

An Adrenal Hepatoid Adenocarcinoma with Left Renal Vein Thrombosis Extending into the Inferior Vena Cava

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Hepatoid adenocarcinoma (HAC) is an uncommon tumor with morphological resemblance to hepatocellular carcinoma. HAC of the adrenal glands is extremely rare. Here, we report the case of an 83-year-old man with adrenal HAC who presented with a greatly increased preoperative serum alpha-fetoprotein level ($> 24,200$ ng/mL). The findings of magnetic resonance imaging and contrast-enhanced abdominal computed tomography revealed a large mass occupying the left adrenal gland region as well as thrombosis of the renal vein extending into the inferior vena cava. Subsequently, the adrenal HAC was treated by surgical resection and targeted sorafenib therapy. However, the patient died 9 months later because of systemic metastasis of the tumor. In conclusion, adrenal HAC with inferior vena cava tumor thrombosis is extremely rare and challenging to diagnose and treat. Pathological and immunohistochemical examination are helpful for diagnosis and surgical excision is the main strategy for treating the tumor.

Keywords: hepatoid adenocarcinoma; adrenal gland; inferior vena cava thrombosis

INTRODUCTION

Hepatoid adenocarcinoma (HAC) is an extremely rare neoplasm which has a similar tissue morphology to hepatocellular carcinoma (HCC) and is associated with frequent expression alpha-fetoprotein (AFP). HAC generally originates from the stomach, ovaries, lungs, gallbladder, pancreas, and uterus⁽¹⁾. However, to date, only sporadic cases of HAC have been reported in the literature to originate from the adrenal glands. In this report, we present

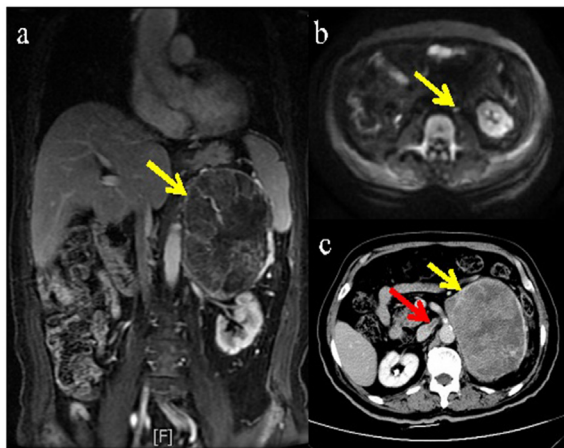


Figure 1. (a) Abdominal magnetic resonance imaging (MRI) revealed a large mass ($13.1 \times 8.7 \times 11.5$ cm) in the left adrenal gland region with compression of the surrounding tissues and organs (yellow arrow). (b) Enlarged retroperitoneal lymph nodes (yellow arrow). (c) CT scan showing a tumor thrombosis in the left renal vein extending into the inferior vena cava (red arrow).



Figure 2. A well-encapsulated tumor with partially necrotic tissue. No infiltration to the left kidney was observed.

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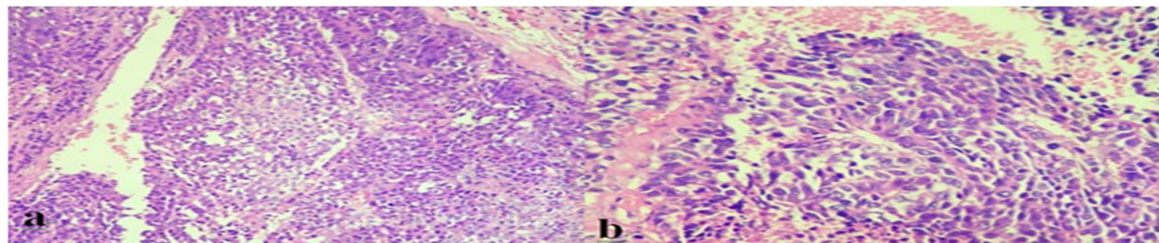


Figure 3. Histopathological features of hepatoid adenocarcinoma of the adrenal gland. The tumor was composed of polygonal cells with atypical nuclei arranged in irregular lamellar and cordlike structures ((a) HE \times 400, (b) HE \times 400).

information regarding a rare adrenal HAC with tumor thrombosis of the renal vein extending into the inferior vena cava.

