC generally progresses to extrahepatic metastasis when the intrahepatic tumour stage is above stage III.[2] Treating the primary malignancy with either chemotherapy or radiotherapy is the most effective first-line treatment for adrenal metastasis.[1] HCC with adrenal metastasis is usually not amenable to surgery due to deranged liver functions, the malignancy being

advanced by the time of detection of adrenal metastasis, and poor fitness for surgery.[14] This patient's HCC with adrenal metastasis was not amenable to surgery and required treatment with chemotherapy. The 1-year survival of HCC with adrenal metastasis after chemotherapy is as low as 20.3-24.9%, with a median survival duration of 4.6-7 months.[2]

Conclusion

Hepatocellular carcinoma is a rare cause of adrenal metastasis and AI. Bilateral asymmetrical large adrenal masses with AI, though rare, should prompt further evaluation for primary malignancy causing adrenal metastasis. Adrenal biopsy for histology is important in diagnostic evaluation. Though metastasis to the adrenals would generally have a high HU >10 with an absolute washout of <60%, HCC can rarely have an absolute washout >60%.

Author declarations

Consent

Informed consent for publication was obtained from the patient prior to his death.

Conflicts of interests

All the authors declare that they have no competing interests.

Criteria for authorship

All the authors contributed equally in the areas of conception and design of the work, drafting, and revising of the manuscript. All authors have read and approved the final manuscript.

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