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CASE REPORT

Rare primary squamous cell carcinoma of the intrahepatic bile duct: A case report and review of literature

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Abstract

BACKGROUND

Cholangiocarcinoma is the most common malignancy of the biliary tree and has a poor prognosis. Adenocarcinoma is the most common pathological type of cholangiocarcinomas, but rare squamous, adenosquamous, and mucinous variants have been reported without adequate clinical data.

CASE SUMMARY

This report describes a rare case of primary squamous cell carcinoma (SCC) of the intrahepatic bile duct. The patient was admitted with a tumor in the hepatic caudate lobe with no obvious clinical symptoms. Examination revealed hepatitis B surface antigen positivity, a slight increase in alfa-fetoprotein to 16.34 ng/mL, and an irregular slightly heterogeneous enhancing lesion in the hepatic caudate lobe, which was initially thought to be hepatocellular carcinoma. Laparoscopic resection was performed, and the final pathology suggested a rare primary SCC of the intrahepatic bile duct. Immunohistochemistry indicated positivity for villin, partial positivity for p63, and negativity for hepatocyte, CK7, CK8, CK19, and CK20. The Ki-67 index was approximately 60%. The patient received six cycles of Tegio chemotherapy. A new lesion was detected in the liver after 15 months. The surgery was performed, and the patient was followed-up at a local hospital. To date, no new lesions have been observed.

CONCLUSION

Surgery is the first choice for resectable lesions, and combined chemotherapy based on pathology is essential for increasing overall survival.

Key Words: Squamous cell carcinoma; Bile duct; Cholangiocarcinoma; Clinical characteristics; Treatment; Case report

Core Tip: We report a case of primary intrahepatic biliary squamous cell carcinoma (SCC) that was initially considered hepatocellular carcinoma. Intrahepatic biliary SCC is a rare pathological type without typical imaging features or serum markers. Its diagnosis depends on biopsy or postoperative pathology. Surgical resection is still considered the first choice for resectable lesions, but the intraoperative pathology of atypical liver lesions is essential for radical resection. Combined chemotherapy or chemoradiotherapy is beneficial for prolonging overall survival and decreasing the risk of recurrence. This case report and related literature review provide a valuable reference for the diagnosis and treatment of this disease.

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INTRODUCTION

Liver cancer is a malignancy that has a severe negative impact on human health worldwide. According to global cancer statistics for 2020, in men, the incidence rate of liver cancer was the sixth highest rate among cancers, and its mortality rate was the third highest. These rates were tenth and seventh highest, respectively, in women[1]. The pathological classification of primary liver cancer includes mainly hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and combined hepatocellular cholangiocarcinoma. The prognosis of ICC is particularly dismal owing to its highly malignant behavior, propensity for lymph node metastasis, and postoperative recurrence[2].

ICC is a cholangiocarcinoma that is located in a secondary or more proximal bile duct and is derived from epithelial cells in the duct. ICC accounts for approximately 10%-15% of primary liver cancers and < 10% of cholangiocarcinomas[3]. The main morphological growth patterns of ICCs are the formation of a mass, periductal and intraductal infiltration, and superficial spread[4]. Adenocarcinoma is the main pathological type, but there are some rare variants, including squamous, adenosquamous, mucinous, signet ring, clear, and undifferentiated cells[5]. Surgery is still the preferred treatment for ICC. However, unlike surgery for HCC, hepatic hilar lymph node dissection following resection of the primary lesion is recommended to improve the prognosis of ICC and prolong overall survival (OS). Chemotherapy, radiotherapy, and targeted or local treatment after pathological diagnosis could achieve a better prognosis for inoperable ICC[6]. However, the diagnosis and treatment strategies for some rare pathological types of ICC might be different from those used for biliary adenocarcinoma and need further exploration and discussion by clinicians.

