



Research Paper

Diagnosis, treatment and outcome of malignant perivascular epithelioid cell neoplasm in the Hilar Biliary Tract

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ABSTRACT

Perivascular epithelioid cell neoplasm (PEComas) of the hilar biliary tract is a rare form of tumor compared to adenocarcinoma of the hilar biliary tract. This review reports a case of a 63-year-old male patient with malignant perivascular epithelioid cell neoplasm of the hilar biliary tract who underwent a radical resection of the lesion. Histopathological examination revealed the solid tumour cells with necrosis diffusely arranged in the bile duct tissue; the cytoplasm was transparent, and the nuclear division was easily observed. Immunohistochemistry of HMB45(+), and SMA(+) were positive. The malignant perivascular epithelioid cell neoplasm of the hilar biliary tract was diagnosed. The imaging findings of this disease are not specific, and there is a lack of specific and sensitive tumour-related serological indicators. Preoperative diagnosis is extremely difficult. The definite diagnosis is made mainly according to histological and immunohistochemical characteristics of the surgically resected tumour. Hence, the surgical treatment is still the main treatment regimen for this tumour.

Key words: Perivascular epithelioid cell neoplasm, hilar biliary tract.

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Abbreviations: AFP: α -fetoprotein; CEA: carcinoembryonic antigen; BP: Blood pressure; CA19-9: Carbohydrate antigen (CA)19-9; BS: Bowel sound; PIVKA-II: human protein induced vitamin K absence or antagonist-II; CT: Computed tomography; HR: Heart rate; TPR: Body temperature; MRI: Magnetic resonance imaging.

INTRODUCTION

Perivascular epithelioid cell neoplasm is a rare entity. This report presents an extremely rare clinical case of malignant perivascular epithelioid cell neoplasm of the hilar biliary tract. On examination, the enhanced liver, bile, pancreas and spleen CT and the enhanced hepatobiliary MR imaging (MRCP, MRU) showed a space occupying lesion in the hepatic hilar area and intrahepatic bile duct dilatation, hence, hilar cholangiocarcinoma was considered. Radical resection of the lesion was performed. Histopathological examination revealed the solid tumour cells with necrosis diffusely arranged in the bile duct tissue and transparent cytoplasm, and the nuclear division was easily observed.

Immunohistochemistry of HMB45(+), and SMA (+) were positive.

Case presentation

The patient was a 63 year old man and admitted to the hospital due to yellowing of the skin and mucous membranes for 10 days. The patient had hepatitis B 18 years ago. The patient did not feel abdominal distension, nausea, vomiting and fever. Physical examination revealed skin and tunica dura of the patient were severely stained



Figure 1: Compared tomography showing intrahepatic bile duct dilatation and a space occupying lesion in the hepatic hilar area.

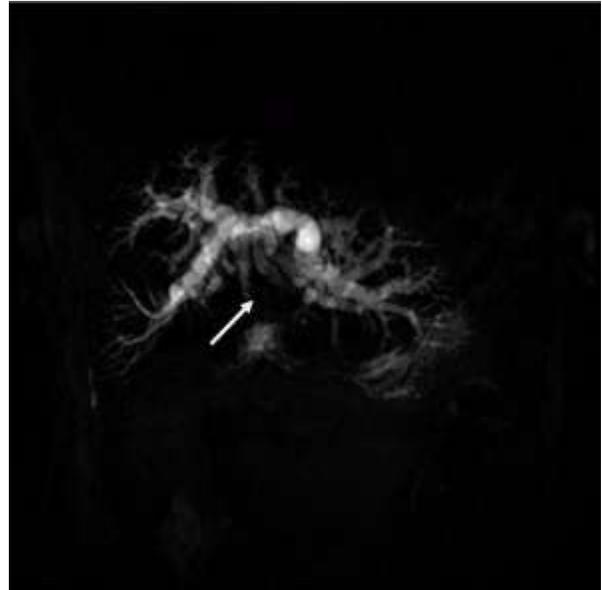


Figure 3: Magnetic resonance cholangiopaneretography (MRCP, MRU) image showing intrahepatic bile duct dilatation and the gallbladder was not clearly observed.

