

Case Report

Primary squamous cell cholangiocarcinoma: a case report

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Abstract: We report a case of primary squamous cell cholangiocarcinoma. A 62-year-old woman was admitted to our hospital with right upper quadrant abdominal pain and jaundice for 2 weeks. Abdominal computed tomography (CT) confirmed a soft tissue mass at the common hepatic bile duct (CHD). Magnetic resonance cholangio pancreatography (MRCP) revealed luminal stenosis of the CHD with dilation of both intrahepatic ducts. We performed curative resection for bile carcinoma and choledochojejunostomy. Histopathologically, tumor cells were arranged in nesting pattern that infiltrated the entire bile duct wall as well as the perineural tissues. Immunohistochemistry was as follows: AE1/AE3 (+), CAM5.2 (+), CK5/6 (+), p63 (+), p40 (+), AB-PAS (-), CGA (-), Syn (-), Ki67 (~30%). These results supported a diagnosis of biliary tract low differentiated squamous cell carcinoma. We also reviewed other 2 cases in our hospital during the past 10 years. Radical surgery should be most effective treatment for these patients, but chemotherapy and/or radiotherapy still need to be further studied.

Keywords: Primary squamous cell carcinoma, cholangiocarcinoma, common hepatic bile duct

Introduction

Cholangiocarcinoma (CC) is a primary cancer arising from the bile duct epithelia. CC morbidity is low, and represents less than 3.0% of all gastrointestinal tumors [1]. Histologically, most CCs are adenocarcinomatous, and other rare types include adenosquamous carcinomas, mucinous adenocarcinomas, and carcinoid, anaplastic carcinomas, of which pure squamous cell CCs are extremely rare. In 1930, the first case of squamous cell CC was reported [2], and only 7 cases have been documented in Chinese journals. Here, we report one case of primary squamous cell CC that represents the third case observed at our hospital during the last decade. We review these 3 cases, as well as describe clinicopathologic characteristics and surgical procedures used. Finally, we discuss current therapeutic strategies for this specific condition.

Case report

A 62-year-old woman was admitted to our hospital with right upper quadrant abdominal pain

and jaundice for 2 weeks. Appetite loss, pruritus, dark urine, pale stools, and weight loss (7 kg in the past 2 months) were noted. Physical examination revealed a chronic faces, jaundice, and deep upper abdominal tenderness. Laboratory tests confirmed ALT of 103 U/L (normal range 7-45 U/L), AST of 93 U/L (normal range: 13-40 U/L); alkaline phosphatase of 199 U/L (normal range 50-135 U/L); total bilirubin of 387.4 μ mol/L (normal range: 1.7-21 μ mol/L); direct bilirubin 287.4 μ mol/L (normal range 0-6.8 μ mol/L); and carbohydrate antigen 19-9 (CA 19-9) of 466.58 U/ml (normal range: 0-20 U/ml). Abdominal computed tomography (CT) confirmed a soft tissue mass at the common hepatic bile duct (CHD). Magnetic resonance cholangiopancreatography (MRCP) revealed luminal stenosis of the CHD with dilation of both intrahepatic ducts (**Figure 1**).

According to the Bismuth-Corlette classification, this was a type I hilar cholangiocarcinoma (CC), so we performed curative resection for bile carcinoma and choledochojejunostomy. Intraoperative frozen-section sample examination confirmed negative surgical margins. The