This report describes a rare case of primary squamous cell carcinoma (SCC) of the intrahepatic bile duct that was initially misdiagnosed as atypical HCC based on imaging and laboratory examinations. The final pathology was determined after resection and guided subsequent chemotherapy. This report summarizes this case and discusses the key points of clinical diagnosis and related therapeutic strategies for biliary SCC, including surgery and chemotherapy regimens.

CASE PRESENTATION

Chief complaints

A 52-year-old man with a tumor of the hepatic caudate lobe that had been detected 14 days earlier in Changguo Hospital of Zibo (Shandong, China) was admitted on June 8, 2021.

History of present illness

Enhanced magnetic resonance imaging of the upper abdomen performed at a local hospital revealed a lesion in the hepatic caudate lobe that was thought to be a malignant tumor. Moreover, gastroscopy and colonoscopy revealed gastric and colonic polyps but did not detect a tumor. No treatment was started at that time.

History of past illness

The patient had a history of hepatitis B virus infection and was hepatitis B surface antigen-positive. However, he was not receiving treatment or undergoing regular examinations.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

Physical examination did not reveal any obvious positive signs.

Laboratory examinations

Laboratory investigations confirmed hepatitis B surface antigen, hepatitis B e-antibody, and hepatitis B core antibody positivity without abnormal hepatitis B virus DNA or liver dysfunction. The alfa-fetoprotein level was slightly increased at 16.34 ng/mL (normal range: 0-8.78 ng/mL), and the carcinoembryonic antigen (normal range: 0-5 ng/mL) and carbohydrate antigen (CA) 19-9 (normal range: 0-27 U/mL) levels were 2.31 ng/mL and 6.1 U/mL, respectively. The patients' preoperative alanine aminotransferase and aspartate aminotransferase levels were 18.30 U/L (normal reference range: < 50 U/L) and 23.30 U/L (normal reference range: < 40 U/L), respectively. The levels of gamma-glutamyl transferase and alkaline phosphatase were 16.30 U/L (normal reference range: < 60 U/L) and 71.00 U/L (normal reference range: 45-125 U/L), respectively. The total bilirubin level was 7.70 μmol/L (normal reference range: 5.0-24.0 μmol/L). The albumin level was 38.30 g/L (normal reference range: 40-55 g/L). The white blood cell and red blood cell counts were 6.05 × 10^9/L [normal reference range: (3.5-9.5) × 10^9/L] and 4.13 × 10^{12}/L [normal reference range: (4.3-5.8) × 10^{12}/L], respectively.

Imaging examinations

An enhanced computed tomography (CT) scan indicated liver cirrhosis and showed an irregular lesion with a maximum diameter of 2.5 cm in the hepatic caudate lobe. The tumor showed slightly heterogeneous enhancement (Figure 1).

Further diagnostic work-up

Three days after admission, the patient underwent laparoscopic liver tumor resection at the First Affiliated Hospital of Shandong First Medical University. He recovered well following treatment with hepatoprotective medication, nutritional support, and human albumin and was discharged on postoperative day 10. Pathologic examination revealed a pale nodular mass measuring 4.0 cm × 3.0 cm × 2.2 cm that had a soft texture, was partially necrotic, had a clear boundary, and had invaded the liver capsule. According to the China Liver Cancer Staging, the tumor stage was I a, and the vascular invasion showed venous invasion. The background liver tissue exhibited hepatitis and cirrhosis, with no presence of cholelithiasis. Hematoxylin-eosin (HE) staining revealed atypical cells arranged in cords, and no keratin pearls were observed (Figure 2). Immunohistochemical examination revealed that the patient was positive for villin, partially positive for p63, and negative for glypican, hepatocyte, CK7, CK8, CK19, and CK20 (Figure 3). The Ki-67 index was approximately 60%.

FINAL DIAGNOSIS

The final pathological examination was considered as a rare primary SCC of the intrahepatic bile duct.