CASE REPORT

An 83-year-old Chinese man with a medical history of herpes zoster, diabetes, and hypertension was admitted to our hospital because of dizziness and fatigue. His cranial magnetic resonance imaging (MRI) showed multiple ischemic demyelination lesions in the brain and senile cerebral atrophy which could not fully justify the occurrence of his dizziness and fatigue. Laboratory investigations showed that the serum AFP level was exceedingly high ($> 24,200$ ng/mL). However, except for an elevated serum neuron-specific enolase level of 61.11 ng/mL (normal range, 0.00 – 16.30 nmol/L), the serum levels of other tumor markers, including carcinoembryonic antigen (CEA) and carbohydrate antigens (CA) 72 - 4 and CA 19 - 9 were completely normal. The patient then underwent abdominal ultrasonography, the

results of which revealed a large hypoechoic mass in the left upper abdomen. The findings of MRI and contrast-enhanced abdominal computed tomography (CT) revealed a large mass (13.1 \times 8.7 \times 11.5 cm) occupying the region of the left adrenal gland, associated with a renal vein and inferior vena cava thrombosis (Mayo I) and enlarged retroperitoneal lymph nodes (**Figure 1**). The liver and lungs showed no significant tumors, and there was no evidence of metastasis. The levels of serological markers for hepatitis B and C viruses were within normal limits. The levels of adrenal function indicators such as corticotrophin, cortisol, serum catecholamine, urinary vanillin-amygdalic acid, and recumbent renin, angiotensin, and aldosterone were also normal on admission. On the basis of these findings, we diagnosed the tumor as a malignant non-functional adrenal tumor with a clinical stage of T3N1M0. Subsequently, the patient underwent surgical resection including left adrenal tumor resection, left nephrectomy, and left renal vein tumor thrombectomy.

The pathological specimen showed an encapsulated tumor with partial ischemic necrotic tissue inside. The surrounding adipose tissue showed no tumor involvement (**Figure 2**). The para-aortic lymph nodes and peripheral vessels showed metastasis (1/1) and tumor thrombus, respectively, while the surrounding nerve plexus showed cancer involvement. Histopathological findings revealed poorly differentiated cells with round atypical nuclei resembling HCC cells under a light microscope. The cells were arranged in irregular lamellar and cordlike structures (**Figure 3**). Immunohistochemical findings showed the cells to be focally positive for hepatocyte paraffin-1 (Hep-1) antigen (**Figure 4.a**) and approximately 50% positive for antigen Ki-67 (**Figure 4.b**) and glypican-3 (GPC-3) (**Figure 4.c**). The tumor cells were also positive for AFP and arginase-1 (Arg-1). After surgery, the serum AFP level of the patient decreased to 2897 ng/mL. On the basis of these findings, the patient was diagnosed with adrenal HAC. He was then administered targeted treatment with sorafenib. At two months after surgery, the serum AFP level of the patient had increased to 8998 ng/mL, and the results of repeated imaging showed multiple nodules in both lungs (**Figure 5.b**) which were considered to be metastatic tumors according to the insignificance observation of tumor in both lungs before surgery (**Figure 5.a**). Eight months after surgery, CT findings revealed further progression of the pulmonary nodules (**Figure 5.c**) as well as metastatic tumors in the liver (**Figure 5.d**). The patient eventually died due to systemic metastasis of the tumor in 2018.

