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Hepatoid adenocarcinoma masquerading as adrenocortical carcinoma in an elderly male

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Abstract

Background:

Hepatoid adenocarcinoma is a malignant lesion arising from an anatomic site other than the liver with histological features similar to hepatocellular carcinoma. Hepatoid adenocarcinoma has been reported from various anatomical sites, but adrenal hepatoid adenocarcinomas are extremely rare.

Case Description:

A 70-year-old male with well-controlled hypertension presented with chronic abdominal pain and was found to have a large left-sided supra renal mass. The lesion showed radiological features suggestive of malignancy with local invasion. There was biochemical evidence of primary aldosteronism and a non-suppressed overnight dexamethasone suppression test. He underwent open left-sided adrenalectomy: histologically the tumour demonstrated features typical of a hepatoid carcinoma with bile production and immunohistochemical staining for Hep Par-1 and CD10 demonstrating a hepatic canalicular pattern. Adrenocortical-specific immunohistochemical markers (Inhibin and melan A) and neuroendocrine markers (synaptophysin and chromogranin) were negative. He did not have clinical or biochemical evidence of cirrhosis, Hepatitis B or C infection. Triple-phase CT scanning of the abdomen before resection of the adrenal lesion and five months following surgery did not show any significant lesion in the liver suggestive of primary hepatocellular carcinoma, except an 8 mm non enhancing benign-appearing cystic lesion.

Conclusion:

Most hepatoid adenocarcinomas originate from the gastro-intestinal tract. We present a patient with hepatoid adenocarcinoma masquerading as adrenocortical carcinoma due to misleading imaging and biochemical evidence. Very little is known about their pathogenesis, especially those with an atypical site of origin such as the adrenal gland.

Keywords: Adrenal, Hepatoid adenocarcinoma, Liver, Case report

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Introduction

A malignant adrenal lesion generally could either arise from adrenal tissues such as the cortex, medulla or stromal tissue, or could be a metastatic deposit from a primary site such as lung, breast, pancreas, colon, ovary or kidney [1, 2]. Rarely, other tumours such as lymphomas may infiltrate the adrenal gland. Adrenocortical carcinomas (ACC) are very rare in contrast to benign adrenal adenomas [3]. Around half of all ACCs are hormonally active and may present with features of Cushing syndrome, virilization or feminization,or hyperaldosteronism. Non-functional ACCs present with symptoms related to mass effects or metastasis, although some are increasingly diagnosed incidentally with CT scanning for an unrelated problem.

Hepatoid adenocarcinoma (HAC) is a rare type of tumour that is morphologically identical to primary hepatocellular carcinoma (HCC) but arises from an anatomic site other than the liver [4]. More than 80% arise in the stomach, with other well-known sites being the gall-bladder, uterus, lung and urinary bladder[4]. Biochemical evidence of primary aldosteronism or subclinical Cushing is not reported in any of the patients with HAC, to the best of our knowledge.

Adrenal HAC is exceedingly rare and is limited to a handful of case reports. We report a patient with adrenal HAC who was initially suspected to have ACC based on imaging and biochemical findings.

Case Report

A 70-year-old male presented with intermittent dull, aching type abdominal pain for 3 months. He had a history of hypertension for 20 years. He was a non-smoker and had consumed alcohol 5 units per day for 10 years. His blood pressure was well controlled with a single anti-hypertensive agent (prazosin 1 mg per day).

A left-sided adrenal mass was found on ultrasound scanning. Further evaluation of the adrenal mass with contrast-enhanced computed tomography (CECT) showed a large 9 x 7.5 x 7 cm left-sided suprarenal mass with irregular edges (Figure 1). The tumor was hyperdense with 35 Hounsfield units on pre-contrast CT scanning. Right adrenal gland appeared normal. A small 8 mm non-enhancing cystic focal lesion was found in the liver.

He was normokalemic. He had high plasma aldosterone, a suppressed plasma renin and raised aldosterone/renin ratio indicative of primary aldosteronism. Overnight 1mg dexamethasone suppression testing (ODST) showed a serum cortisol of 97 nmol/L; 24-hour urinary vanillylmandelic acid excretion was normal (Table 1). Other estimates of catecholamine excess were not available.

