Case Report

Alpha-fetoprotein-producing hepatoid adenocarcinoma of the gallbladder: a case report and review of literature

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Abstract: Hepatoid adenocarcinoma (HAC) is an uncommon type of malignancy in extrahepatic tissues. It was named for its histopathological resemblance of hepatocellular carcinoma, the most common form of liver cancer. The occurrence of HAC in the gallbladder is very low, and tumours that produce alpha-fetoprotein are even rarer. Clinically, it is usually diagnosed histopathologically; and the prognosis is generally poor, largely due to its metastasis to the liver and peripheral lymph nodes. Currently, laparoscopic cholecystectomy combined with lymphadenectomy is the major therapeutic strategy for this type of cancer. Postoperative chemotherapy and periodic review are required to reduce the chance of recurrence. Because of the low occurrence of HAC in the gallbladder, our knowledge and therapeutic options against this malignancy are limited. Understanding the characteristics of the progression of this malignancy would be beneficial to its diagnosis and treatment in future clinical practice. In this study, we report a case of HAC of the gallbladder in a 55-year-old male, who presented a significant increase of alpha-fetoprotein and a marginal elevation of carcinoembryonic antigen in serum. The patient underwent laparoscopic cholecystectomy and lymphadenectomy, followed by sorafenib administration. As a result, no recurrence was found during the follow-up period, and the patient maintained a general quality of life.

Keywords: Alpha-fetoprotein, hepatoid adenocarcinoma, gallbladder cancer, hepatocellular carcinoma, metastasis

Introduction

Hepatoid adenocarcinoma (HAC) is an extraordinary type of adenocarcinoma with hepatocellular features [1]. Histologically, it contains both adenocarcinoma and hepatocellular carcinoma components, manifesting morphological and functional characteristics of liver-like differentiation [2-4]. Hepatoid adenocarcinoma producing alpha-fetoprotein (AFP) was first reported in 1985 as a subtype of stomach cancer [1, 5, 6], which was later found in other organs such as lung [7, 8], kidney [9, 10], spleen [11], and female genital tract [12, 13]. In this study, we report a case of AFP-producing HAC in the gallbladder, which was treated at our clinic by surgery and chemotherapy.

Case report

In 2014, a 55-year-old male patient, who had otherwise been healthy, presented at the First Affiliated Hospital of Jilin University with intermittent discomfort in the upper right abdomen that lasted for two weeks. Physical examination at admittance showed no yellowing of the skin and sclera. The abdomen was flat, but with tenderness in the upper right area; and no Blumberg’s sign or muscular tension was found. Abdominal ultrasound indicated a 43×20 mm irregularly-shaped solid lesion on the posterior gallbladder wall, extending to the end of the gland. The lesion protruded into the gallbladder cavity and showed no mobility with the change of body postures. The liver capsule was smooth and intact, and its shape was normal. Fine and dense dotty resonance was seen in the liver parenchyma. Horizontal and three-phase spiral computed tomography (CT) demonstrated irregular thickening of the gallbladder wall, with localized soft tissue masses of up to 3.4×2.1 cm in size. Arterial phase enhancement was obvious, and pathology has likely spread to the serous layer (Figure 1). Laboratory analysis suggested that the patient had a significantly high-
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Serum AFP level (440.9 ng/ml; normal value is ≤ 7.0 ng/ml). Carcinoembryonic antigen (CEA) in serum increased to 4.8 ng/ml (normal value is < 3.4 ng/ml) and carbohydrate antigen 19-9 (CA19.9) was 23.4 U/ml (normal value is < 27.0 U/ml). Liver function was normal, and no infection by hepatitis B and C were detected. Based on these clinicopathological features, the patient was diagnosed with gallbladder cancer; and radical resection surgery was scheduled.

During the operation, the surface of the liver was observed to be smooth; but the gallbladder shrank to 6.0×4.0×2.0 cm. Folded dysplasia with a tough and stringy texture was found on the gallbladder wall, and a cauliflower-like mass could be reached. The gallbladder adhered with the surrounding liver tissues. Therefore, the gallbladder and the attached liver tissues were removed. Then, lymphadenectomy was performed along the liver-duodenum ligament. The size of the gallbladder was 7×3×1.5 cm and the thickness of the gallbladder was 0.1-0.2 cm, as confirmed by post-operative pathological analysis. Close to the gallbladder end, a 3.3×2.5×1.0 cm cauliflower-like mass was found with a greyish cutting surface and a solid and hard texture (Figure 2). In the vicinity of the tumour mass, the serous layer of the gallbladder attached to a portion of the liver tissue, which was 6.0×4.0×1.5 cm in size with a red-brownish cutting surface and soft texture. No lymph node metastasis was found along the liver-duodenum ligament. In addition, there was a mobile gallbladder stone, which was green in colour and 2 cm in diameter.

