Non-α-fetoprotein-producing adrenal hepatoid adenocarcinoma
A case report and literature review

Jietao Lin, MD, Yang Cao, MD, Ling Yu, MS, Lizhu Lin, MD

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 × 9.7 × 9.1 mm³) 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 5-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: ¹⁸F-FDG PET/CT =¹⁸F-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, TPM7 = thiopeurine 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

1. Introduction

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

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 × 8.9 × 9.7 cm³) above the upper pole of the
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, $9.9 \times 9.7 \times 9.1 \text{cm}^3$ 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 $9.8 \times 9.3 \times 10.8 \text{cm}^3$ in size. A soft tissue lesion, $2.3 \times 1.7 \text{cm}^2$ 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 $1.3 \times 1.4 \text{cm}^2$ 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 (Geneseq, www.geneseq.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) (I105V 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 ($10 \times 10 \times 11 \text{cm}^3$ 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
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

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### Table 1

| 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     | —                                              | —                      | —              | —             |
| CA125     | —                                              | —                      | —              | —             |
| TPMT      | —                                              | —                      | —              | —             |

ATM = ataxia-telangiectasia gene, BIM = BCL2-like 11, 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.
### Table 2

Patient demographic and clinicopathologic and treatment characteristics.

| No. | Authors                          | Sex | Age, y | Tumor location          | Tumor size     | AFP, ng/mL | Treatment                                                                 | Immunohistochemistry                  | Outcome                      |
|-----|----------------------------------|-----|--------|-------------------------|----------------|------------|----------------------------------------------------------------------------|----------------------------------------|------------------------------|
| 1.0 | Current authors                  | M   | 64     | Left adrenal gland      | 9.3 x 8.9 x 9.7 cm³ (at admission); 10 x 10 x 11 cm³ | 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 |
| 2.0 | Yoshioka M., 1994                 | M   | 57     | Left adrenal gland      | 8 x 5 cm²      | 30,500     | Thoracoabdominal nephro-adrenalectomy                                      | NA                                     | NA                           |
| 3.0 | Zhang and Hua, 2016               | M   | 77     | Left adrenal gland      | 13 x 10 x 9 cm³ | >13000     | Surgery + gemcitabine and oxaliplatin                                      | EMA (+++), CK8 (+++), AFP (+++), hepatocyte (+), CK18 (+++), CD10 (+++) | Alive at 7 mo of follow-up  |
| 4.0 | Liu et al, 2015                   | M   | 53     | Left adrenal gland, lungs | 13 x 10 x 8 cm³ | 31,353     | Oxaliplatin and capetabine                                               | Hep-par1 (+), OK (+), AFP (+), K67 (30% +), CD34 (+) | Alive at 7 mo of follow-up  |
| 5.0 | Malya et al, 2014                 | F   | 48     | Right adrenal gland     | 4 x 5 cm²      | 39000      | Surgery + radiotherapy + fluorouracil and gemcitabine                     | AFP (+), Gilpan (+), OK8+, Hep-Par+, OK17 (+), OK19 (+), luminal/focal (+) polygonal CEA (+) | NA                           |
| 6.0 | Liu et al, 2009                   | M   | 57     | Left adrenal gland      | 3.5 x 2.2 x 2 cm³ | 570        | Surgery                                                                   | Hep-Par1 (+++), AFP (+), ferritin (+), CEA (+), CK8 (+), OK18 (+), α1-ACT, α1-AT (+) | NA                           |

α1-ACT = alpha1-antichymotrypsin, α1-AT = alpha1-antitrypsin, AFP = alpha-fetoprotein, CD 34 = cluster of differentiation 34, CD 10 = cluster of differentiation 10, CEA = carcinoembryonic antigen, CK 19 = cytokeratin 19, CK = cytokeratin, CK5/6 = cytokeratin 5/6, CK7 = cytokeratin 7, CK8/18 = cytokeratin 8/18, F = female, M = male, NA = not available, P63 = tumor protein 63, TTF-1 = thyroid transcription factor 1.
tumor, prostate carcinoma, renal cell carcinoma, and hepatocellular carcinoma.\(^\text{[1,22]}\)

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 Winczewicz et al.\(^\text{[13]}\) 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, capcitabine, and fluorouracil. Zeng et al.\(^\text{[19]}\) 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.\(^\text{[20]}\) reported a patient of gastric hepatoid adenocarcinoma receiving the FOLFOX regimen. Lucas et al.\(^\text{[21]}\) 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.\(^\text{[22]}\) reported a patient with metastatic pancreatic hepatoid carcinoma receiving sorafenib, with 8 months of progression-free survival. Gavranic and Park\(^\text{[23]}\) reported partial response to sorafenib in combination with platinum-based chemotherapy in 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. Regardless, our case highlights the importance 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.
Data curation: Jietao Lin.
Investigation: Jietao Lin, Yang Cao, Ling Yu.
Methodology: Jietao Lin, Yang Cao.
Project administration: Lizhu Lin.
Writing – original draft: Jietao Lin.
Writing – review & editing: Jietao Lin.
Lizhu Lin orcid: 0000-0001-8283-6534