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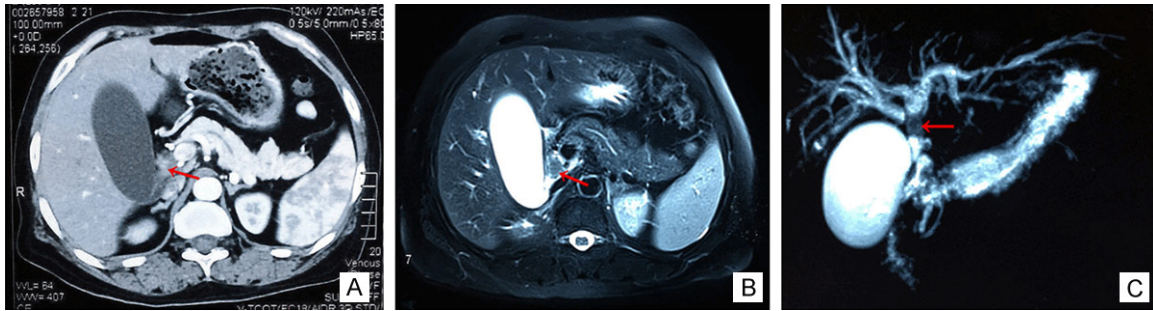


Figure 1. A. Selected CT images show a soft tissue mass at the CHD at the arterial phase (arrow). B and C. MRCP revealed luminal stenosis of the CHD with dilation of both intrahepatic ducts (arrow).

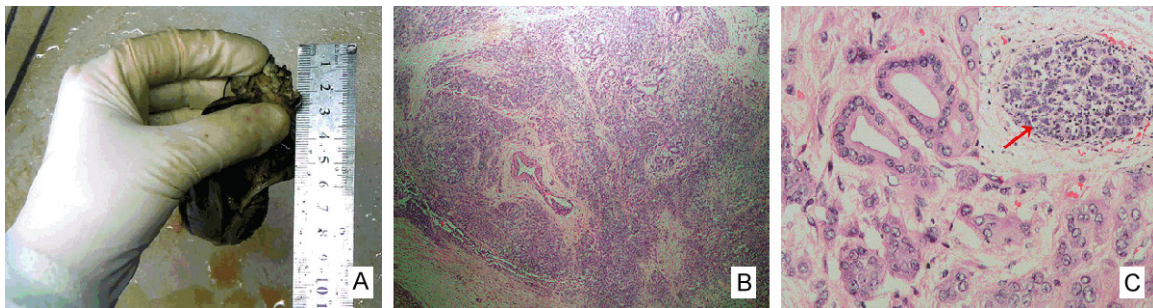


Figure 2. A. Macroscopically, tumor was located in the CHD (1.5 × 1 cm). B and C. H&E staining revealed tumor cells arranged in a nesting pattern that infiltrated into the entire layer of bile duct wall, invading perineural tissues (arrow, B 4 ×, C 20 ×).

removed tumor was 1.5 × 1 cm, at the CHD under the bifurcation (**Figure 2A**). Using hematoxylin and eosin staining, we noted tumor cells arranged in nesting pattern that infiltrated the entire bile duct wall as well as the perineural tissues (**Figure 2B, 2C**), but the peribiliary metastatic lymph node was negative. Immunohistochemistry was as follows: AE1/AE3 (+), CAM5.2 (+), CK5/6 (+), p63 (+), p40 (+), AB-PAS (-), CGA (-), Syn (-), Ki67 (~30%) (**Figure 3**). These results supported a diagnosis of biliary tract low differentiated squamous cell carcinoma. Postoperative recovery was uneventful, and the patient was discharged 12 days after surgery. Then, 2 weeks later, the patient received the oral fluoropyrimidine S-1 (40 mg/m², bid for 4 weeks, po). However, chemotherapy was discontinued due to a hepatic abscess. Five months after surgery, the patient died from cancer-related cachexia.

Discussion

The single paper to report the incidence of squamous cell carcinoma of the extrahepatic

bile duct suggested it was less than 1.4% [3]. Yamana's group described 15 cases documented in English-language journals [4]. The patient depicted here is the first primary squamous cell CHD carcinoma observed in our team, so we researched data from 780 patients with diagnosed bile duct carcinoma at our hospital over the past decade and only 3 cases (incidence: 0.38%, including our patient) were primary squamous cell carcinoma (**Table 1**).

