Hepatoid adenocarcinoma in the peritoneal cavity
Two case reports

Xiao Chen, MD, Anqin Li, MD, Qixia Wang, PhD, Yaqi Shen, MD, PhD, Zhen Li, MD, PhD, Jian Peng, MD, Daoyu Hu, MD, PhD

Abstract

Rationale: Hepatoid adenocarcinoma (HAC) is a rare extrahepatic adenocarcinoma that histologically resembles hepatocellular carcinoma (HCC). HAC of peritoneal cavity can present as a solitary mass or disseminated nodules indicating different treatment.

Patient concerns: In this study, we present the cases of a 29-year-old man and a 64-year-old woman who suffered from HAC.

Diagnosis: The serum alpha-fetoprotein (AFP) of both patients and ascites of 1 patient were markedly elevated. One patient presented with multiple nodular disseminated in the peritoneal cavity and the other patient has a mass between the left diaphragm and the spleen on computed tomography and magnetic resonance imaging.

Intervention: The first patient underwent laparoscopic examination and multiple nodules were found in the peritoneal cavity, and only received chemotherapy. The second patient underwent surgery and resected the mass between left diaphragm and the spleen.

Outcome: Histological examinations showed the nodule of the peritoneal cavity and mass belong to moderately differentiated HCC. HAC has a poor prognosis, but the 2 patients responded well to treatment.

Lesson: HAC is frequently associated with elevated serum AFP without neoplasm in the liver. Histological and Immunohistochemistry examinations can help differential diagnosis.

Abbreviations: AFP = alpha-fetoprotein, CT = computed tomography, HAC = hepatoid adenocarcinoma, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, MRI = magnetic resonance imaging.

Keywords: alpha-fetoprotein, hepatoid adenocarcinoma, magnetic resonance imaging, peritoneal cavity

1. Introduction

Hepatoid adenocarcinoma (HAC) was first described as an alpha-fetoprotein (AFP) producing tumor by Bourreille et al.[1] Ishikura et al.[2] first proposed the term of the HAC of the stomach in 1985, and reviewed 7 cases of AFP-producing lung carcinoma in 1990 in the English literature and 5 patients were diagnosed as HAC.[3]

HAC was defined as a primary extrahepatic tumor and has been reported most commonly in the stomach. Other organs include ovary, lung, biliary system, pancreas, uterus, urinary bladder, esophagus, colon, and fallopian tube. Single reports described HAC in rectum, kidney, thymus, adrenal glands, and skin.[4,5] HAC distribution in the peritoneal cavity has been reported only several cases, one of the patients in this report may be the third patient of primary diffuse HAC on the peritoneum.

2. Case reports

2.1. Case 1

A 29-year-old man was admitted to our hospital with anorexia and abdominal distention for 2 weeks. The patient infected hepatitis B virus (HBV) from mother-neonatal transmission, and had a history of appendectomy 1 year ago. He went to a local hospital 2 weeks ago. Serological tests indicated positive of hepatitis B surface antigen. Liver function test revealed a high level of alanine aminotransferase, aspartate aminotransferase, and normal level of total bilirubin, direct bilirubin, and albumin. Coagulation function test was normal. Routine examination of ascites revealed red, turbid ascites with nucleated cell count 1.26 × 10⁷/L and mainly leukomonocytes. He accepted supportive treatment but no sign of improvement.

The patient was referred to our center for further treatment. On physical examination, patient’s blood pressure was 118/97 mm Hg, pulse rate of 102 beats per minute, respiratory rate of 20 breaths per minute, body temperature of 36.8 °C. Routine laboratory tests revealed microcytic hypochromic anemia. His HBV DNA was elevated at 1.45 × 10⁷ IU/ml (normal value, <20 IU/ml), HCV RNA test was negative. His serum AFP level was remarkably elevated over 60,500 ng/ml (normal value, ≤7.0 ng/ml), NSE was elevated at 22.87 µg/L (normal value, <16.30 µg/L), and CA125 was elevated at 1343.6 U/ml (normal value, ≤35.0 U/ml).
Peritoneocentesis yielded bloody ascites with AFP level over 60500 ng/ml, positive Rivalta test, red blood cell count 870,000 x 10^6/L, nucleated cell count 790 x 10^6/L. The bacterial culture test was negative.

