Clinical Case Report

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Non-α-fetoprotein-producing adrenal hepatoid adenocarcinoma

A case report and literature review

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Abstract

Rationale: Adrenal hepatoid adenocarcinoma typically secretes alpha-fetoprotein (AFP). Here, we report a case of non-AFP-producing adrenal hepatoid adenocarcinoma. Next-generation sequencing (NGS) was conducted to identify gene mutations.

Patient concerns: A 64-year-old man presented with mild back pain and unexplained weight loss for 3 months.

Diagnoses: Contrast-enhanced magnetic resonance imaging (MRI) showed a mass ($9.9 \times 9.7 \times 9.1\,mm^3$) above the upper pole of the left kidney. The left renal artery and vein were compressed. The tumor was positive for CK8/18, CK19, CK7, hepatocyte marker (Hepatocyte), and Hep Par 1, but negative for AFP. Plasma AFP was 2.75 ng/mL (normal range: 0–7 ng/mL). NGS revealed mutations of the following genes: *ATM*, *CDKN2A*, *EGFR*, *STK11*, *TP53*, *BIM*, and *MLH1*. A diagnosis of adrenal hepatoid adenocarcinoma was established.

Interventions: The treatment included 4 cycles of the mFOLFOX6 regimen (oxaliplatin, leucovorin, and fluorouracil), transcatheter arterial chemoembolization, and apatinib.

Outcomes: The patient died 9 months after the diagnosis.

Lessons: This case highlights the importance of thorough clinical, radiological, and immunohistochemical investigation for suspected adrenal hepatoid adenocarcinoma. Metastasis from other primary tumors should be ruled out. Furthermore, AFP is not necessarily elevated in adrenal hepatoid adenocarcinoma. NGS could be helpful in establishing the diagnosis and selecting treatments.

Abbreviations: ^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, ACTH = adrenocorticotropic hormone, AFP = alpha-fetoprotein, ATM = ataxia-telangiectasia gene, BIM = BCL2 like11, CA = carbohydrate antigen, CD = cluster of differentiation, CDA = cytidine deaminase, CDKN2A = cyclin dependent kinase inhibitor 2A, CEA = carcinoembryonic antigen, CK = cytokeratin, c-Kit = KIT proto-oncogene receptor tyrosine kinase, c-SRC = proto-oncogene SRC, CT = computed tomography, EGFR = epidermal growth factor receptor, GSTP1 = glutathione S-transferase pi 1, GSTT1 = glutathione S-transferase theta 1, HAC = hepatoid adenocarcinoma, Ki67 = proliferation marker, MLH1 = mutL homolog 1, MRI = magnetic resonance imaging, NGS = next-generation sequencing, NSE = neuron specific enolase, P63 = tumor protein 63, STK11 = serine/threonine kinase 11, SUV = standardized uptake value, TACE = transcatheter arterial chemoembolization, TP53 = tumor protein p53, TPMT = thiopurine S-methyltransferase, TTF-1 = thyroid transcription factor-1, VEGFR-2 = vascular endothelial growth factor receptor-2.

Keywords: adrenal hepatoid adenocarcinoma, alpha-fetoprotein, multimodality imaging, mutations, next-generation sequencing, pathology

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JL and YC equally contributed to this work.

The authors report no conflicts of interest.

The patient's family members provided written informed consent for the publication of the present case report. Ethical approval was not applicable.

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1. Introduction

Hepatoid adenocarcinoma is an extrahepatic malignancy with morphologically and immunohistochemically distinct foci of hepatic differentiation.[1] The tumor mostly occurs in the stomach, but could arise from many other organs.[2–10] Only sporadic cases of adrenal hepatoid adenocarcinoma have been reported,[11–15] with most producing alpha-fetoprotein (AFP).[12–14]

Herein, we present a case of non-AFP-producing adrenal hepatoid adenocarcinoma. Next generation sequencing (NGS) was conducted to identify candidate gene mutations. A literature review of published cases was also conducted.