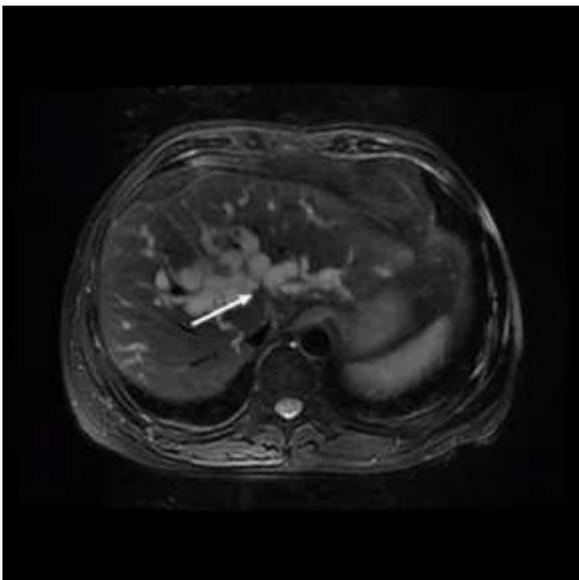


Figure 2: The enhanced hepatobiliary-phase MR imaging at 3T + magnetic resonance showing a space occupying lesion in the hepatic hilar area.

yellow. The patient felt light tenderness in the right upper quadrant without rebound tenderness and muscle tonus. Murphy sign was negative.

Auxiliary examination

Liver function showed TP 63.82 g/L, ALB 37.20 g/L, TBIL

292 umol/L, DBIL 151.6 umol/L, IBIL 140.4 umol/L, GGT 216 U/L, ALP 196 U/L, AST 52 U/L, ALT 45 U/L. Carbohydrate antigen (CA)19-9(71.89 U/ml), α - fetoprotein(AFP)(65.95 ng/ml) and human protein induced vitamin K absence or antagonist-II(PIVKA-II) (7586 mAU/ml) were high, and carcinoembryonic antigen (CEA)(2.77 ng/ml) was normal including HBS-AG(-), AHBS(+), HBE-AG(-), AHBE (+), AHBC(+). **Figure 1** shows the enhanced liver, bile, pancreas and spleen CT performed in the local hospital indicated intrahepatic bile duct dilatation and a space occupying lesion in the hepatic hilar area. The enhanced hepatobiliary-phase MR imaging at 3T + magnetic resonance cholangio- paneretography (MRCP, MRU) showed a space occupying lesion in the hepatic hilar area and intrahepatic bile duct dilatation (**Figures 2 and 3**), thus, hilar cholangiocarcinoma was considered, and the gallbladder was not clearly observed.

RESULT

Surgical procedure

Preoperative diagnosis: Hepatic hilar cholangiocarcinoma. After necessary preoperative preparation, radical resection of hepatic hilar lesion was performed under general anesthesia. During the operation, it was observed that the tumour was a grayish white nodule of about 2 × 2.3 cm which was located in the hepatic hilar area, and its texture was brittle (**Figure 4**). The lesion was located at the confluence of the left and right hepatic ducts, while the right and left hepatic ducts and common hepatic duct were



Figure 4: The image of the tumor body.