References

[1] Ishikura H, Fukasawa Y, Ogasawara K, et al. An AFP-producing gastric carcinoma with features of hepatic differentiation. A case report. Cancer 1985;56:840–8.
[2] Kumashiro Y, Yao T, Aishima S, et al. Hepatoid adenocarcinoma of the stomach: histogenesis and progression in association with intestinal phenotype. Hum Pathol 2007;38:857–63.
[3] Gakipoulou H, Givalos N, Lipis G, et al. Hepatoid adenocarcinoma of the gallbladder. Dig Dis Sci 2007;52:3338–62.
[4] Liu Q, Bannan M, Melamed J, et al. Two cases of hepatoid adenocarcinoma of the intestine in association with inflammatory bowel disease. Histopathology 2007;51:123–5.
[5] Hayashi Y, Takanashi Y, Ohsawa H, et al. Hepatoid adenocarcinoma in the lung. Lung Cancer 2002;38:211–4.
[6] Rotellini M, Messerini L, Storni N, et al. Hepatoid adenocarcinoma of the urter: unusual case presenting hepatic and ovarian metastases. Appl Immunohistochem Mol Morphol 2011;19:478–83.
[7] Ishikura H, Ishiguro T, Etanu C, et al. Hepatoid adenocarcinoma of the renal pelvis producing alpha-fetoprotein of hepatic type and bile pigment. Cancer 1991;67:3051–6.
[8] Lopez-Beltran A, Luque RJ, Quintero A, et al. Hepatoid adenocarcinoma of the urinary bladder. Virchows Arch 2003;442:381–7.
[9] Hameed O, Xu H, Siddighi S, et al. Hepatoid carcinoma of the pancreas: a case report and literature review of a heterogeneous group of tumors. Am J Surg Pathol 2007;31:146–52.
[10] Yigit S, Uyaroglu MA, Kus Z, et al. Hepatoid carcinoma of the ovary: immunohistochemical finding of one case and literature review. Int J Gynecol Cancer 2006;16:1439–41.
[11] Zhang R, Hua J, One case of left adrenal hepatoid adenocarcinoma. Chin J Endocr Surg 2016;10:527–8.
[12] Liu J, Zhang R, Zhou P, et al. Clinopathological analysis of adrenal hepatoid adenocarcinoma. Pratntal J Cancer 2015;30:194–7.
[13] Malaya FU, Rozkurt S, Hashbecheh M, et al. A rare tumor in a patient with hepatic hyalyc cyst: adrenal hepatoid adenocarcinoma. Case Rep Med 2014;2014:824574.
[14] Liu X, Lu J, Wang X, et al. Clinopathological observation of adrenal primary hepatoid adenocarcinoma. Chin J Diagn Pathol 2009;16:15–7.
[15] Yoshioka M, Ihara H, Shimai H, et al. Adrenal hepatoid carcinoma producing alpha-fetoprotein: a case report. Hinyokika Kiyo 1994;40:41–4.
[16] Fan Z, van de Ruij M, Montgomery K, et al. Hep par 1 antibody stain for the differential diagnosis of hepatocellular carcinoma: 676 tumors tested using tissue microarrays and conventional tissue sections. Mod Pathol 2003;16:137–44.
[17] Chu P, Wu E, Weiss LM. Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. Mod Pathol 2000;13:962–72.
[18] Winczewicz A, Kowalik A, Ziemba S, et al. (-Fetoprotein-producing hepatoid gastric adenocarcinoma with osteclast-like giant cells and neuroendocrine differentiation: a case study with molecular profiling. Int J Surg Pathol 2015;23:537–41.
[19] Zeng X, Zhang P, Xiao H, et al. Clinicopathological features and prognosis of intestinal hepatoid adenocarcinoma: evaluation of a pooled case series. Oncotarget 2018;9:2715–25.
[20] Velut G, Mary F, Wind P, et al. Adjuvant chemotherapy by FOLFOX for gastric hepatoid adenocarcinoma. Dig Liver Dis 2014;46:1135–6.
[21] Lucas ZD, Shah M, Trivedi A, et al. Hepatoid adenocarcinoma of the peritoneal cavity: Prolonged survival after debulking surgery and 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) therapy. J Gastrointest Oncol 2012;3:139–42.
[22] Petrelli F, Ghilardi M, Colombo S, et al. A rare case of metastatic pancreatic hepatoid carcinoma treated with sorafenib. J Gastrointest Cancer 2012;43:97–102.
[23] Gavranic T, Park YH. A novel approach using sorafenib in alpha fetoprotein-producing hepatoid adenocarcinoma of the lung. J Natl Compt Canc Netw 2015;13:387–91, quiz 391.
[24] Kou P, Zhang Y, Shao W, et al. Significant efficacy and well safety of apatinib in an advanced liver cancer patient: a case report and literature review. Oncotarget 2017;8:20510–5.