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Hepatoid adenocarcinoma of the renal pelvis in a 59-year-old male with nephrolithiasis: Case report and review of the literature

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A B S T R A C T

Background: Hepatoid adenocarcinoma arising from urological system is extremely rare, and the pathogenesis and therapeutic regimen have been poorly understood. Case report: we report a unique case of α-fetaprotein (AFP)-producing neoplasm of renal pelvis associated with nephrolithiasis. A 59-year-old male patient was diagnosed with right renal tumor and nephrolithiasis with no evidence of lesions in his digestive or reproductive system. He was successfully treated with right laparoscopic radical nephroureterectomy and lymph node dissection. Pathology analysis showed moderately or poorly hepatocellular differentiation and adenocarcinoma differentiation with lymph node reactive hyperplasia. Immunohistochemical analysis demonstrated that the cancer cells were positive for AFP, HepPar-1, GPC3, CK7, and PLAP. The patient's recovery was on schedule and no sign of recurrence was observed for 3 months. We recently reviewed AFP-producing nongerm cell tumors in upper urinary tract and discussed the clinical aspect, morphology features, pathogenesis, and therapeutic regimen for a better understanding of this rare entity. Conclusion: The present case is the first documented of hepatoid adenocarcinoma of renal pelvis complicated with nephrolithiasis, which was treated with laparoscopic approach. The prognosis of the hepatoid adenocarcinomas arising from renal pelvis and ureter seems good.

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Introduction

α-Fetaprotein (AFP) is considered as an important tumor marker of liver tumor and germ cell tumor. Elevation of serum AFP is rarely associated with malignancies in the urological organs. AFP-producing neoplasms in renal pelvis are rare.[1] Hepatoid adenocarcinoma is an AFP-producing neoplasm mostly observed in stomach, lung, and pancreas, and it can also be seen in esophagus, colon, ovaries, uterus, and bladder.[2-4] Hepatoid adenocarcinoma are commonly characterized with polygonal atypical cells with eosinophilic and granular cytoplasm arranged in solid nests with immunoreactivity to AFP.[5] In the literature, less than 1% malignancies of renal pelvis and ureter were related to adenocarcinoma.[6] To our best knowledge, only 6 previous cases of renal pelvis and ureteral hepatoid adenocarcinoma were reported in the literature. We recently experienced a case of a 59-year-old male patient who suffered from hepatoid adenocarcinoma of renal pelvis complicated with nephrolithiasis, which prompted us to study the clinical significance of renal hepatoid adenocarcinoma and review the literature of AFP-producing tumors in the urological system. This seemed to be the first documentation of hepatoid adenocarcinoma of renal pelvis complicated with nephrolithiasis, which was treated with laparoscopic approach.

Case report

A 59-year old Chinese male was admitted to our hospital complaining of gross hematuria for 1-month duration. He had undergone left-side ureteroscope pneumatic lithotripsy at another hospital. With his intent for further treatment of calculus in the right kidney, he was referred to our hospital. Urinalysis revealed an increase of erythrocytes and leukocytes. Blood examinations showed obvious elevated serum levels of AFP (63.98 ug/L, normal< 10 ug/L). The serum creatinine was 132.5 umol/L. He had no history of hepatitis, liver fibrosis, or cirrhosis. Abdominopelvic contrast-enhanced computed tomography was then performed. An irregular, heterogeneous soft tissue mass was demonstrated in the right subrenal calyx associated with a large number of calculi (Fig. 1). There was no evidence of malignant changes in the liver, gallbladder, pancreas, and reproductive system. To figure out whether there was a tumor in the right kidney, per-

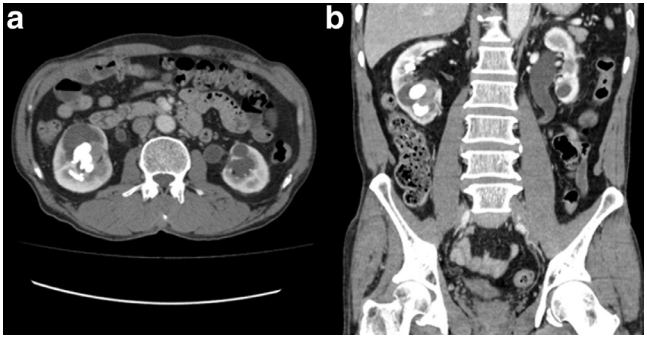

Fig. 1. Axial (a) and coronal (b) enhanced CT scan revealed an irregular soft tissue mass in the right subrenal calyx with multi calculus.