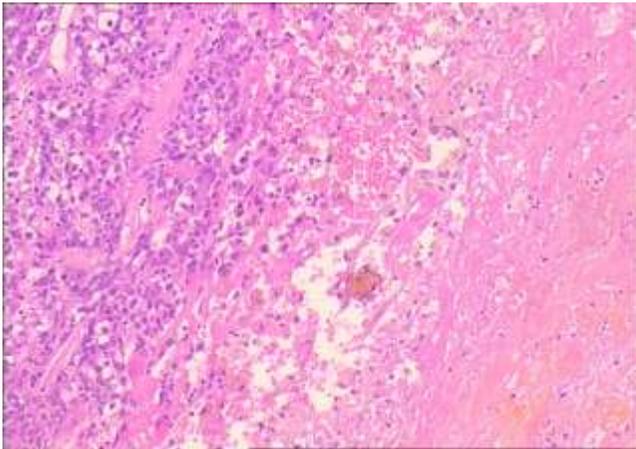


Figure 5: Photomicrograph of the tumor showing the neoplastic cell makr-fusiform shape. The interstitial blood sinus was abundant. The neoplastic cells were with abundant eosinophilic and vacuolated cytoplasm, arranged in sheets and nests (HE×200).

invaded. There were no metabasis nodus and swelling of lymphoid nodes on ligament hepatoduodenale, stomach, small intestine, pelvic cavity, abdominal membrane and root of mesentery. Radical resection of the lesion was performed: extrahepatic cholangiectomy, cholecystectomy, segment IVb-V liver resection and hepaticojejunostomy were carried out respectively.

Histopathological examination

A grayish white nodule of about 2 × 2.3 cm was removed from hilar biliary duct. Microscopic examination revealed that neoplastic cells were the solid tumour cells with necrosis and diffusely arranged in the bile duct tissue, the cytoplasm was transparent, while the nuclear division was



Figure 6: Photomicrograph of immunostained section using HMB45 showing cytoplasmic positivity in the tumors cell (SP: Streptavidin-peroxidase × 200).

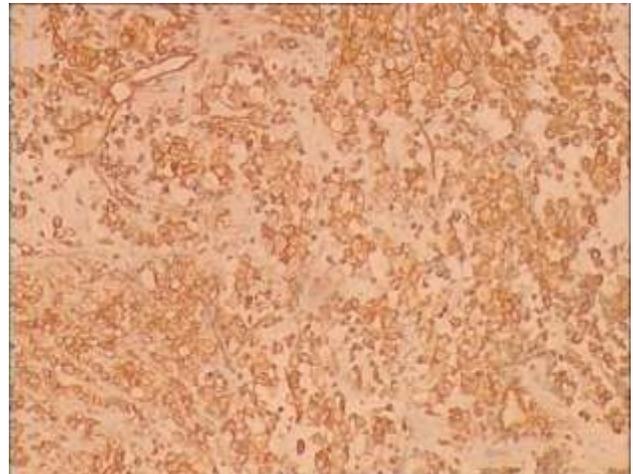


Figure 7: Photomicrograph of immunostained section using SMA showing cytoplasmic positivity in the tumors cells (SP: Streptavidin-peroxidase × 200).

easily observed (>10/10 HPF), and the interstitial blood sinus was abundant with abundant eosinophilic and vacuolated cytoplasm, arranged in sheets and nests (Figure 5). The lymphoid nodes of 12a (hepatic artery nearby), 12b(bile duct nearby), 12c(portal vein nearby), 8 groups (hepatic common artery nearby), 13 groups (after head of pancreas nearby) showed no neoplastic cells.

Immunohistochemistry

Figures 6, 7, 8 and 9 shows CK(-), CK7(-), HMB45(++), VIM(+), Melan-A(-), CK19(-), SMA(+), desmin(-), CD117(-), S-100 (-), Arg (-) and a ki-67 positive rate of 40%.



Figure 8: Photomicrograph of immunostained section using VIM showing cytoplasmic positivity in the tumors cells (SP: Streptavidin-peroxidase × 200).