He underwent open left-sided adrenalectomy: the tumor was adherent to the posterior abdominal wall but without invasion of kidney, stomach or spleen, and was resected (apparent R0 resection). Right adrenal was normal. There were no enlarged abdominal lymph nodes, so none was removed.

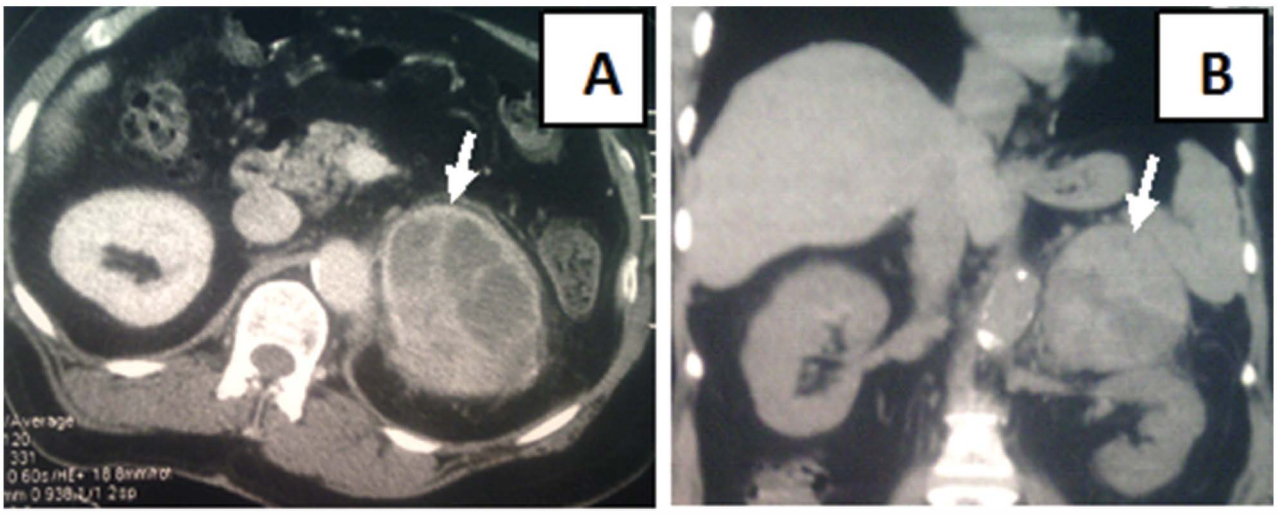

Figure 1 : Contrast enhanced CT abdomen showing a heterogeneous left-sided suprarenal mass with irregular margins (White arrow). A, axial plane. B, sagittal plane.

Table 1: Adrenal hormone profile of the patient before surgery

Test (units)	Patient value	Reference range
Plasma Aldosterone (ng/dL)	27.3	<21
Plasma Renin (ng/L)	3.6	5.41-34.53
Aldosterone/ renin ratio (ng/dL per ng/L)	7.58	>5.7 suggests primary aldosteronism
Overnight dexamethasone suppression test- cortisol (nmol/L)	97	<50
24-hour urinary vanillylmandelic acid (mg/24h)	6.6	1-11

The tumor was histologically compatible with a well-differentiated hepatocellular carcinoma (HCC). Macroscopically, 110 × 105 × 85 mm tumor was solid with multiple green yellow nodules. Most of the tumor appeared necrotic. Non-neoplastic adrenal tissue was not identified. Microscopically, the tumor was composed of polygonal cells with abundant eosinophilic cytoplasm and well-defined cell borders showing a predominant trabecular architecture. The cells had rounded vesicular nuclei and prominent nucleoli. Focal pseudoacinar formations were noted, and these spaces contained a thick yellow green pigment resembling bile (Figure 2). Mitotic activity was prominent (12/10 mitoses per hpf) and the tumor breached the capsule (R1 resection). Hepatocyte Paraffin 1(Hep Par-1) positivity and cannalicular CD10 staining pattern characteristic of HCC were noted on immunohistochemistry. However, alpha-feto protein (AFP), glypican-3 (GPC -3) and thyroid transcription factor (TTF) were negative. Immunohistochemical markers specific for adrenocortical tumours (Inhibin and melan A), neuroendocrine markers (synaptophysin and chromogranin) and adrenocorticotrophic hormone (ACTH) immunostaining were negative. Markers expressed by gastric hepatoid adenocarcinomas such as epithelial membrane antigen (EMA), cytokeratin 7 (CK7) and cytokeratin 20 (CK20) were also negative.