1.1. Case report

A 64-year-old man presented with mild back pain and weight loss for 3 months. His medical, family, and psychosocial history was unremarkable. Computed tomography (CT) scan at admission revealed a mass ($9.3 \times 8.9 \times 9.7\,cm^3$) above the upper pole of the

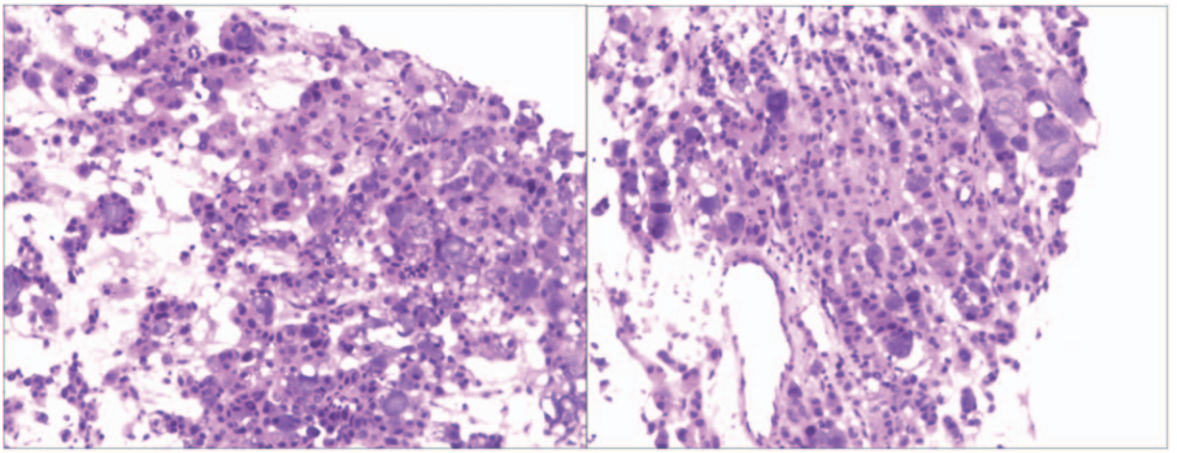

Figure 1. Histologic examination of the suprarenal mass shows atypical cells, arranged in acinar and cord-like patterns, with mucus secretion. H&E staining; magnification: ×100.

left kidney, a 7-mm nodule in the right lung, and a 3-mm nodule in the left hepatic lobe. Contrast-enhanced magnetic resonance imaging (MRI) demonstrated a mass, $9.9 \times 9.7 \times 9.1\,cm^3$ in size, compressing against the left renal artery and vein. A biopsy revealed poorly differentiated cells with abundant eosinophilic cytoplasm and round nuclei, resembling hepatocellular carcinoma cells. The cells were arranged in acinar and cord-like patterns (Fig. 1). The tumor was positive for CK8/18, CK19, CK7 and hepatocyte and negative for AFP, suggesting that these cells were hepatoid. No tumor mass was identified in the liver by contrast enhanced MRI. Lung cancer and neuroendocrine tumor were ruled out as the source of the adrenal tumor by immunostaining. Poorly differentiated adenocarcinoma with unknown origin was considered at this point of time.

Laboratory investigations showed elevations in carcinoembryonic antigen (95.75 ng/mL; normal range: 0–5 ng/mL), carbohydrate antigen (CA) 125 (1512 U/mL; normal: 0–35 U/mL), CA 15–3 (438.5 U/mL; normal: 0–25 U/mL), and CA19–9 (36.01 U/mL; normal: 0–27 U/mL). Plasma AFP, adrenocorticotropic hormone, and cortisol were normal. ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) showed a moderate increase in ^{18}F-FDG uptake in the left adrenal gland with a maximum standardized uptake value (SUVmax) between 2.4 and 7.8 and a mean between 2.1 and 6.9. The tumor was $9.8 \times 9.3 \times 10.8\,cm^3$ in size. A soft tissue lesion, $2.3 \times 1.7\,cm^2$ in size, with increased ^{18}F-FDG uptake (SUVmax = 6.04) was detected in the retroperitoneal region (Fig. 2).

Multiple nodules were noted in bilateral upper lungs as well as the oblique pleura. The largest nodule was $1.3 \times 1.4\,cm^2$ in size, with heterogeneous ^{18}F-FDG uptake (SUVmax = 3.7, mean = 3.2). Lung metastasis was considered. Immunohistochemistry revealed that the tumor tissue was negative for vimentin and positive for Hep Par1, thus excluding adrenocortical carcinoma (Fig. 3). Endoscopic ultrasound showed no tumor in the stomach. A diagnosis of hepatoid adenocarcinoma of the adrenal gland was established.