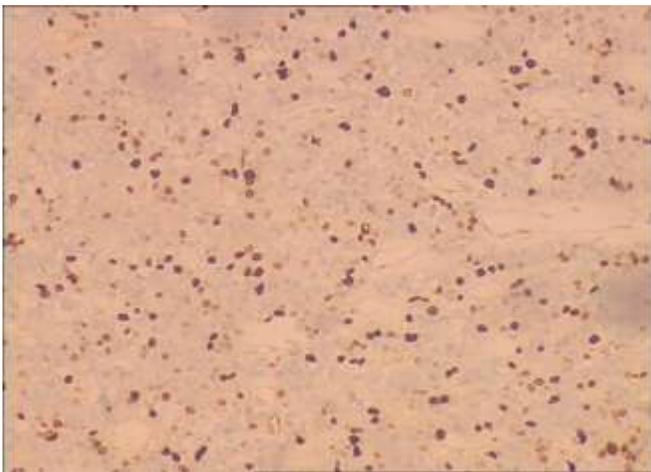


Figure 9: Photomicrograph of immunostained section using ki-67 showing 40% nucleus positivity in the tumors cells (SP: Streptavidin-peroxidase × 200).

Follow-up

Post-operative recovery of the patient was smooth. After 11 days of hospitalization, he was discharged and received regular outpatient follow-up. Eighteen months postoperatively, CT examination showed no recurrence or metastasis (Figure 10), and routine blood tests, tumor markers CA19-9, AFP, and CEA, liver function tests, blood glucose, and blood and urine amylase were all within normal ranges.

DISCUSSION

Bonetti et al. (1992) proposed the concept of perivascular



Figure 10: Computed tomographic image at 18 months postoperatively shows no recurrence and metastasis.

epithelioid cells (PEC), which have characteristics such as melanocyte marker immune response, epithelioid cell morphology, transparent eosinophilic cytoplasm and perivascular distribution. WHO (2002) put forward the definition of perivascular epithelioid cell neoplasm (PEComas), which is a mesenchymal tumour composed of perivascular epithelioid cells that are morphologically and immunohistochemically unique (Folpe, 2002). PEComas often consist of epithelial-like cells in a nested and flaky form, but occasionally spindle-shaped cells with eosinophilic granules in their transparent cytoplasm were seen and locally attached to the blood vessel walls. For melanocyte marker (HMB-45 or MelanA) and smooth muscle cell markers (actin and/or desmin), PEComas usually have immune responses that are very helpful for the diagnosis of diseases (Charli-Joseph et al., 2014). The PEComas family includes angiomyolipoma (AML), clear cell sugar tumour (CCTL), lymphangioliomyomatosis (LAM), clear cell myomelanocytic tumour (CCMMT) and some rare clear cell tumours in other areas.

At present, it has been reported that PEComas have been detected in locations such as uterus, rectum, lungs, heart and retroperitoneal area, but it has not been reported that a rare mesenchymal tumour occurs in the hepatic hilar bile duct. The diagnosis and treatment of PEComas in the hepatic hilar bile duct were further discussed.

Clinical manifestation

The PEComas in the hepatic hilar bile duct is mainly characterized by obstructive jaundice. The skin and mucosa

in this patient were severely yellow-stained, accompanied by abdominal distension, nausea, itchy skin, dark colored urine and clay colored stool.

Histopathological and immunohistochemical staining characteristics

In this case, the PEComas in the hepatic hilar bile duct was a solid and fragile lesion with a yellow-brown to gray-white appearance. The lesion was localized and infiltrated with a slightly clear boundary, but there was no existence of a clear envelope. Under the microscope, the solid tumour cells with necrosis were diffusely arranged, while the cytoplasm was transparent, the nucleoli were small, and perivascular epithelioid cells were characterized by perivascular distribution and arranged radially around the blood vessels (Lu et al., 2015; Fadare, 2008). In this case, the immunohistochemistry of PEComas in the hepatic bile duct indicated HB45(+), VIM(+), Melan-A(-), SMA(+) and a ki-67 positive rate of 40%, which were consistent with the characteristic such as co-expression of smooth muscle actin and melanin markers in PEComas.