Two theories exist to explain primary squamous cell bile duct carcinoma. One suggests that cholelithiasis or choledochal cysts cause chronic inflammation that inflames the epithelial tissue to promote squamous metaplasia. Subsequently, squamous cells transform into malignant cells, proliferate and replace the epithelial area without an adenoid component [2]. **Table 1** shows that there was no source of chronic inflammation in our case, but in the other two. Second, pluripotent bile duct stem cells are malignantly transformed and these might account for cases that lack the pathology depicted above [5].

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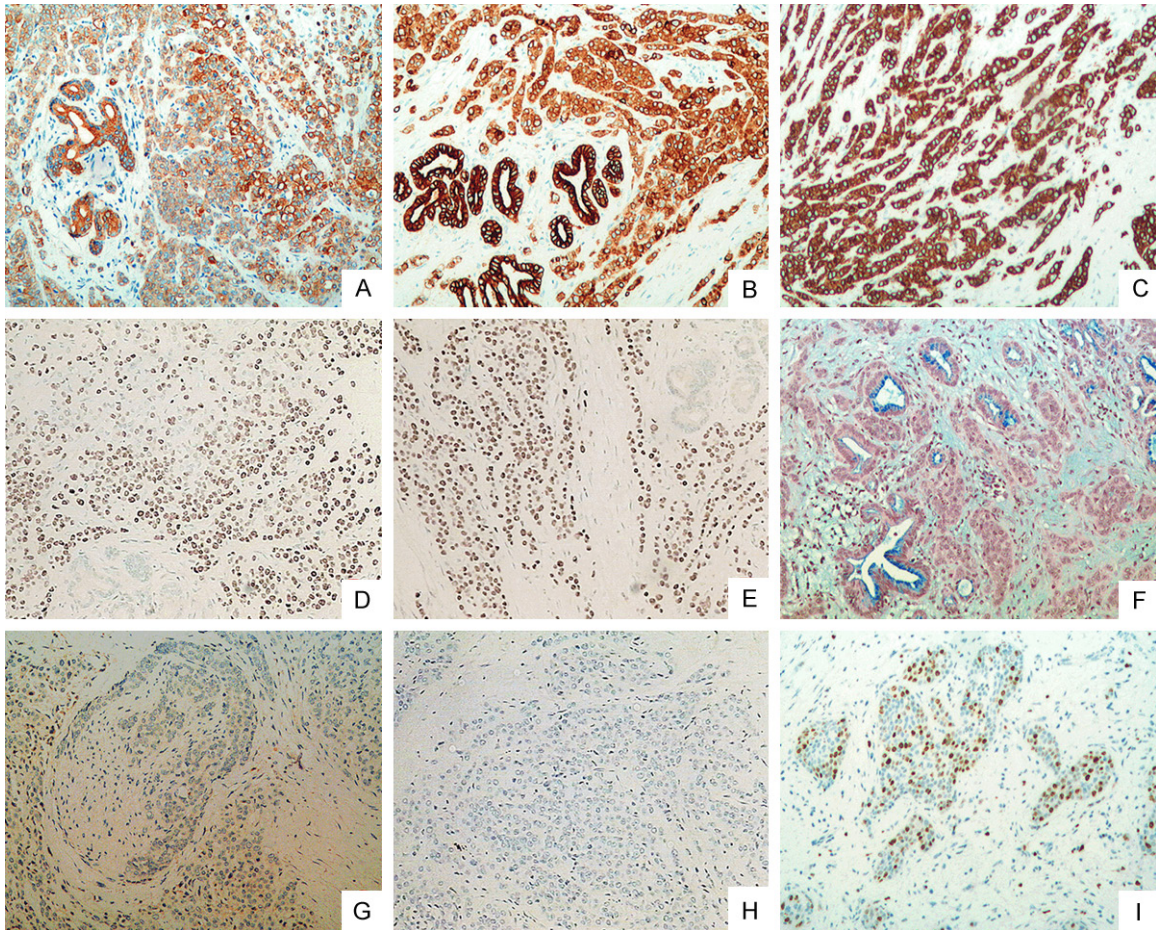


Figure 3. Immunohistochemical staining: A. AE1/AE3 (+), B. CAM5.2 (+), C. CK5/6 (+), D. p63 (+), E. p40 (+), F. AB-PAS (-), G. CGA (-), H. Syn (-), I. Ki67 (~30%).