TREATMENT

Six cycles of Tegio (50 mg orally twice daily) were recommended after consultation with an oncology expert, and the patient opted for postoperative follow-up at a local hospital.

OUTCOME AND FOLLOW-UP

A new lesion was detected in the liver after 15 months, and surgery was performed at a local hospital without post-operative chemotherapy. To date, no new lesions have been detected.

DISCUSSION

Cholangiocarcinoma is a relatively rare malignant tumor of the digestive tract that may arise anywhere in the biliary duct and can be divided into intrahepatic, perihilar, or distal depending on the primary site[7]. Based on clinical data from single-center and multicenter analyses, the incidence of perihilar and distal disease is > 90%, and that of ICC is < 10%[3, 8]. Based on the above classification, the corresponding operations and complete lymph node dissection, such as hepatectomy and duodenopancreatectomy, are the first choices for prolonging OS. For advanced cholangiocarcinoma, chemotherapy consisting of gemcitabine and cisplatin is recommended as the standard first-line treatment for improving progression-free survival and OS[9]. Folinic acid, fluorouracil, and oxaliplatin (FOLFOX) plus active symptom control is considered the second-line choice because a study showed that the median OS and the 6-month and 12-month OS rates were better in patients who received FOLFOX plus active symptom control than in those who received active symptom control alone[10]. In addition to chemotherapy and radiotherapy, immunotherapy in combination with targeted therapy (*e.g.*, pembrolizumab + lenvatinib) and immunotherapy alone are being explored for treating cholangiocarcinoma[11].

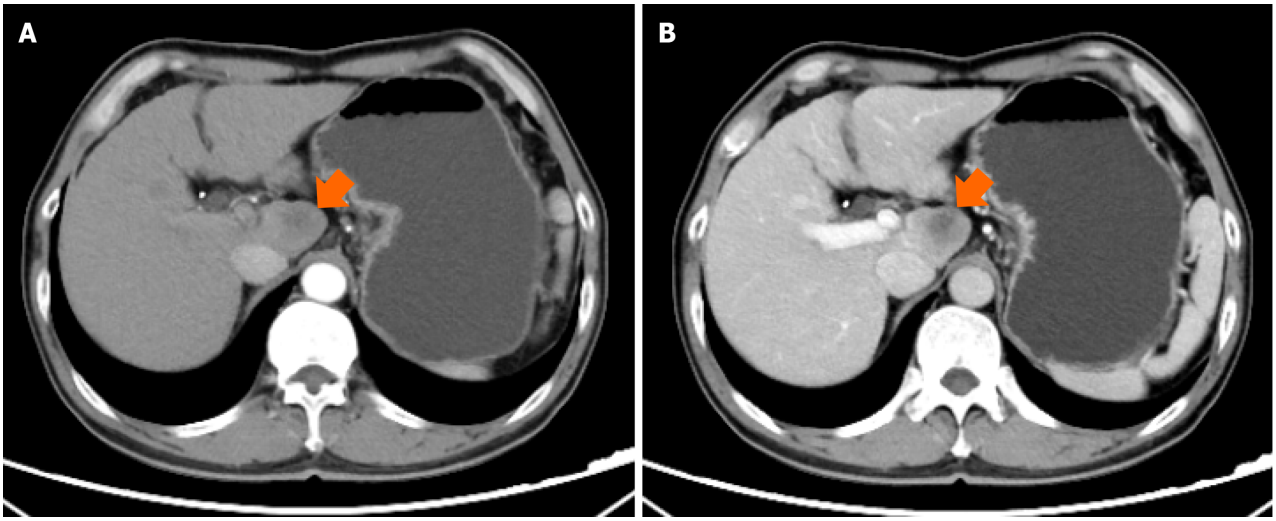

Figure 1 Computed tomography imaging of liver lesion. A: The arterial phase of computed tomography (CT) showed no obvious enhancement (orange arrow); B: The venous phase of CT showed slightly heterogeneous enhancement (orange arrow).