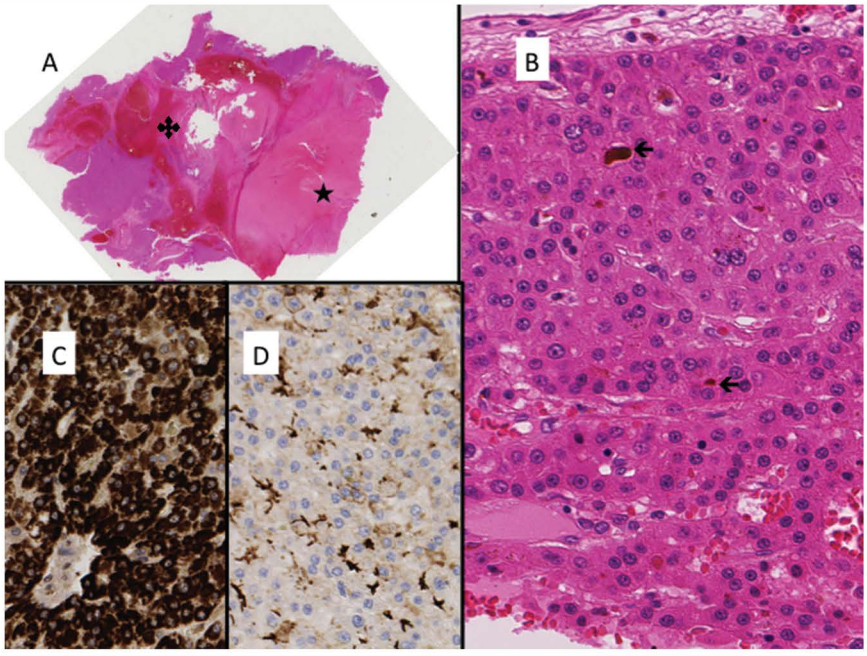

Figure 2 : Tumour Histology. **A**, Hematoxylin & eosin-stained section of adrenal tumor showing areas of hemorrhage (✣) & necrosis (★) (3.5 x magnification). **B**, Polygonal tumor cells with abundant pink cytoplasm show trabecular and focal pseudo-acinar growth patterns, bile production ( ) is identified (400 x magnification). **C**, Immunohistochemistry for Hep Par-1 (200x magnification). **D**, Immunohistochemistry for CD10 staining showing a canalicular staining pattern (200x magnification).

A serum AFP level was not performed prior to surgery: however, a post-operative serum AFP was normal (2.43 IU/ml, normal range 0-7.2 IU/ml). Liver enzyme and bilirubin profile was normal and there were no features of cirrhosis clinically or radiologically. A hepatitis screen was negative for hepatitis C and B. Triple-phase CECT scanning of the abdomen did not show any lesions in the liver other than the benign looking sub-centimeter cystic lesion seen earlier and then stable in size five months after the adrenalectomy.

Resection of the tumor did not have a significant impact on his blood pressure control. Post-operative ODST remained non-suppressed. He was subsequently loss to follow up and was reported to have died about one year after the surgery.