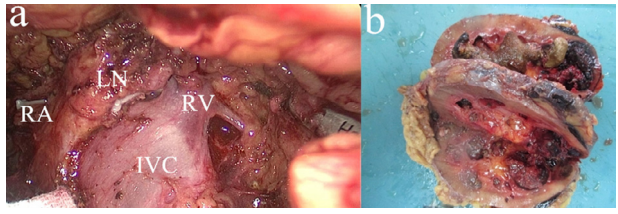

Fig. 2. (a) LN, enlarged lymph nodes; IVC, inferior vena cava; RV, right renal vein; RA, the right renal artery had been ligated. (b) Resected right kidney.

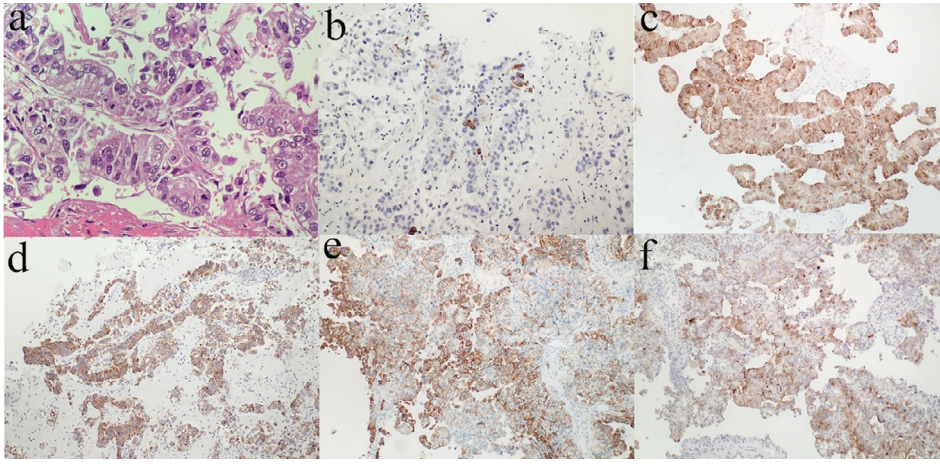

Fig. 3. (a) Hematoxylin–eosin staining of surgical specimen showed large, round tumor cells with eosinophilic and granular cytoplasm arranged in solid nests; (b) The tumor cells were focally positive for AFP immunostaining (original magnification a, 400×; b-f, 100×); diffuse immunoreactive for GPC3 (c); HepPar-1 (d); CK7 (e); PLAP (f).

cutaneous management was performed. Cauliflower-like neoplasm and blood clots were observed in the right subrenal calyx. Postoperative pathology and immunohistochemical analysis revealed hepatoid adenocarcinoma of the right renal pelvis. Then, a radical laparoscopic of right nephroureterectomy was performed with the patient's informed consent. Enlarged lymph nodes of the inferior vena cava and right external iliac artery were identified during the surgery and complete dissection was achieved (Fig. 2). Pathology analysis showed markedly atypical cells with eosinophilic and granular cytoplasm arranged in solid nests revealing its adenocarcinomatous natures. Formation of cords of polygonal cells was observed in verifying its hepatoid differentiation. The histology of lymph node showed reactive hyperplasia. Immunohistochemical analysis of the tumor demonstrated that the cancer cells were strongly positive for HepPar-1, GPC3, CK7, and PLAP. Staining for AFP and CK20 was focal positivity, while that for CD10 was negative (Fig. 3). The serum level of AFP decreased to 51.03 ug/L the day after surgery and to 21.63 ug/L a week later. The patient was carefully followed and the serum level of AFP decreased to 2.5 ug/L 45 days after surgery (Fig. 4).