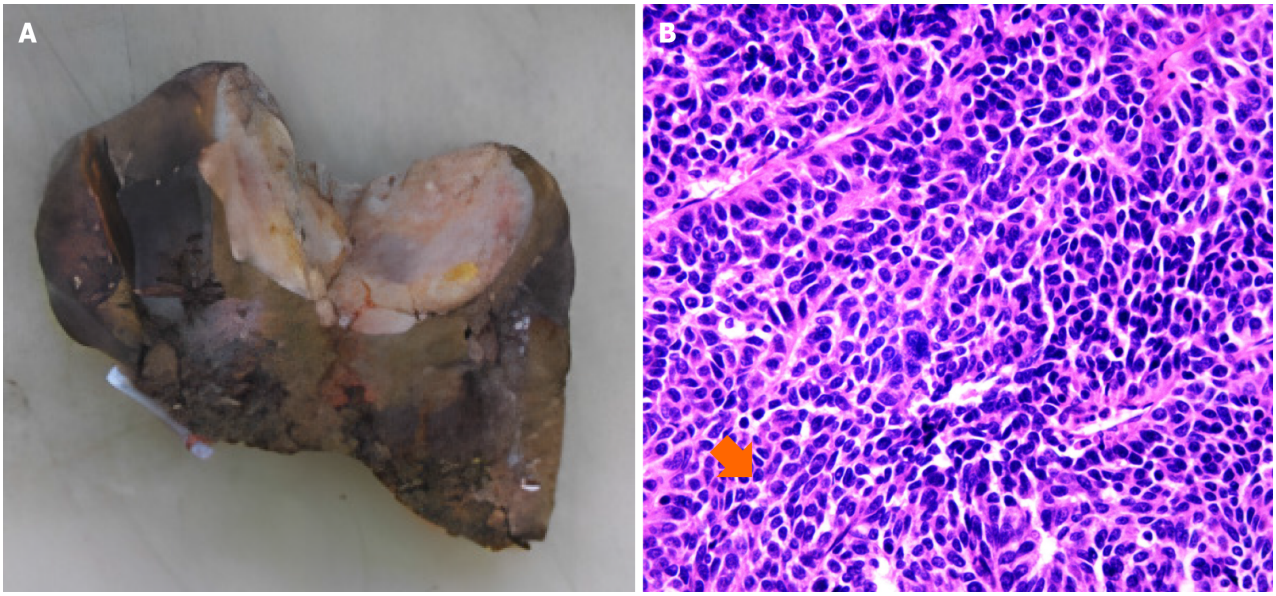

Figure 2 The pathology of liver lesion. A: The lesion owned soft texture, partially necrosis, clear boundary, and invasion of liver capsule; B: Hematoxylin and eosin staining indicated atypical cell arranged in nests (orange arrow), and no obvious keratin pearl was observed.

The main risk factors for cholangiocarcinoma are biliary diseases, biliary malformations/choledochal cysts, cholelithiasis, cholecystitis/cholecystectomy, liver flukes, hepatitis C virus infection, and type 2 diabetes[12]. The prognosis of biliary SCC is worse than that of intrahepatic bile duct adenocarcinoma or HCC because of lymph node metastasis, irregular margins, and vascular invasion. The most common pathologic type is adenocarcinoma, and exploration of therapeutic strategies is focused mainly on this type[13]. However, we sometimes encounter rare types of cholangiocarcinoma, such as biliary SCC, which has a poor prognosis owing to a lack of effective clinical therapies and limited relevant research data[14]. Therefore, we explored the published literature on the epidemiology, clinical features, and diagnosis and treatment of SCC of the bile duct.