Benignancy and malignancy of the tumour

PEComas have a variety of biological behaviors. Folpe et al. (2005) proposed the criteria to differentiate benignancy and malignancy of PEComas in biology including:

- 1) Benign lesions: There are no high-risk factors such as tumour diameter <5 cm, no invasive growth, no high nuclear grading and cell density, mitotic count $\leq 1/50$ HPF, no cell necrosis, no vascular invasion;
- 2) Uncertain potential malignant lesion: There is one of the following factors, nuclear pleomorphism or multinucleated giant cells or tumour diameter > 5 cm;
- 3) Malignant lesion: There are two or more following high risk factors including tumour diameter > 5 cm, invasive growth, high nuclear grading and cell density, mitotic count $\geq 1/50$ HPF, tumour cell necrosis or vascular invasion. In this case, the choledochoscopy of PEComas in the hepatic hilar area indicated obvious necrosis and infiltrating growth of tumour cells and mitotic count $> 10/10$ HPF, hence, malignant PEComas were considered.

Imaging performance

In the study of the imaging features of PEComas, the correct rate of preoperative diagnosis by CT and MRI was only 31.3 to 40% (Tan et al., 2010). In the study of liver PEComas, most MRI scans showed that the tumour showed a long T₁

signal, a long T₂ signal and no fat signal; enhanced CT and MRI showed that the lesion had markedly uneven enhancement in the arterial phase and weakened enhancement in the portal vein phase or delayed phase. In this case, there was lack of characteristics in preoperative CT and MRI findings of PEComas in the hepatic hilar area, and the preoperative diagnosis indicated hepatic hilar cholangiocarcinoma. It was observed that imaging can confirm the presence of tumour, tumour size, location and blood supply, but cannot make a definite diagnosis, and the diagnosis depends mainly on postoperative histopathological characteristics and immunohistochemical staining characteristics.

Treatment and prognosis

Since most PEComas are benign lesions, the surgical treatment is not a treatment regimen that must be taken (Maebayashi et al., 2015). There is a lack of clear consensus on the treatment of PEComas. PEComas are diagnosed as benign or malignant PEComas in many cases only when surgical resection is performed, and as such limits the application of feasible non-surgical treatment options. In this case, PEComas in hepatic hilar bile duct regardless of benignancy and malignancy should be treated surgically due to the obstructive jaundice caused by tumour preoperatively.

In addition to surgical treatment, the efficacy of systemic chemotherapy for malignant PEComas is poor when metastatic lesions occur; targeted therapy represented by mTOR inhibitors has a good application prospect (Bleeker et al., 2012; Benson et al., 2014) and the use of mTOR inhibitors (such as sirolimus) for PEComas with large tumours and high invasiveness may be beneficial for surgical treatment and early control of potentially metastatic lesions (Bergamo et al., 2014). In this case, the patient has not received any adjuvant therapy (after over 18 months of follow-up) and there is no evidence of local recurrence and distant metastasis (Figure 8).

Conclusions

Most PEComas are benign lesions, and the changes in this tumour can be detected by clinical follow-up. However, the imaging findings of this disease are not specific, and there is a lack of specific and sensitive tumour-related serological indicators. Preoperative diagnosis is extremely difficult, while the definite diagnosis is made mainly according to histological and immunohistochemical characteristics of the surgically resected tumour. Therefore, the surgical treatment is still the main treatment regimen for this tumour.

Tumour histopathology indicated a special type of epithelioid cells or spindle cells. Transparent and

eosinophilic cytoplasm and perivascular distribution can be used as an important clue for the diagnosis of this disease, suggesting that pathologists should further conduct immunohistochemical staining for definite diagnosis to reduce missed diagnosis and misdiagnosis. The biological behaviors of PEComas are still not very clear. It has been reported that most of the recurrence and metastasis of this disease occur at 5 years after surgical resection, and thus long-term follow-up tests are needed to more accurately predict the biological behavior of PEComas, so as to obtain more knowledge for the preoperative diagnosis and optimal treatment of this tumour.

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