Table 1. Summary of 3 Patients with Bile Duct Primary Squamous CC

	Patient 1*	Patient 2	Patient 3
Sex	Female	Male	Female
Age (years)	62	77	67
HbsAg	-	-	-
Cholelithiasis	-	+	+
AST/ALT (U/L)	103/93	228/193	10/15
TBIL/DBIL (μmol/L)	387.4/287.4	465.7/301.7	30.6/23.1
CA19-9 (U/ml)	466.58	285.90	61.07
Position	CHD	CHD and Cholecyst**	CHD
Operation	Choledocho-jejunostomy	Choledocho-jejunostomy	Pancreatico-duodenectomy
Chemotherapy	Yes	No	No
Radiotherapy	No	No	No
Prognosis	5 m, dead	32 m, dead	47 m, dead

HbsAg: hepatitis B surface antigen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TBIL: total bilirubin; DBIL: direct bilirubin; CA19-9: carbohydrate antigen 19-9. *Our patient; **Squamous cell carcinoma of CHD combined with adenocarcinoma of cholecysts.

Similar to other types of CC, jaundice is usually the first symptom noticed. Nonspecific symp-

oms include abdominal pain, dyspepsia, and fever and elevated liver function tests support

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these observations. Imaging with CT, MRI, and MRCP, or positron emission tomography (PET) can confirm tumor size, location, relationship to adjacent tissues, and potential lymphatic metastasis. Critical to diagnosis of squamous cell CC carcinoma is pathology. In our case, due to poorly differentiation, keratin pearls and/or intercellular bridges which typically manifests in squamous cell tumors were not observed. Because immunohistochemistry data were positive (AE1/AE3, CK5/6, p63, and p40) and these are negative with adenocarcinomas, primary squamous cell carcinoma was virtually a certain diagnosis. p40, which is a subtype p63 protein, is superior to p63 for diagnostic specificity for squamous cell carcinoma [6].

The best treatment for squamous cell CC carcinoma is surgical resection. A study including 225 hilar CC cases compared palliative treatment with surgical resection and patient survival. If the surgical margins were positive for malignant residue, patients did not benefit from resection [7]. Efficacy of adjuvant therapy such as chemotherapy and/or radiotherapy for biliary ductal adenocarcinoma is unclear but it is less effective than for squamous-cell carcinoma. Few reports of adjuvant methods have been depicted. Yamana's group [4] treated a patient with postoperative chemotherapy and saw no benefits. Our patient received one S-1 treatment and also did not benefit. We assumed squamous cell CCs would be sensitive to radiotherapy in a manner similar to lesions at other sites, but limited information suggests that this approach is controversial. Abbas and colleagues [8] reported that radiation delivered during intraoperative and postoperative periods reduced local tumor recurrence but Yoo's group [9] reported that squamous cell CC is resistant to radiation therapy.

Surgical treatment of CC is improving but prognosis is still unacceptable; patients live approximately only one additional year. Compared with bile duct adenocarcinomas, squamous cell CC is reported to be more aggressive with greater malignancy and earlier distant metastases. For 11 cases of CC, squamous and adenocarcinoma components were collected and contrasted with 82 cases of adenocarcinoma. Data show that mean survival for CC cases was significantly shorter than for adenocarcinomas [5].

Mean survival for all 3 cases diagnosed at our hospital was 28 months; but obviously, 3 patients are insufficient for statistical significance. In contrast, risk factors that influence prognosis are numerous, such as positive surgical margins and lymph node metastasis. Although in our samples, margins and lymph nodes were negative, perineural invasion may have contributed to poor prognosis.

Conclusion

Squamous cell CC is rare and relatively understudied. Radical surgery is the most effective treatment, but to measure efficacy of other approaches, more patients must be studied.

Disclosure of conflict of interest

None.

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