The pathogenesis of SCC of the bile duct remains unclear, and we explored it mainly *via* case reports because of the lack of clinical studies. Several theories have been suggested. First, anaplastic carcinoma of the bile duct could differentiate into adenocarcinoma or SCC[15]. Second, SCC could derive from adenocarcinoma, and Iemura *et al*[16] described the possible transformation from adenocarcinoma to SCC in a mouse model of cholangiocarcinoma. Third, the metaplastic squamous epithelium of the bile duct has the potential to transform into SCC, and the inflammation associated with choledochal cysts, cholelithiasis, sclerosing cholangitis, and Caroli disease could be an important cause of metaplasia[17]. Some experts have suggested that the "inflammation-cancer" transformation is an inescapable risk factor for the occurrence of cholangiocarcinoma, although SCC is rarer than adenocarcinoma[18]. Fourth, ectopic squamous epithelium may be another etiology. In our patient, the final pathology was considered to be poorly differentiated biliary SCC possibly derived from anaplastic carcinoma. The positive expression of p63 and the arrangement of atypical cells in

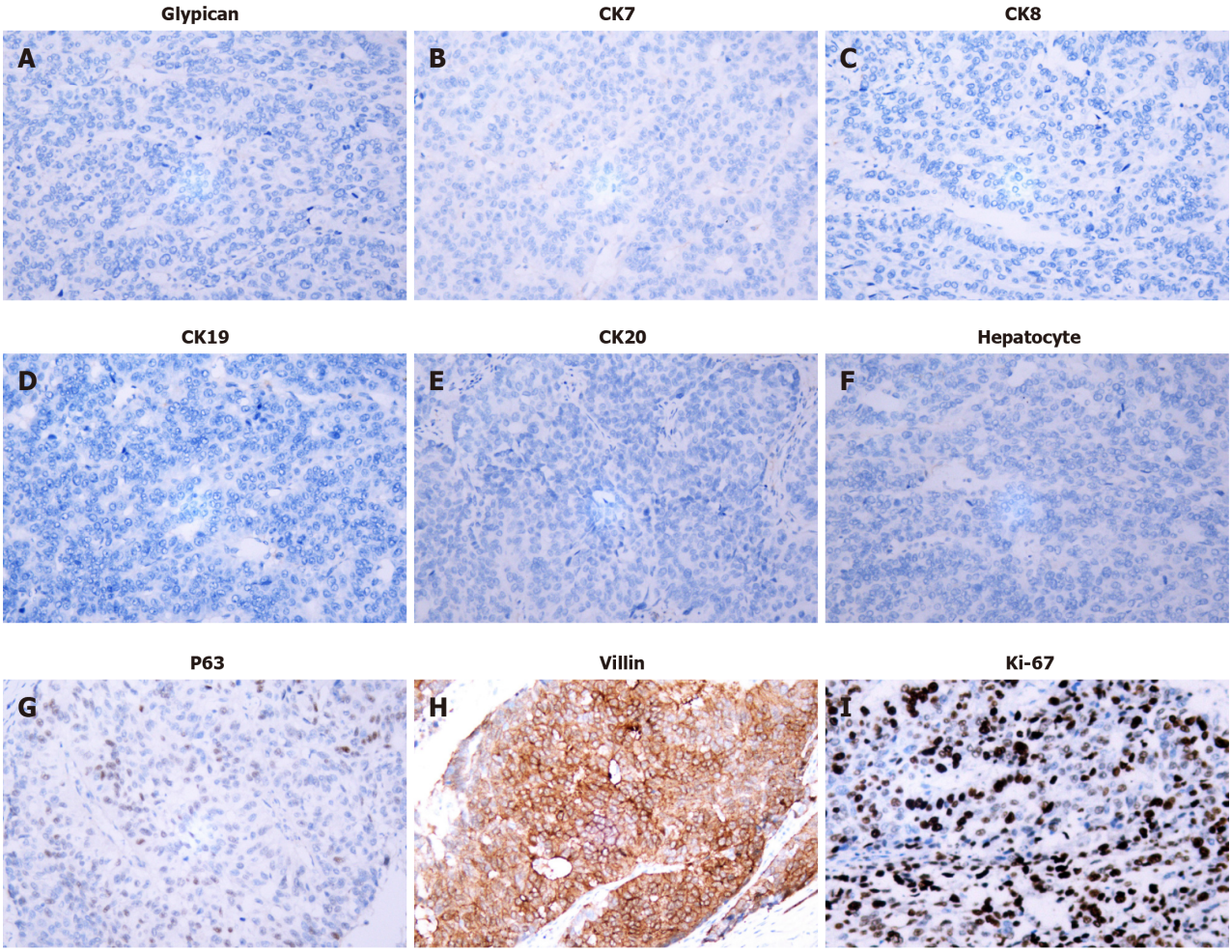

Figure 3 Immunohistochemistry of liver lesion. The immunohistochemical examination was positive for villin, p63, and negative for glypican, hepatocyte, CK7, CK8, CK19, and CK20, the Ki-67 index was about 60% (× 200). A: Glypican; B: CK7; C: CK8; D: CK19; E: CK20; F: Hepatocyte; G: P63; H: Villin; I: Ki-67.

nests were the basis for the diagnosis of SCC (Figures 2 and 3).

According to our literature review, biliary SCC is most common in the extrahepatic bile duct, and clinical reports of the intrahepatic type are rare. Unlike for that of cholangioadenocarcinoma, an accurate diagnosis of biliary SCC is difficult owing to its rarity and lack of typical manifestations. We found that the common clinical symptoms of biliary SCC were abdominal pain, jaundice, and gastrointestinal abnormalities, which could be caused by biliary obstruction, inflammation, neuronal invasion, or biliary spasm[14]. However, some patients have no significant symptoms, especially if they have the intrahepatic type, as in our case. Laboratory examinations indicated impaired liver function with elevated