NGS of the primary adrenal tumor and blood using Illumina Hiseq (Geneseen, www.genseeq.com, reference genome: GRCh37/hg19) revealed the following mutations (Table 1): *ATM* (c.A3078-2T), *CDKN2A* (D84H), epidermal growth factor receptor (*EGFR*) (P546L), serine/threonine kinase 11 (*STK11*) (p.331fs insertion frameshift mutation), *TP53* (H193L), *BIM* (loss of heterozygosity), and *MLH1* (V384D hybrid germline mutation). The following drug metabolism-related polymorphisms were detected: cytidine deaminase (*CDA*) (K27Q heterozygous polymorphism), glutathione *S*-transferase pi 1 (*GSTP1*) (I105 V homozygous polymorphism), glutathione *S*-transferase theta 1 (*GSTT1*) (homozygous gene deletion), and thiopurine *S*-methyltransferase (*TPMT*) (Y240C heterozygous polymorphism).

After 4 cycles of mFOLFOX6 regimen (oxaliplatin, leucovorin and fluorouracil), the tumor became larger ($10 \times 10 \times 11\,cm^3$ upon contrast-enhanced CT) and invaded the left kidney as well as the left psoas muscle. The patient then received transcatheter arterial chemoembolization (TACE) as well as apatinib (Hengrui Pharmaceuticals, Lianyungang, China) at an initial dose of 850 mg/day for 1 week, and then 500 mg/day. After 1 month, the patient refused apatinib therapy because of severe fatigue and

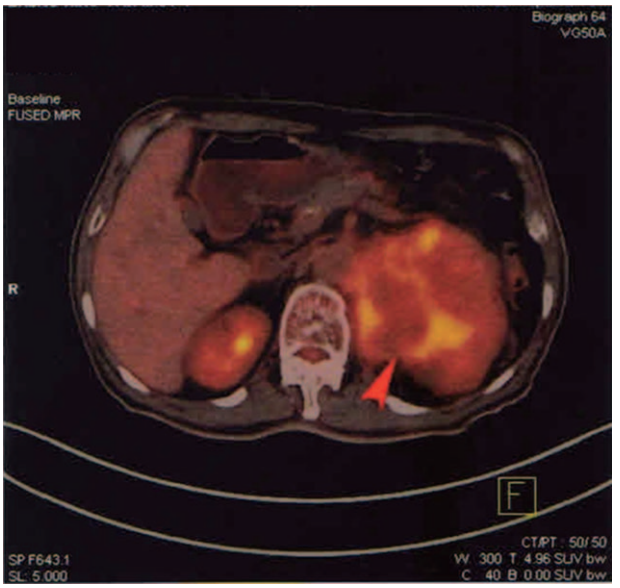

Figure 2. ^{18}F-FDG imaging of the suprarenal mass. The tumor size is $9.8 \times 9.3 \times 10.8\,cm^3$. SUV max value is between 2.4 and 7.8, with an average between 2.1 and 6.9.

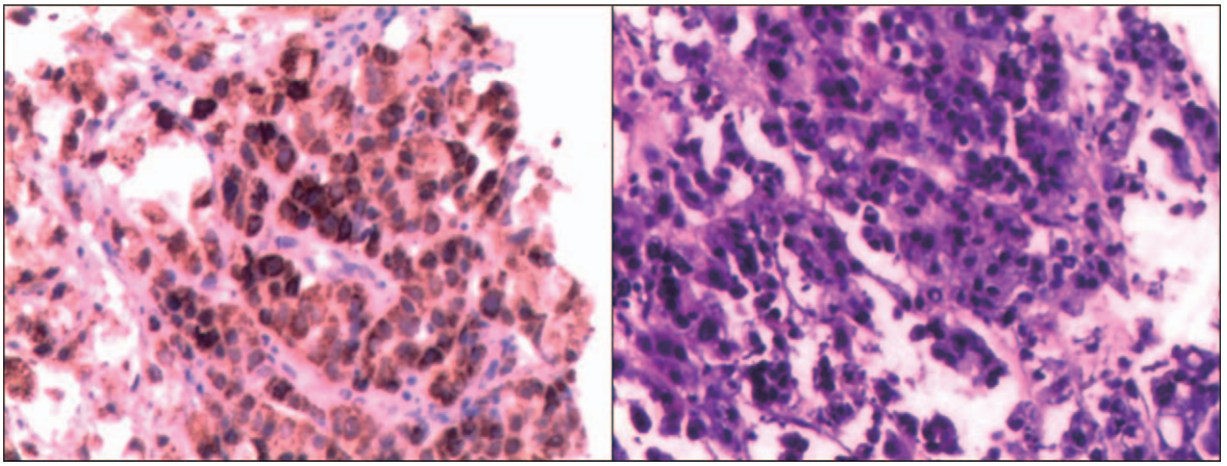

Figure 3. Immunostaining of the lesion. Left: Hep Par1 (+); right: vimentin (−). Magnification: ×100.