Computed tomography (CT) scan (Fig. 1) and magnetic resonance imaging (MRI) (Fig. 2) showed diffuse nodular thickening of epiploon and peritoneum, massive ascites and splenomegaly, small nodule of gallbladder wall. Contrast-enhanced abdominal CT scan demonstrated that small nodule of gallbladder wall, thickened epiploon and peritoneum were homogeneous enhanced. In addition, no hepatic lesions were identified. MRI scan revealed that the lesions were isointensity on T1-weighted images (T1WI) and isointensity on T2-weighted images (T2WI), diffusion-weighted imaging (DWI) showed the lesions were hyperintensity with B value 1000 s/mm^2. Abdominal contrast-enhanced MRI scan showed the same behavior to contrast-enhanced CT scan.

Laparoscopic examination revealed massive bloody ascites, and dense small nodules on epiploon and peritoneum, while the surface of the liver was smooth. A 4 x 3 cm specimen was isolated from epiploon for biopsies. Twelve days after the surgery, the patient accepted the first cycle of xelox chemotherapy, 24 days for the second cycle, and 51 days for the third cycle.

Histological examinations showed solid carcinoma belong to moderately differentiated hepatocellular carcinoma (HCC) (Fig. 3). Immunohistochemistry analysis demonstrated that the specimen was positive for Glypican-3, Arginase1, AFP, PCK (weak), CK8/18, CK19 (a few), CD34 (endothelial cells), and was negative for EMA, Hepatocyte, CK20, calretinin, VIM. Expression of proliferation marker of Ki-67 was slightly elevated and the labeling index was about 5% to 10%.

Eight days after the first chemotherapy, the serum AFP level was 35351 ng/ml, CA125 level was 439.2 U/ml. Twenty-four days after the second chemotherapy, the serum AFP level was 2089 ng/ml, and HBV DNA turned negative. MRI scan showed the peritoneum under the right diaphragm was significantly thinner than before and ascites was significantly reduced (Fig. 4).

2.2. Case 2

A 64-year-old woman was admitted to our hospital with intermittent left upper abdominal pain for 3 months, and the pain increased after inhalation. One month ago, she went to the local hospital. Serum AFP was elevated at 1210 ng/ml. She tested negative for hepatitis b surface antigen. MRI scan at the local hospital showed a mass above the spleen.
The patient was then referred to our hospital as having a tumor above the spleen for surgical intervention. The patient had a history of partial thyroidectomy 40 years ago and hysterectomy 30 years ago. On physical examination, patient’s blood pressure was 159/94 mm Hg, pulse rate of 72 beats per minute, respiratory rate of 20 breaths per minute, body temperature of 36.5 °C. She tested negative for both hepatitis B surface antigen and HBV DNA. Laboratory blood tests showed a slight elevation of alkaline phosphatase, gamma-glutamyl transpeptidase, blood glucose, and a slight decrease of serum calcium.

Figure 3. Photomicrograph shows hepatoid pattern (H-E stain).

Figure 4. After the first cycle of XELOX chemotherapy, (a) axial T2-weighted and (b) diffusion-weighted images showed that the peritoneum under the right diaphragm was significantly thinner than before (arrow), and ascites was significantly reduced. On contrast-enhanced MRI arterial phase (c) and vein phase images (d), the lesion was significantly smaller than before, and signal intensity of the lesion was significantly reduced. MRI = magnetic resonance imaging.
Endoscopy of the upper gastrointestinal tract did not show any primary tumor. Ultrasound examination showed an irregular hypoecho mass above the spleen and below the left diaphragm. Abdominal contrast-enhanced CT scan (Fig. 5) demonstrated an irregular mass that was mainly located between the left diaphragm and the spleen and was partially protruded out of the diaphragm, possibly connected to the left hepatic lobe and the spleen. There was nodule of calcification within the mass. MRI scan (Fig. 6) revealed that the mass was slightly hypointensity on T1WI and slightly hyperintensity on T2WI, DWI showed the mass was hyperintensity with B value 1000 s/mm².

The surgeon found the tumor located in the upper part of the spleen, the boundary was not clear. The mass adhered to epiploon and invaded left diaphragm. No connection was identified between the tumor and the edge of the left hepatic lobe. The mass, the spleen, and partial left diaphragm were removed. Partial left hepatic lobe was removed for better excision of lienohperrnic ligaments. The tumor had invaded the diaphragm; however, there was a clear boundary between the tumor and the spleen.