CA19-9 levels. However, only five of the 14 patients listed in Table 1 had elevated CA19-9 levels, suggesting that the specificity of CA 19-9 is lower for SCC than for cholangioadenocarcinoma[19]. However, the relevant data are limited. Analysis of large-scale multicenter clinical data remains important, as is examination of the levels of the hepatobiliary tumor markers carcinoembryonic antigen, CA 19-9, and alfa-fetoprotein. On imaging, HCC is always presented as markedly enhanced in the arterial phase and has low-density contrast in the venous phase. Moreover, ICC adenocarcinoma has delayed enhancement in the venous phase, sometimes accompanied by dilation of the distal bile duct on CT or magnetic resonance imaging. However, biliary SCC may present as an avascular and delayed or heterogeneous enhancement mass similar to that of the ICC adenocarcinoma[18,20] (Table 1). Our patient's CT manifestations revealed an avascular and heterogeneous enhancement mass. The above data indicate that biliary SCC has no classical serologic or radiologic findings. Biopsy is essential for advanced hepatobiliary tumors; needle biopsy is suitable for intrahepatic lesions. However, surgery remains the first option for resectable lesions because of the risk of needle transfer during biopsy. Rapid intraoperative pathology is required for accurate diagnosis and complete resection. Endoscopic retrograde cholangiopancreatography, intraductal ultrasonography, or spy glass are valuable for the biopsy of extrahepatic lesions[14]. Even if SCC of the bile duct has been confirmed, gastroenteroscopy and positron emission tomography-CT are still necessary in view of reports of biliary metastasis of esophageal SCC[21,22]. The immunohistochemistry results vary widely among differentiated cases. Keratin pearls and CK5/6 positivity are consistently observed, but the final pathology should include both clinical features and cytologic morphology[23] (Table 1). In our case, the patient tested positive for villin, which was not previously observed in SCC patients. However, we cannot deny that villin is not a specific marker for SCC. The detection of villin was used to identify the source of the tumor, and the final diagnosis should be determined by its combination with other markers, such as p63[24].