Table 1

Gene mutational profile by next-generation sequencing.

Genes	Mutations	Mutation abundance (%)	
		Blood (plasma)	Primary tumor
ATM	c.A3078-2T	1.4	28.3
CDKN2A	D84H mutation	1.4	44
EGFR	P546L mutation	2.5	25.7
STK11 (LKB1)	p.331fs Insertion frameshift mutation	3.4	54
TP53	H193L mutation	1.7	39.7
BIM	BCL2L11 Loss of heterozygosity polymorphism	—	—
MLH1	V384D Hybrid germline mutation	—	—
GSTP1	—	—	—
GSTT1	—	—	—
CDA	—	—	—
TPMT.	—	—	—

ATM = ataxia-telangiectasia gene, BIM = BCL2-like 11, CDA = cytidine deaminase, CDKN2A = cyclin-dependent kinase inhibitor 2A, EGFR = epidermal growth factor receptor, GSTP1 = glutathione S-transferase pi 1, GSTT1 = glutathione S-transferase theta 1, MLH1 = mutL homolog 1, STK11 = serine/threonine kinase 11, TP53 = tumor protein p53, TPMT = thiopurine S-methyltransferase.

declined further evaluation. The patient died 9 months after diagnosis.

1.2. Literature review

We searched Medline/PubMed, CNKI, and Wanfang databases for literature on adrenal hepatoid adenocarcinoma published between January 1994 and March 2018. The search terms included "hepatoid adenocarcinoma" and "adrenal." The search limits were: type of article (all types); languages (English, Chinese, and Japanese); species (humans); sexes (both male and female); subsets (all types and fields); ages (all ages); search field tags (titles). Studies without pathological or clinical data were excluded. A total of 5 articles including 5 patients were identified. The clinicopathologic features of these cases, together with our case, are summarized in Table 2. The median age of the patients was 57 years (range: 48–77 years). Five of 6 patients were male. All patients except the current case had elevated serum AFP (range 570–30,500.0 ng/mL). Four patients underwent surgery and 4 patients received chemotherapy. For the 3 patients with survival data, survival was 7 to 9 months after diagnosis.

2. Discussion

In the present report, we described a case of non-AFP-producing adrenal hepatoid adenocarcinoma with lung metastasis. The patients died 9 months later despite chemotherapy, TACE, and tyrosine kinase inhibitor treatment. NGS revealed mutations of multiple genes, including driver gene mutations such as *EGFR* and genes involved in DNA repair like *TP53* and *MLH1*.

Adrenal hepatoid adenocarcinoma typically shows morphologic similarity to hepatocellular carcinoma. However, a definite diagnosis is difficult based on histological findings alone. Immunohistochemical studies are usually required for differential diagnosis. In this case, primary lung cancer and neuroendocrine tumor were excluded because of negative immunostaining for a panel of tumor-specific markers. Hep Par1 is a marker for hepatocellular mitochondria.[16] In our case, plasma AFP was undetectable, whereas the tumor tissue was positive for hepatocyte and Hep Par 1. AFP or HepPar1 was positive in all 5 patients with available immunohistochemistry (including our own case). The tumor in the current case was positive for epithelial markers CK, CK8/18, CK7, and CK19. In this case, CK7 was positive while CK20 was negative. This profile is helpful in differentiating from adrenal cortical carcinoma, germ cell

Table 2

Patient demographic and clinicopathologic and treatment characteristics.