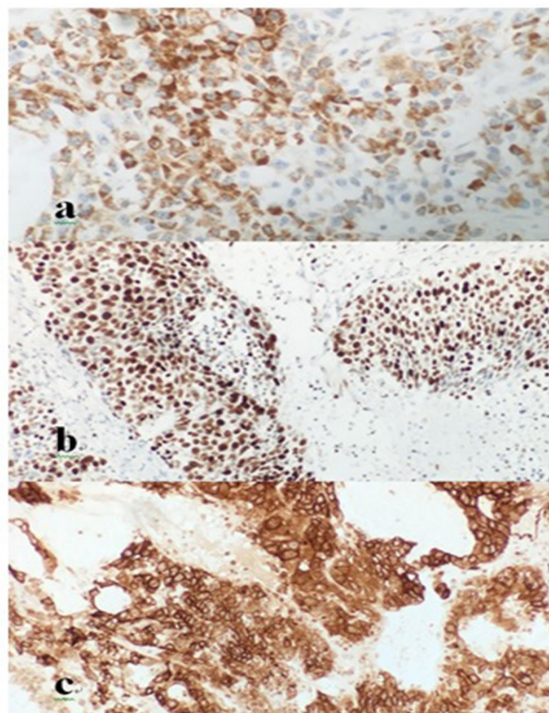


Figure 4. Immunohistochemical staining of adrenal hepatoid adenocarcinoma. (a) Hep1 positivity of tumor cells (\times 200). (b) Ki-67 positivity of tumor cells (\times 100). (c) Glypican-3 positivity of tumor cells (\times 200).

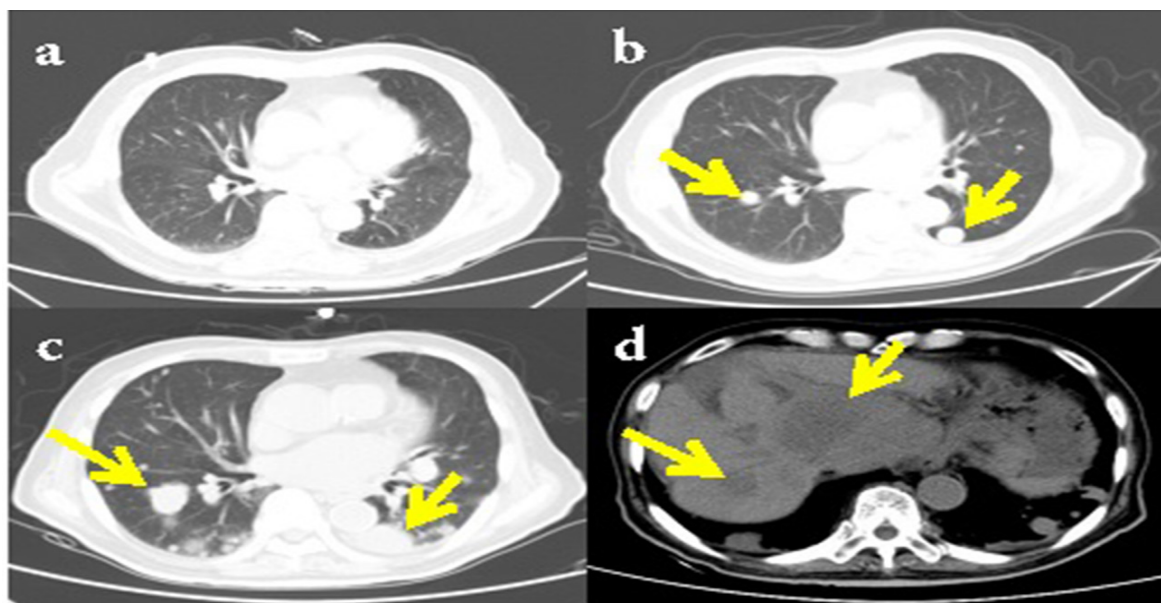


Figure 5. (a) Chest CT did not show any significant mass before surgery (b) Two months after surgery multiple high-density nodules were seen (c) At eight months after surgery the tumor had progressed. (d) As shown by the arrows, liver metastasis occurred eight months after surgery.