Table 1 The review of literature for squamous cell carcinoma of bile duct

Ref.	Case	Symptoms	Serum study	CT/MR	Pathology	Treatments
Gatof *et al*[14], 2004	A 86-year-old female	Abdominal pain and jaundice	-	Cholelithiasis of CBD and dilated bile duct	SCC with pancytokeratin stains (+)	Chemotherapy and high-dose radiation
Sewkani, *et al*[17], 2005	A 60-year-old male	Jaundice	-	A thickening of the distal BD	keratin pearl (+)	Surgery
Abbas *et al*[27], 2008	A 28-year-old female	Abdominal pain and jaundice	-	An avascular liver mass	SCC with dysplasia of the bile-duct epithelium	Extended left lobectomy and image guided external beam radiation
Price *et al*[31], 2008	A 41-year-old female	Painless jaundice, diarrhea	ALP↑, CA199↑	Choledochal cysts with cholelithiasis and a mass	SCC with keratin pearl	Chemotherapy and radiation
Avezbadalov *et al*[29], 2014	A 78-year-old Hispanic woman	Somnolent	ALP↑, GGTP↑	Liver carcinoma with 17.5 cm invading colon–hepatic flexure	poorly diferentiated SCC: CK5/6(+), p63(+), CK19(+), CK20(-), CK7(-), HMB-45(-), TTF-I(-)	Home hospice
Goto *et al*[23], 2016	A 77-year-old female	Jaundice with fatigue	DBIL↑, TBIL↑, ALP↑, normal CA199	A solid mass in the junction of the cystic and common bile ducts	Keratinization, CK5/6(+), p53(+), MIB-1(+), periodic acid staining(-)	Surgery and adjuvant chemotherapy with gemcitabine
Nishiguchi *et al*[26], 2016	A 78-year-old male	Brown urine	Normal CA199 and CEA, elevated hepatobiliary enzyme	The thickening and enhancement of distal BD	keratin pearl(+)	Surgery and chemotherapy with cisplatin and tegafur/gimeracil/oteracil
Tamaoka *et al*[20], 2018	A 82-year-old male	No significant symptoms	CA199↑	Liver mass with homogeneous density and delayed enhancement	CK 5/6(+), Keratin pearls(+), p40(-)	Extended right lobectomy
Knudsen *et al*[28], 2019	A 66-year-old female	Dark-colored urine	ALT↑, ALP↑, GGT	CBD dilation with a tumor in distal BD	Keratin pearl(+), CK5/6(+), p40(+)	Surgery
Wang *et al*[18], 2020	A 32-year-old female with choledochal cyst	Nausea, abdominal pain	ALP↑, DBIL↑, TBIL↑	Choledochal cyst complicated a tumor	SCC with scattered distribution of heteromorphic epithelial cells	Surgery and postoperative chemotherapy with gemcitabine and cisplatin
Bacha *et al*[30], 2021	A 35-year-old male	Epigastric pain, jaundice and fatigue	DBIL↑, TBIL↑, GGTP↑, ALP↑, normal CA199 and CEA	Irregular wall thickening in the distal CBD	Keratinization, CK 19(+)	Biliary drainage
Zhong *et al*[19], 2021	A 76-year-old male	Jaundice	TBIL↑, GGTP↑, ALP↑, CA199↑	A low signal intensity area in the middle CBD	CK5/6(+), p63(+), CK20(-), no keratin pearls	Surgery and postoperative chemotherapy with gemcitabine and cisplatin
Shrestha *et al*[32], 2021	A 21-year-old male	Abdominal pain and jaundice	DBIL↑, ALP↑, CA199↑	Choledochal cysts with cholelithiasis	SCC with atypical cells arranged in cords and nests	Surgery and paclitaxel-based chemotherapy