Pathological analysis demonstrated that cancer cells were organized in a nest or trabecular pattern (Figure 3), showing the histological features of a medium-to-poorly differentiated adenocarcinoma with a HAC component. Immunohistochemical staining showed AFP in cancer cells (magnification, 200×).
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**Table 1.** Clinical and pathological features of patients with hepatoid adenocarcinoma of the gallbladder reported in the literature

<table>
<thead>
<tr>
<th>Tumor size (cm)</th>
<th>Stone</th>
<th>Cellular order</th>
<th>Liver metastasis</th>
<th>Lymph node metastasis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
<td>No</td>
<td>Nest, trabecular</td>
<td>Multiple</td>
<td>No</td>
<td>(Nakashima, 2000) [21]</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>Trabecular</td>
<td>Multiple</td>
<td>Multiple</td>
<td>(Sakamoto, 2004) [24]</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>Nest, trabecular</td>
<td>No</td>
<td>No</td>
<td>(Sakamoto, 2005) [23]</td>
</tr>
<tr>
<td>6.5</td>
<td>No</td>
<td>Nest, trabecular</td>
<td>No</td>
<td>No</td>
<td>(Sakamoto, 2005) [23]</td>
</tr>
<tr>
<td>2.5</td>
<td>No</td>
<td>Nest, trabecular</td>
<td>No</td>
<td>Not recorded</td>
<td>(Gakiopoulou, 2007) [20]</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Trabecular</td>
<td>Yes</td>
<td>Yes</td>
<td>(Lee, 2011) [15]</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Trabecular</td>
<td>No</td>
<td>No</td>
<td>(Koswara, 2007) [25]</td>
</tr>
<tr>
<td>11</td>
<td>No</td>
<td>Nest, trabecular</td>
<td>Yes</td>
<td>No</td>
<td>(Ellouze, 2011) [17]</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>Not recorded</td>
<td>No</td>
<td>Yes</td>
<td>(Hu, 2010) [36]</td>
</tr>
<tr>
<td>3.5</td>
<td>Yes</td>
<td>Sheets, trabecular</td>
<td>No</td>
<td>Yes</td>
<td>(Lin, 2008 16) [29]</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>Clusters and cords</td>
<td>No</td>
<td>No</td>
<td>(Li, 1999 14) [37]</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>Nest, trabecular</td>
<td>No</td>
<td>No</td>
<td>(Yi, 1997 13) [38]</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>Nest, trabecular</td>
<td>Yes</td>
<td>Yes</td>
<td>(Li, 1998 12) [27]</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Nest, trabecular</td>
<td>No</td>
<td>No</td>
<td>Current case</td>
</tr>
</tbody>
</table>

**Table 2.** Immunohistochemical characteristics of hepatoid adenocarcinoma reported in the literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>AFP</th>
<th>Hep Par-1</th>
<th>Cytokeratin 8</th>
<th>Cytokeratin 7</th>
<th>Cytokeratin 19</th>
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<tr>
<td>{Sakamoto, 2005 7} [23]</td>
<td>N</td>
<td>P</td>
<td>P</td>
<td>N</td>
<td>P</td>
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<tr>
<td>{Sakamoto, 2005 7} [23]</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>N</td>
<td>P</td>
</tr>
<tr>
<td>{Gakiopoulou, 2007 6} [20]</td>
<td>WP</td>
<td>SP</td>
<td>NC</td>
<td>N</td>
<td>NC</td>
</tr>
<tr>
<td>{Koswara, 2007 19} [25]</td>
<td>SP</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>{Ellouze, 2011 4} [17]</td>
<td>P</td>
<td>P</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>{Hu, 2010 15} [36]</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>{Lin, 2008 16} [29]</td>
<td>N</td>
<td>P</td>
<td>SP</td>
<td>SP</td>
<td>SP</td>
</tr>
<tr>
<td>{Li, 1999 14} [29]</td>
<td>P</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td>{Yi, 1997 13} [38]</td>
<td>P</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td>{Li, 1998 12} [27]</td>
<td>P</td>
<td>NC</td>
<td>NC</td>
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<td>NC</td>
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</tbody>
</table>

Follow-ups at three and six months after surgery revealed that AFP levels were 38.5 and 35.6 ng/ml, respectively; which remained higher than normal. However, color Doppler ultrasound and CT demonstrated no obvious abnormality in the cavity. The patient was on a normal diet, had been urinating and defecating normally, and body weight of the patient remained unchanged. The general life quality of the patient was maintained.