DISCUSSION

HAC is a very rare type of extrahepatic adenocarcinoma with pathological and morphological similarity to HCC^(1,3). In 1985, Ishikura et al. reported the first case of an AFP-producing gastric carcinoma with features of hepatic differentiation, which they termed “gastric hepatic adenocarcinoma”⁽⁴⁾. Since then, HAC has been identified in various organs of the abdominal cavity with the stomach being the most common location. Here, we have reported an HAC of the adrenal glands. To date, only seven cases of adrenal HAC have been reported in the literature⁽⁵⁾, with the first one being reported by Yoshioka et al. in Japan in 1994⁽⁶⁾. Serum AFP level is generally considered to be an effective marker for diagnosing HCC and HAC. In the present case, our patient showed an extremely elevated serum AFP level. However, AFP, a well-known marker of HCC, is usually produced by HCC and gonadal tumors, and tissues of these tumors can be positive for this marker⁽⁷⁾. Moreover, adrenal cortex cancer can also cause elevated AFP levels⁽²⁾. Therefore, histopathological results are necessary for diagnosing HAC. In most cases, diagnosis of HAC is straightforward if the patient shows increased serum AFP levels, positive tumor tissue AFP expression upon immunohistochemical analysis, and hepatocyte differentiation upon histological analysis. However, Lin et al. recently encountered a case of non-AFP-producing adrenal HAC⁽⁵⁾ and they used next-generation sequencing to establish the diagnosis. There is currently no conclusive evidence for differentiating between HAC and HCC during clinical diagnosis. Su et al. performed a literature review of the clinicopathological characteristics used for differential diagnosis of HAC over a 10-year period (2001–2011)⁽⁷⁾. They identified 98 eligible studies (involving 217 patients) and found that immunohistochemical markers can help clearly differentiate HAC from HCC. HCC should be diagnosed based on the results of dynamic imaging (such as CT or MRI) and/or liver tumor bi-

opsy. A typical dynamic image of HCC shows intense arterial uptake followed by contrast washout in the venous and/or delayed phases⁽⁷⁾. In contrast, HAC can be definitively diagnosed on the basis of pathological and immunohistochemical findings. HACs are composed of polygonal cells with nuclei at the centre of sheet-like or trabecular portions, and they occasionally show bile production and/or bile canaliculi formation⁽³⁾. Generally, AFP, Arg-1, GPC-3, Ki-67, and Hep-1 antigen are positive indicators of HCC. In the present case, the tumor cells were positive for AFP, Arg-1, GPC-3, and Hep-1 antigen. Recently, several studies have suggested that PET/CT might play a role in the diagnosis of this individual disease. Wang et al. reported a case of HAC revealed by FDG PET/CT whose primary tumor and metastases showed a moderate FDG uptake⁽⁸⁾. Hu et al. also reported positive findings in patients with HAC⁽⁹⁾. However, another study reported a case without any uptake on PET-CT⁽¹⁰⁾.

Surgical resection is the main treatment for HAC in combination with adjuvant chemotherapy and radiotherapy. Adrenal HAC with inferior vena cava tumor thrombosis has not been previously reported. The safety and efficacy of radical adrenal tumor resection and inferior vena cava tumor thrombectomy have not been fully studied. Complete resection with negative margins represents the best chance of cure for the patient⁽¹¹⁾. A research by Danuel et al.⁽¹²⁾ compared 65 patients undergoing resection of adrenocortical carcinoma with and without inferior vena cava (IVC) tumor thrombosis which indicated that the median survival for patients with IVC involvement was 14.8 months compared to 43 months for patients without IVC thrombosis. The short-term safety and survival were similar to two groups while survival beyond 36-months was limited in patients with inferior vena cava tumor thrombosis. Because of its high malignancy rate, HAC generally has a worse prognosis than common adenocarcinoma. In addition, HAC is usually metastatic at initial pres-

entation⁽¹³⁾. The most common sites of metastasis are the lymph nodes, liver, and lungs⁽⁷⁾. In the present case, the patient first presented with lymph node metastasis, followed by lung and liver metastasis, which suggested that the tumor cells are extremely aggressive. Furthermore, most cases of adrenal HAC have been reported from Asian countries, especially Japan and China⁽⁵⁻⁶⁾. Whether this trend is consistent with the incidence area of HCC remains to be studied.

CONCLUSIONS

Having in mind this rare pathological type of adenocarcinoma which manifests as a non-uniformly enhanced soft-tissue mass on imaging and is accompanied by an increase in AFP level is important for timely diagnosis and treatment. Despite the lack of literature regarding adrenal HAC, radical surgery is still the preferred treatment for cases associated with inferior vena cava tumor thrombosis.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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