Discussion

Hepatoid adenocarcinoma is a rare extrahepatic neoplasm with poor prognosis, which is characterized by a high serum level of AFP. The most common site of origin for hepatoid adenocarcinoma is stomach (63%). Other sites of origin include ovary (10%), lung (5%), gallbladder (4%), pancreas (4%), and uterus (4%).[7] Hepatoid adenocarcinoma arising from upper urinary tract is

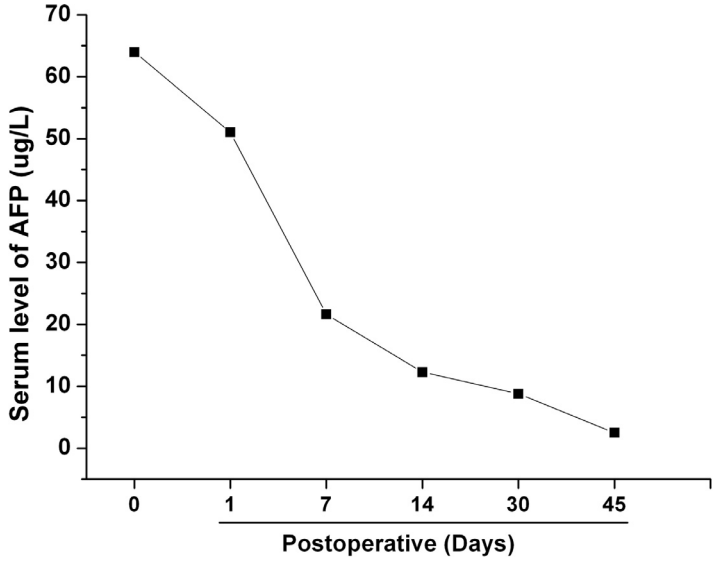

Fig. 4. The follow-up of the serum level of alpha-fetoprotein (AFP) (ug/L).

extremely rare. There are only 6 previous cases of AFP-producing tumor of the renal pelvis and ureter in the literature. In all of the cases, patients were >40 years old and extremely elevated serum AFP levels were detected. Our case was unusual as the pretreatment AFP level was not extremely elevated compared to previous cases. While in some previous research, the serum AFP were negative, as was the case with the immunohistochemistry staining.[8] Nagai et al reviewed 28 cases of hepatoid adenocarcinoma of the stomach and found that in 13 cases of the tumor's cells were stained negative for AFP.[9]

Immunostaining for CK7, CK19 was noted in 2 cases and carcino-embryonic antigen (CEA) was detected in 1 case, respectively.[1,5,10] The hepatoid adencarcinoma-related markers (HepPar1, GPC3) were not reported in detail. Hiroshi et al pointed out the features of the hepatoid adenocarcinoma of renal pelvis compared to non-AFP-producing adenocarcinoma, including (1) the production of AFP; (2) sheet-like proliferation of tumor cells resembling hepatocellular carcinoma cells; and (3) the production of bile.[1] In 2 of the cases, the tumor was associated with transitional cell carcinoma that was not stained with AFP.[11,12] On the contrary, in another reported case of AFP-producing tumor in renal pelvis, the transitional cell carcinoma was strongly immunoreactive for AFP staining.[13] Both AFP and CA19-9 producing tumors of the renal pelvis and ureter were reported in 2013 for the first time. The pathologic diagnosis was moderately differentiated intestinal-type adenocarcinoma with immunoreactive for AFP, but the immunohistochemistry of CA19-9 was not performed for further confirmation of their conclusions.[14] In another literature, the patient had high stage of disease with ovarian, small bowel, and hepatic involvement at presentation.[5]

Diagnosis of hepatoid adenocarcinoma in renal pelvis is very difficult, which can be supported by careful evaluation of clinical and pathology data. In this case, percutaneous management and biopsy were performed to make a definitive diagnosis, for the reason that a kidney stone associated with carcinoma might be possible. On histological examination, formation of cords of polygonal cells was observed in indentifying its hepatoid differentiation. Cytoplasmatic AFP staining was positive, which revealed its production from the renal pelvis neoplasm. In addition, the tumor cells showed strong positive immunostaining for hepatoid adencarcinoma-related markers (HepPar1, GPC3). No primary malignancy or metastatic tumor was detected in the patient, and the serum AFP level decreased markedly after the surgery.

