Original Article

Mixed large cell neuroendocrine carcinoma and adenosquamous carcinoma of gallbladder: a case report

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Abstract: Here we present an extremely rare case of mixed large cell neuroendocrine carcinoma and adenosquamous carcinoma of gallbladder. The patient was a 52-year-old Chinese male who was admitted to our hospital twice. Because of severe adhesion obscuring the Calot’s triangle, the patient went through cholecystostomy and biopsy of the wall of the gallbladder instead of cholecystectomy in the first admission. Pathological results showed inflammatory changes without tumor cells. The patient was readmitted to our hospital for cholecystectomy as the infection was relieved 3 months later. The pathological results confirmed adenocarcinoma (accounted for about 40%) with squamous cell carcinoma (accounted for about 50%) and large cell neuroendocrine carcinoma (accounted for about 10%), with Ki-67 labeling index 80%. The patient underwent an uneventful postoperative course and then received chemotherapy with gemcitabine/oxaliplatin, he would be followed up every 3 weeks.

Keywords: Carcinoma, adenosquamous, gallbladder, neuroendocrine carcinoma, large cell, cholecystectomy

Introduction

Large cell neuroendocrine carcinoma (LCNEC) of the gallbladder is extremely rare, the first case was reported in 2000 by Papotti et al [1]. More than ten cases of the LCNEC of the gallbladder have been reported in the English literatures, as an isolated histological type or associated with other histological components, such as adenocarcinoma [2]. And only one case report of the LCNEC of the gallbladder associated with adenosquamous cell carcinoma was reported previously as we known. The clinical symptoms and radiological findings of the neuroendocrine tumors of the gallbladder were nonspecific. The clinical behavior of LCNEC of neuroendocrine carcinomas is aggressive and the mortality is high as a result of delayed diagnosis and treatment [3].

Case report

A 52-year-old male patient presented to our hospital in July, 2015, with a chief complaint of fever, intermittent epigastralgia for 2 weeks. His condition aggravated in recent 1 day. The patient had no fever (37.5 degrees Celsius), nausea, vomiting, diarrhea, hematemes or hematochezia. Physical examination revealed tenderness in the right upper quadrant of abdomen, and positive Murphy’s sign. Laboratory examination revealed elevated leukocyte count (12.38 × 10⁹/L), and a normal hemoglobin. The tumor marker carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and α-fetoprotein (AFP) level were all normal. Liver function tests revealed that Gamma-glutamyl transpeptidase were increased to 232 U/L. Emergency CT scan (Figure 1) revealed cholecystitis accompanied with perforation in the bottom of the gallbladder. During the emergency surgery, laparoscopic cholecystectomy was suspended because of severe adhesion obscuring Calot’s triangle, the cholecystostomy and biopsy of the gallbladder-wall were performed. The gallbladder-wall biopsy pathological results showed inflammatory changes. The patient was treated with antibiotics conservatively and the gallbladder drainage-tube was removed 7 weeks later.
Figure 1. CT scan demonstrating cholecystitis accompanied with perforation in the bottom of the gallbladder. (A) An enlarged thick-walled gallbladder, the density of hepatic parenchyma around the gallbladder decreased. (B) The density of fat space around the bottom of gallbladder increased as exudation around the bottom of gallbladder.

Figure 2. Enhanced MR scanning after cholecystostomy and antibiotics. (A, B) T2-weighted MR image and T1-weighted MR image showed an enlarged thick-walled gallbladder. (C) Enhanced T1-weighted MR image showed the smooth gallbladder wall with no obvious neoplasm. (D) The coronal image showed patchy abnormal signal intensity in liver above the gallbladder with prolonged enhancement.
The patient was readmitted to our hospital for cholecystectomy 3 months later, as the infection was relieved. The preoperative contrast-enhanced MR examination (Figure 2) showed smooth diffuse gallbladder wall thickening, without obvious neoplasm or lymph node enlargement. The MR findings suspected xanthogranuloma cholecystitis more than malignant tumors. During the operation, intraoperative quick frozen pathology showed gallbladder adenosquamous carcinoma. The extended radical resection made no sense (stage III-IV according to the FIGO classification).

Figure 3. Histological examination demonstrating the combination of the mixed adenosquamous carcinoma cells (A) and large cell neuroendocrine carcinoma cells with the formation of rosettes (B). Immunohistochemical staining showing that the large cell neuroendocrine carcinoma cells were positive for chromogranin A (C), synaptophysin (D), squamous carcinoma were positive for P40 (E), adenocarcinoma were positive for CK7 (F).
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to the American Joint Committee on Cancer TNM system), so simple cholecystectomy was chosen.

The final pathological findings (Figure 3) confirmed adenocarcinoma (accounted for about 40%) with squamous cell carcinoma (accounted for about 50%) and large cell neuroendocrine carcinoma (accounted for about 10%) with continuous diffuse infiltration of the gallbladder wall. Microscopically, the tumor was composed of a substantial component adenocarcinoma and squamous cells, as well as exhibiting round cells; the formation of rosettes could be focally demonstrated. The immunohistochemical examination revealed that the large cell neuroendocrine carcinoma cells were diffusely positive for CD56, chromogranin A, and synaptophysin. Adenocarcinoma was positive for CK7, Muc-4, Muc-5 and CK-20. Squamous carcinoma was positive for P63, P40. What's more, Ki-67 labeling index was 80%.

Discussion

Most common malignant tumors of the gallbladder are adenocarcinomas, whereas primary adenosquamous and neuroendocrine carcinomas are rare. Histologically, the LCNECs of the gallbladder are associated with other types commonly associated with adenocarcinoma [4]. As we know, the present case report is the second one which the LCNEC of the gallbladder associated with adenosquamous cell carcinoma in the English literature. The pathogenesis of such mixed tumor is not well understood, however most experts and researchers support the theory of tumor occurrence from common stem cells [3, 5, 6].

The diagnosis of neuroendocrine carcinomas of gallbladder is rarely made preoperatively since the presentation generally consists of non-specific symptoms and laboratory examination [2]. It is very difficult to differentiate gallbladder carcinoma from cholecystitis with atypical imaging findings, such as slight diffuse gallbladder wall thickening, no neoplasm of gallbladder or lymph node enlargement. And besides, there are few studies on imaging features of neuroendocrine carcinomas of gallbladder.

It was hard to confirm the occurrence time of carcinomas. The initial gallbladder-wall biopsy pathological results showed inflammatory changes with perforation on the fundus of the gallbladder. However, the final diagnosis according to the pathological results of the cholecystectomy was malignant mixed tumor after 3 months. The possibility that the mixed carcinoma cells may have existed when the first admission cannot be eliminated, as the mixed carcinoma cells were covered up by severe inflammation since the biopsy was just a small piece of the gallbladder wall.

The clinical behavior of LCNEC of gallbladder is more aggressive than other malignant tumors, pathologists should be aware of it. The patient underwent an uneventful postoperative course and then received chemotherapy with gemcitabine/oxaliplatin, he would be followed up every 3 weeks.

Disclosure of conflict of interest

None.

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