Discussion

The differentiation between primary HCC and an extra-hepatic hepatoid tumour is based mainly on the demonstration of the presence or absence of a primary lesion suggestive of a HCC in the liver. Common metastatic sites of HCC include the lung (55%), abdominal lymph nodes (53%), musculoskeletal tissue (28%) and the adrenal gland (11%) (7, 9). Contrarily, HACs are usually large at presentation and mostly metastasize to the abdominal lymph nodes and liver. Microscopically, HAC demonstrate polygonal cells with abundant, eosinophilic cytoplasm, evidence of bile production and bile canaliculi formation similar to HCC [4]. This poses a diagnostic difficulty due to a lack of differentiating features in morphological assessment from HCC. Therefore, the diagnosis can be a highly problematic when there are hepatic metastases at the time of presentation. Certain immunohistochemistry stains help differentiation though there is no consistent pattern. Some studies suggest that a negative Hep Par 1 and positive CK19 and CK20 are more in favour of HAC rather than HCC [4, 5]. However, these reports are mostly based on gastric HAC, so the validity of these observations in the light of other anatomical sites is still questionable. The absence of malignancy in the liver along with supportive histology and immunohistochemistry helped establish a diagnosis of HAC in our patient. A small (8mm) cystic lesion raised the concern as a potential for primary, but after detailed radiological assessment it was deemed extremely unlikely to be a malignant lesion.

Hepatoid adenocarcinoma originating from adrenal gland is extremely rare. We performed asystematic literature search in *PubMed* ((hepatoid[Title/Abstract]) AND (adrenal[Title/Abstract])) and *Google Scholar* (all in title: hepatoid adrenal) to retrieve available reports on adrenal HAC. This was followed by cross-referencing on available full-text articles. Abstracts were reviewed for eligibility of the reports and selected reports were read in full text. Articles in languages other than English were translated into English. Nine case reports were available in the literature [6-14].The findings of the case reports are summarised in Table 2.

Except for one female who was 48 years, all the others were men over 50 years of age. The reported cases show marked geographical predilection to China. Serum alpha fetoprotein (AFP) is reported in 8, of which 6 had elevated levels. In our patient AFP was not measured pre-operatively since HAC was not suspected until after surgery. Another interesting finding was that 7/9 reported patients plus our patient had left adrenal involvement, the reason for which is unclear. Further studies to reveal any potential embryological association would be valuable.

AFP staining was positive in 6 patients and negative in 3 patients. In 7, Hep Par 1 staining was positive while this was not mentioned specifically in the other two. There was variable positivity of cytokeratin staining, including CK19 in the reported patients. This immunohistochemical pattern is different to that reported commonly with HAC at other sites, where there was low positivity for Hep Par 1 and almost 100% positivity for CK19 [3] .

The other remarkable feature found in our patient is positive case detection test for primary aldosteronism without morphological or immunohistochemical evidence of adrenal tissue in the tumor. The level of aldosterone in our patient was not suggestive of an aldosterone-producing ACC, which generally produces aldosterone levels many times higher than the normal [15]. Primary aldosteronism has not been associated with HAC in the available reports. HCCs have been shown to express high levels of angiotensinogen, or angiotensin I with stimulation of aldosterone level through angiotensin II [16]. HCC can also produce renin causing secondary hyperaldosteronism [17]. A post-operative aldosterone renin ratio would have been valuable in ascertaining the role of HAC on this biochemistry, but unfortunately this could not be arranged due to logistical reasons. Hypertension which was there prior to surgery did not show any improvement post-operatively. It is possible, indeed likely, that there was mild primary hyperaldosteronism due to a microadenoma in the contralateral adrenal. We have highlighted this association to allow close assessment and evaluation by clinicians in any future encounters