**Literature review and discussion**

In this study, we report a case of HAC of the gallbladder producing high level of AFP. For this rare case, we have detailed the clinico-pathological characteristics and diagnosis, therapeutic decision, and clinical outcome. This case study increased the awareness of HAC of the gallbladder. The diagnosis and treatment procedure will be helpful in future clinical practice to avoid its misinterpretation as metastatic hepatocellular carcinoma.

A previous statistical analysis on 262 cases of HAC suggested that this malignancy commonly occurred in the stomach and ovary, which accounts for 63% and 10% of cases, respec-
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Metzgeroth et al. demonstrated that HAC of the gallbladder commonly occurred in elderly patients (74 years old in average) at a male to female ratio of 1:4.5 [14]. However, our patient was young and had a gallbladder stone, a pathological feature frequently observed in patients with HAC of the gallbladder. In Table 2, 5 of 13 patients had a history of gallbladder stones, suggesting the potential association of HAC with the gallbladder stones. In fact, asymptomatic stones larger than 2 cm had been recommended as a risk factor for gallbladder cancer [26-28].

HAC of the gallbladder is currently diagnosed based on the clinicopathological features of the patients, particularly the elevation of a group of liver-specific proteins in blood, including AFP, albumin, transferrin, and α1-antitrypsin. However, the reliability of these proteins as markers in the diagnosis of HAC is questionable. For example, AFP is most relevant to HAC, however, its increase is not essential for HAC of the gallbladder [15], as indicated by the previously reported cases with no increase of AFP in serum [21, 23, 24, 29]. Hepatocyte specific antigen (Hep Par-1) has been regarded as a marker for the hepatic differentiation of cancer cells [30, 31], but its specificity and sensitivity are in dispute [20]. Thus, further studies are needed to screen for appropriate markers for HAC in the gallbladder.

Furthermore, differentiating HAC of the gallbladder from the metastases of hepatocellular carcinoma to the gallbladder is critical for its clinical outcome [17, 32]. Hepatocellular carcinoma is usually associated with liver cirrhosis, hepatitis, and other risk factors which cause damage to the liver function [33]. Patients with normal liver function rarely have hepatocellular carcinoma spreading to the gallbladder [34]. At molecular level, the expression of cytokeratin 19 can be helpful in the diagnosis of HAC, because this protein is rarely expressed in hepatocellular carcinoma but commonly expressed in HAC [35]. In addition, HAC of the gallbladder exhibited an intensified signal on the edge on T2 weighted magnetic resonance imaging, but without a visible capsule.

The mechanism of HAC tumourigenesis remains unknown. These tumours were originally believed to be adenocarcinomas acquiring hepatic differentiation features during progression, or tumours arising from the endoderm that are capable of differentiating into glandular and hepatoid cells [24, 25]. A recent study suggested that this malignancy may originate from hepatobiliary stem cells and progenitors (Dettoni, 2014 1). Future phylogenetic studies, particularly genetic fingerprinting by cancer genome and transcriptome sequencing, are needed to identify the origin of this type of cancer.

In summary, HAC of the gallbladder is a rare but aggressive malignancy, which mostly occurs in the elderly population. The tumour often metastasizes to liver and peripheral lymph nodes, which predicts a poor prognosis. Although the occurrence of gallbladder stone, increase of AFP in serum, and imaging are important, pathological and immunohistochemical confirmation is essential for the diagnosis of HAC. Currently, laparoscopic cholecystectomy with lymphadenectomy represents an ideal therapeutic strategy [15], and postoperative chemotherapy and periodic re-examination are usually recommended. When surgery is unfeasible or tumour metastasis occurs, sorafenib or other tyrosine kinase inhibitors can be used [18]. In general, an early and precise diagnosis, radical resection surgery, and appropriate chemotherapy are key strategies in the treatment of HAC in the gallbladder.

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Disclosure of conflict of interest

None.

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