SCC: Squamous cell carcinoma; ALP: Alkaline phosphatase; GGTP: Gamma-glutamyl transpeptidase; DBIL: Direct bilirubin; TBIL: Total bilirubin; PGE 1: Prostaglandin E 1; DVT: Deep venous thrombosis; TIPS: Transjugular intrahepatic portosystemic shunt; TACE: Transarterial chemoembolization; DIC: Disseminated intravascular coagulation; AST: Aspartate aminotransferase; ALT: Alanine transaminase; CA199: Carbohydrate antigen 199; CEA: Carcinoembryonic antigen; CBD: Common bile duct; GGT: Gamma-glutamyl transferase; CT: Computed tomography; MR: Magnetic resonance.

Due to its highly fibroproliferative nature, complex tumor microenvironment, and genetic heterogeneity, cholangiocarcinoma is prone to developing drug resistance[25]. Owing to its rarity, the clinical behavior of biliary SCC is still poorly understood, and targeted treatment options are inadequate. Moreover, SCC is likely to progress to an advanced stage, with a short survival time, large tumor size, aggressive intrahepatic spread, and frequent metastasis[15]. Surgical resection remains the preferred treatment for biliary SCC depending on the primary site. For patients with advanced disease and those who have undergone surgery, the recommended chemotherapy strategy is gemcitabine plus oxaliplatin or gemcitabine plus cisplatin. Chemotherapy with S1 plus cisplatin or docetaxel plus cisplatin plus 5-fluorouracil has also been reported to be helpful[26]. SCC has mainly been reported *via* case reports and treated by surgery, radiation, and chemotherapy. However, advanced SCC patients only receive relieving treatment, such as biliary drainage and analgesic treatment (Table 1), and these chemotherapy regimens mainly refer to the Guidelines of Chinese Society of Clinical Oncology (CSCO) Biliary Tract Cancer 2020 and Guidelines of Chinese Society of Clinical Oncology (CSCO) Biliary Tract Cancer 2023[6,7,12]. Intraoperative radiation to the surgical margins combined with postoperative external beam radiation is an option for decreasing the risk of local recurrence[27]. The limited data available suggest that targeted chemotherapy or chemoradiotherapy has prognostic benefits, including prolonged OS and decreased risk of recurrence, but confirmation is required in multicenter clinical studies. The importance of intraoperative pathology for all liver lesions should be recognized, and a standardized diagnostic process could decrease the rate of misdiagnosis, allow more precise treatment strategies, improve prognosis, and prolong OS.

Furthermore, some genetic polymorphisms have been shown to increase the risk of cholangiocarcinoma, to be involved in DNA repair (MTHFR, TYMS, GSTO1, and XRCC1), to protect cells from toxins (ABCC2, CYP1A2, and NAT2), and to play a role in immune surveillance (KLRK1, MICA, and PTGS2)[7]. After encountering the case reported here, we reviewed the clinical features and treatment options for biliary SCC. Knudsen *et al*[28] reported that alterations in FBXW7, CREBBP, CTCF, FAT1, MAGI2, MLL2, and NOTCH1 can predict the risk of extrahepatic biliary SCC.

CONCLUSION

In conclusion, the preoperative diagnosis of biliary SCC is difficult, and surgery is still the first choice for treating resectable lesions. Postoperative chemotherapy treatment requires multidisciplinary consultation, and Tegio therapy alone could be considered to improve postoperative outcomes. Furthermore, whole-genome sequencing of tumor specimens may be necessary to achieve precise and personalized molecular targeted therapy and improve OS. Since SCC is rare, its clinical, pathological and therapeutic outcomes still need to be further explored *via* multicenter cooperation.

FOOTNOTES

Author contributions: Ma QJ and Yang NN designed the report and wrote the paper, they contributed equally to this manuscript; Wang FH and Liu F performed the surgery; Wei HL collected the patient's clinical data; Wang FH analyzed the data and revised the paper; all authors have read and approved the final version of this manuscript.

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