Table 2 : Summary of reported patients with adrenal hepatoid adenocarcinoma

Case report	Patient details	Bio chemistry	Imaging	Histology	Outcome	Notes
Yoshioka 1994 (Japan)	57, male	AFP 30500 ng/mL.	8×5 cm mass in the left adrenal. 10mm lesion in segment 8 of the liver.	AFP positive tumor	Not mentioned	Initial lesion in liver: histology chronic hepatitis, lesion detected 7 months post-op: HCC
Liu, 2009 (China)	57, male	AFP 570 ng/mL.	3.5×2.2×2 cm lesion in left adrenal gland.	Positive Hep Par 1, ferritin, AFP, CEA, CK8, CK18, α1-AT and α 1-ACT.	Not mentioned	
Malya 2014 (Turkey)	48, female	AFP 3900 ng/mL.	4×5 cm mass close to right hepatic lobe and crus of the diaphragm seen in FDG-PET.	Positive AFP, glipan and CK 8, Hep par 1, CK 17 and 19, pCEA. Negative chromogranin, CD 20, ER, PR, GCDFP15.	Not mentioned	
Gouiaa 2015 (Tunisia)	70, male	Serum AFP not assessed	11.5×7.8×7 cm heterogeneous mass in the left adrenal	Positive Hepatocyte cell antibody. Negative AFP, alpha inhibin, cytokeratin, keratin 19, chromogranin.	At 3 months follow up patient is alive	
Liu 2015 (China)	53, male	AFP 31353 ng/mL.	13×10×8 cm lesion in left adrenal. Lung lesions were present	Positive Hep Par 1, CK, AFP, CD 34. Ki67 30% positivity.	At 7 months patient is alive	
Liu 2016 (China)	60, male	AFP normal. Aldosterone 27.5 ng/dL (posture not specified). Cortisol 748 nmol/L (timing not specified)	5×7 cm cystic and solid lesion in the right adrenal	Positive Hep Par 1, glapican 3, CD34, CK, arginase 1. Negative AFP, α-inhibin, CgA, CEA. 30% Ki-67 positivity,	Survival at 30 months (during reporting)	

Case report	Patient details	Bio chemistry	Imaging	Histology	Outcome	Notes
Zhang, 2016 (China)	77, male	AFP>13000 ng/mL.	13×10×9 cm lesion in left adrenal gland	Positive Hep Par1, AFP, CK8, CK18, CD10, EMA. Negative Inhibin α.	Well up to 13 months	
Lin 2018 (China)	64, male	Normal plasma AFP. Elevated CEA, CA 125, CA 15-3, CA19-9. Normal Cortisol and ACTH.	9.1×9.7×9.2 cm lesion of upper pole of left kidney Left renal artery and vein compressed, 7mm nodule in right lung and 3 mm nodule in left hepatic lobe. FDG-PET showed lung metastasis,	Positive CK8/18, CK 19, CK 7, Hepatocyte marker, Hep Par 1. Negative AFP and CK 20, synatophysin, chromogranin A.	Died after 9 months	NGS mutations in ATM, CDKN2A, EGFR, STK11, TP53, BIM, MLH1
Deng 2018 (China)	83, male	AFP>24200 ng/mL, elevated serum NSE level. Normal CEA, CA17-4, CA19-9, Cortisol, ACTH, catecholamine, renin & aldosterone.	13.1×8.7×11.5cm mass in left adrenal with tumor thrombosis of the left real vein extending to IVC. Liver and lung normal. Lymph node metastases seen.	Positive Hep Par 1, Arg, AFP, glapican. Ki-67 positivity 1%.	Died after 9 months	Developed lung metastases initially and liver metastases later.

of similar patients.

Similarly, a non-suppressed ODST suggested the possibility of subclinical Cushing, but further biochemical testing was not arranged since there was need to proceed for surgery without a delay. It seems more likely that this was a false positive due to physical and psychological stress leading to activation of hypothalamo-pituitary-adrenal axis. Post-operative persistence of non-suppressed ODST favors this rather than tumor being the source of cortisol excess, and such false-positives to the ODSST are seen in some 20% of patients. Indeed, in the light of the primary aldosteronism, this may also reflect co-secretion of cortisol and aldosterone by a contralateral adenoma [18].

The origin of adrenal HAC is poorly understood. The possibility of the presence of ectopic hepatic tissue in organs derived from foregut endoderm is a suggestive speculation of the pathogenesis of HAC in sites such as stomach and pancreas[19]. However, the adrenal cortex originates from the intermediate mesoderm, and it is therefore possible that dormant pluripotent cells in the adrenal gland undergo hepatoid differentiation later in life.

Conclusions

Large adrenal lesions may not simply consist of benign or malignant adrenocortical or adrenomedullary tissue, or metastases from distant sites. Rare HAC arising from the adrenal seems to behave distinctly from other HAC of the commoner sites. Studies on cellular and molecular origin would shed light on these interesting findings.

Declarations

Funding: There was no funding involved in relation to this case report.

Conflicts of interest:All authors declare that there is no conflict of interest related to this paper.

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