AFP is a fetal serum protein released by fetal liver, yolk sac, and gastrointestinal tract which decreases commonly after birth. Serum AFP is also produced in patients with hepatocellular tumors and germ cell tumors. Moreover, AFP can be increased in conditions that are present similarly in hepatocellular tumors or germ cell tumors, as in the case of hepatoid adenocarcinoma in the renal pelvis. In recent years, AFP-producing non-germ cell tumors of the urological system have been reported. These include different types of tumors of adrenal glands, kidney, ureter, bladder, and testis.[15] It is important to be aware that AFP-producing neoplasm in urological system should be considered in differential diagnosis in patients with elevated serum AFP. However, elevated serum AFP should not be a criterion for diagnosis, although it increased in the majority of the cases.[16,17] A definitive diagnosis of hepatoid adenocarcinoma depends on the histological morphology which shows hepatocellular differentiation and adenocarcinoma differentiation. Besides, the immunostaining of HepPar1 and GPC3 ought to be positive, due to their high sensitivity and specificity for hepatocyte differentiation.[18]

The pathogenesis of hepatoid adenocarcinoma remained debatable. Several studies in intestinal hepatoid adenocarcinoma have proposed the hypothesis that chronic inflammation contributes to the occurrence of the neoplasm, as is similarly the case with other gastrointestinal cancers, such as esophageal cancer originating from Barrett's esophagus, gastric adenocarcinoma due to Helicobacter pylori-associated chronic gastritis, and hepatocellular carcinoma caused by hepatitis B and C viral infections.[19] There is limited understanding of the molecular changes associated with AFP expression in hepatoid adenocarcinoma. It has been reported that the α transcriptional enhancer (AT) motif binding factor 1 (ATBF1) play an important role in the malignance of the tumor. ATBF1 is a transcription factor that is bound to AFP regulatory element and down-regulates AFP gene expression in human hepatic cells. In gastric carcinoma, the absence of ATBF1 might be responsible for the malignant phenotype of AFP -producing gastric cancer.[12] Similarly, AFP-positive hepatoid adenocarcinoma might present its malignant phenotype due to absence of ATBF1.

The prognosis of advanced stage of gastric hepatoid adenocarcinoma was considered to be extremely poor.[20] However, the prognosis of tumors occurred in urological system seemed not bad. Patients with AFP, CA19-9, or CEA producing tumors in most cases in which patients did not receive adjuvant chemotherapy were alive without recurrence for at least 6 months.[1,13,14,21,22] A treatment that consists mainly of radical surgery when feasible is followed by chemotherapy. In previous cases, all patients were treated with open radical surgery whereas laparoscopic nephroureterectomy was carried out in the present case for shorter hospital day and better cosmetic outcomes. No signs of recurrence were observed for 3 months and the patient is currently fine. In one recurrent case, the tumor was treated with taxel, isofamide and platin (TIP chemotherapy regimen) (175 mg/m^2 paclitaxel on day 1, 1.2 mg/m^2 ifosfamide on days 2-5, and 20 mg/m^2 cisplatin on days 2-5) for 3 courses and showed complete responses.[12] In another case, gemcitabine and carboplatin were treated as adjuvant chemotherapy after radical surgery, and no signs of recurrence or severe side effects were observed for 11 months.[14] Treatment of metastatic cases remains to be defined due to the uniqueness and rareness of this neoplasm, and the efficacy of the targeted therapy in hepatoid adenocarcinoma is not clear so far. Further study is needed in the molecular pathogenesis and the efficacy of chemotherapy and targeted therapy in hepatoid adenocarcinoma to determine the best medical therapy.

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