No.	Authors	Sex	Age, y	Tumor location	Tumor size	AFP, ng/mL	Treatment	Immunohistochemistry	Outcome
1	Current authors	M	64	Left adrenal gland	$9.3 \times 8.9 \times 9.7\,cm^3$ (at admission); $10 \times 10 \times 11\,cm^3$	2.75	Chemotherapy: 4 cycles of mFOLFOX6; transcatheter arterial chemoembolization; apatinib	TTF-1 (−), CK5/6 (−), P63 (−), NSE (−), synaptophysin (−), CD56 (−), chromogranin A (−), CK8/18 (+), CK19 (+), CK7 (+), CD20 (−) hepatocyte (+); vimentin (−), and Hep-par1 (+)	Death at 9 mo post diagnosis
2	Yoshioka M., 1994[15]	M	57	Left adrenal gland	$8 \times 5\,cm^2$	30,500	Thoracoabdominal nephro-adrenalectomy	NA	NA
3	Zhang and Hua, 2016[11]	M	77	Left adrenal gland	$13 \times 10 \times 9cm^3$	>13000	Surgery + gemcitabine and oxaliplatin	EMA (+++), CK8 (+++), AFP (+++), hepatocyte (+++), CK18 (+++), CD10 (+++)	Alive at 7 mo of follow-up
4	Liu et al, 2015[12]	M	53	Left adrenal gland, lungs	$13 \times 10 \times 8cm^3$	31,353	Oxaliplatin and capecitabine	Hep-par1 (+), CK (+), AFP (+), ki67 (30% +), CD34 (+)	Alive at 7 mo of follow-up
5	Malya et al, 2014[13]	F	48	Right adrenal gland	$4 \times 5\,cm^2$	3900	Surgery + radiotherapy + fluorouracil and gemcitabine	AFP (+), Glipan (+), CK8+, Hep-Par+, CK17 (+), CK19 (+), luminal/focal (+) polygonal CEA (+)	NA
6	Liu et al, 2009[14]	M	57	Left adrenal gland	$3.5 \times 2.2 \times 2cm^3$	570	Surgery	Hep-Par1 (+++), AFP (+), ferritin (+), CEA (+), CK8 (+), CK18 (+), α1-ACT, α1-AT (+)	NA

α1-ACT = alpha1-antichymotrypsin, α1-AT = α1-antitrypsin, AFP = alpha-fetoprotein, CD 34 = cluster of differentiation 34, CD10 = cluster of differentiation 10, CEA = carcinoembryonic antigen, CK 19 = cytokeratin 19, CK = cytokeratin, CK20 = cytokeratin 20, CK5/6 = cytokeratin 5/6, CK7 = cytokeratin 7, CK8/18 = cytokeratin 8/18, F = female, ki67 = proliferation marker, M = male, NA = not available, P63 = tumor protein 63, TTF-1 = thyroid transcription factor-1.

tumor, prostate carcinoma, renal cell carcinoma, and hepatocellular carcinoma.[17]

For rare tumors, NGS could also be helpful in establishing the diagnosis as well as guiding treatment. However, such data are scant in literature. The patient is this case had mutations in multiple genes, including driver gene mutation like *EGFR* and genes involved in DNA repair such as *TP53* and *MLH1*. This finding is consistent with a previous report by Wincewicz et al,[18] in which mutations in a patient with hepatoid gastric carcinoma included *TP53*, *EGFR*, *ATM*, and *CDKN2A*.

Four patients in the literature underwent surgery and chemotherapy with gemcitabine, oxaliplatin, capecitabine, and fluorouracil. Zeng et al[19] reported a series of 42 intestinal hepatoid adenocarcinoma patients and 40 (95.2%) patients underwent curative or palliative surgical resection and only 18 (42.9%) received chemotherapy. Velut et al[20] reported a patient of gastric hepatoid adenocarcinoma receiving the FOLFOX regimen. Lucas et al[21] reported a patient with hepatoid adenocarcinoma of the peritoneal cavity undergoing debulking surgery and FOLFOX therapy. Based on these reports, we selected mFOLFOX6 as the first-line therapy for our patient.

The use of targeted therapy has also been reported. Petrelli et al[22] reported a patient with metastatic pancreatic hepatoid carcinoma receiving sorafenib, with 8 months of progression-free survival. Gavrancic and Park[23] reported partial response to sorafenib in combination with platinum-based chemotherapy in a case of AFP-producing hepatoid adenocarcinoma of the lungs. Our patient refused sorafenib therapy owing to financial reasons, and opted to receive apatinib, a small molecule inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase, as well as KIT proto-oncogene receptor tyrosine kinase (c-Kit) and SRC proto-oncogene tyrosine kinases (c-SRC tyrosine kinases).[24]

This study is apparently limited in several aspects. First, this is a case report. As a result, generalizability to other patients is questionable. Second, the diagnosis of adrenal hepatoid adenocarcinoma was made by ruling out other possibilities. Third, multiple mutations were detected, but the relationship of these mutation with treatment response could not be possibly examined. Regardless, our case highlights the importance of thorough clinical, radiological, and immunohistochemical investigation of adrenal hepatoid adenocarcinoma. Metastasis from other primary tumors should be ruled out. Furthermore, AFP may not be elevated in adrenal hepatoid adenocarcinoma. NGS could be helpful in establishing the diagnosis and selection of treatments.

Author contributions

Conceptualization: Lizhu Lin.
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