Histological examinations confirmed the diagnosis of moderately to low differentiated HCC (Fig. 7). The boundary between the solid carcinoma and spleen was clear. Immunohistochemistry analysis demonstrated that the specimen was positive for Hepatocyte, Glypican-3, Arginase1, AFP (weak), PCK (weak), EMA, CK8/18, CD34 (endothelial cells), and was negative for GATA, PAX8. The proportion of Ki-67 positive cells was about 30% to 40%.

3. Discussion

The clinical manifestation, laparoscopic and histological findings suggesting hepatocellular differentiation along with no evidence of primary HCC on CT or MRI scan supported the diagnosis of HAC which originated from the peritoneal cavity. Patient 1 appeared to have an intraperitoneal HAC and metastasis in the gallbladder wall.

Ishikura et al firstly proposed HAC of the stomach which produce a large amount AFP and morphologically and immunohistochemically distinctive foci of hepatic differentiation.[2] HAC cells morphologically resemble HCC cells and are composed of polygonal tumor cells arranged in both trabecular and glandular structures.

HAC is commonly immunohistochemically positive for AFP regardless of origin organ. Serum AFP was elevated in most patients of HAC. AFP can also elevate in the serum of yolk sac tumors and HCC patients. Differential diagnosis included metastatic HCC or hepatoid germ cell tumor. Metastatic HCC always presents primary HCC in liver. Su et al[6] found that HAC is strongly suggested if AE1/AE3, CK18, and CK19 stain show strong positive when differentiate between HAC and HCC for AFP-producing liver tumors. According to Gopaldas,[7] the canalicular staining pattern with polyclonal carcinoembryonic antigen was commonly reported in hepatoid carcinomas. Glypican-3 was positive in all HAC patients included in the review.[6] In accordance with our study, the 2 patients in present were both positive for glypican-3. In addition, the 2 patients both stained positive for Arginase 1.
Kim et al.\(^8\) reported a patient of HCC in an ectopic liver that mimicking a mass in the spleen, but they failed to find normal liver tissue within the mass even on microscopy. With similar clinical manifestation, this may fall into a HAC of the peritoneal as patient 2.

Gopaldas et al described an unusual patient of colonic adenocarcinoma and hepatoid tumor probably originating from the peritoneum.\(^7\) Debulking of the tumor was performed and followed by chemotherapy, resulting in decrease of AFP. Kitamura et al reported a patient of diffuse HAC which was developed primarily in the peritoneum.\(^9\) In this report, the patient was characterized by multiple nodular lesions which were disseminated only in the peritoneal cavity. The patient received peritoneal chemotherapy, but eventually died 6 months after diagnosis. Metzgeroth et al report another patient of primary HAC in the peritoneal cavity.\(^4\) The study also reviewed 261 HAC patients published in the English literature so far and concluded that the diagnostic panel of HAC should include AFP, HepPar1, and EpCAM antibodies. The patient received 2 kinds of chemotherapy treatment. Though sorafenib showed the better effect, the patient died 6 months after diagnosis.

Patients of primary peritoneal HAC with localized tumors underwent surgery resection, followed by chemotherapy. Lucas et al showed a patient of HAC with a peritoneal mass located between the right lateral abdominal wall and the wall of the ascending colon.\(^10\) After removal of the peritoneal mass and a gallbladder fossa nodule with similar histopathological features, the patient received chemotherapy with FOLFOX and lived more than 3 years without evidence of recurrence. The other patient underwent partial resection and adjuvant chemotherapy. He had an initial response resulting in the disease under control for 2 years, but then had hepatic metastases and died 3 years after diagnosis.\(^11\) Another patient with localized tumor refused excision.

In conclusion, HAC is a heterogeneous group of extrahepatic adenocarcinoma that has characteristics of both HCC and gastrointestinal adenocarcinoma. HAC is frequently associated with elevated serum AFP without neoplasm in the liver. Histological and immunohistochemistry examinations can help differential diagnosis. There is no standard treatment for diffuse peritoneal HAC, and chemotherapy may be helpful in part of the patient.

**Author contributions**

**Conceptualization:** Xiao Chen.

**Data curation:** Anqin Li, Qiuxia Wang.

**Formal analysis:** Yaqi Shen, Zhen Li.

**Writing – original draft:** Xiao Chen, Anqin Li.

**Writing – review and editing:** Jian Peng, Daoyu Hu.

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