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Case reports of interest

Undifferentiated carcinoma of the common bile duct: case report and review of the literature

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Abstract A 78-year-old Japanese man with undifferentiated carcinoma of the common bile duct is presented. Upon gross examination, the common bile duct was found to be obstructed by a nodule measuring 10 × 10 mm. Microscopically, the nodule was ill-defined and composed of atypical spindle-shaped and pleomorphic tumor cells. The spindle-shaped cells proliferated in a whirled or interlacing pattern simulating a sarcoma, and the pleomorphic tumor cells had abundant eosinophilic cytoplasm and bizarre nuclei. Histochemically, a few tumor cells contained mucosubstances stained with the alcian blue (AB) method in their cytoplasm. Immunohistochemically, the tumor cells were diffusely positive for CAM5.2 and AE1/AE3. The histological diagnosis was undifferentiated carcinoma (spindle cell carcinoma) of the common bile duct. Other than our patient, only four other cases of undifferentiated carcinoma in the extrahepatic bile duct have been reported in the literature.

Key words Common bile duct · Polypoid growth · Undifferentiated carcinoma · Spindle cell carcinoma

Introduction

Most malignant neoplasms in the gallbladder and bile duct are adenocarcinomas, most frequently of the well-differentiated type. Undifferentiated carcinoma is one of the rarest malignant tumors arising not only in the biliary tract but also in other organs such as the upper respiratory tract,[1,2] alimentary tract,[3,4] skin,[5] breast,[6] and female genital tract.[7] In the biliary tract, undifferentiated carcinoma sometimes occurs in the gallbladder but rarely in the extrahepatic bile duct. Only four cases have been reported in the literature.[8–11] We report here another case of undifferentiated carcinoma of the common bile duct and demonstrate that this neoplasm exhibits a wide variety of immunohistochemical profiles.

Case report

A 78-year-old Japanese man was admitted to Kitakyushu City Wakamatsu Hospital complaining of severe general fatigue and a fever. Physical examination revealed jaundice, but otherwise the patient appeared normal. Laboratory tests revealed the following: alkaline phosphatase 211.4 KAU (normal 3–18 KAU); γ-glutamyltranspeptidase 873 U/ml (normal < 50 U/ml); total bilirubin 4.76 mg/dl; direct bilirubin 3.59 mg/dl; and serum glutamic oxaloacetic transaminase (SGOT) 67 U (normal 5–40 U). The patient also had diabetes mellitus.

Ultrasonography and computed tomography (CT) scanning of the abdomen showed dilated intra- and extrahepatic biliary ducts and a distended gallbladder, with no evidence of gallstones. Endoscopic retrograde cholangiopancreatography (ERCP) revealed a stricture in the distal common bile duct (CBD) and dilatation of the proximal bile ducts (Fig. 1).

The patient underwent laparotomy for the presumptive diagnosis of bile duct cancer. During laparotomy a nodular lesion was palpable at the distal CBD and was confined within the wall of the bile duct. A complete abdominal exploration demonstrated no other tumor-like lesions. No tumor metastasis could be identified in either the liver or the lymph nodes surrounding the bile duct. Therefore, pancreaticoduodenectomy was performed. The patient has been doing well for 15 months since the operation.

Materials and methods

Surgical specimens were cut into 5-mm stepwise tissue sections, fixed with 10% formalin, and embedded in

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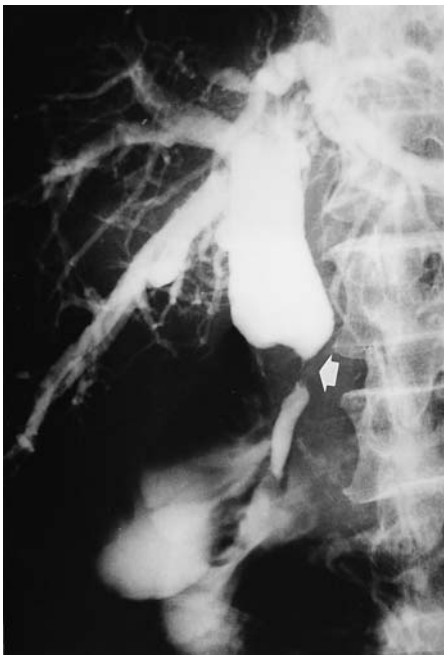

Fig. 1. Endoscopic retrograde cholangiopancreatography reveals a stricture of the common bile duct and dilatation of the proximal bile ducts

paraffin. Histologic sections (5 μm thick) were stained by the hematoxylin and eosin (H&E), alcian blue (AB), and periodic acid-Schiff (PAS) procedures.

Sections (5 μm thick) of the 10% formalin-fixed, paraffin-embedded materials were mounted on poly-L-lysine-coated slides and deparaffinized. Immunohistochemical examination was performed using the streptavidin-biotin method with the following antibodies: CAM 5.2 (monoclonal, 1:20; Becton Dickinson, Mountain View, CA, USA); anti-AE1/AE3 (monoclonal, 1:20; Boehringer, Mannheim, Germany); anti-cytokeratin 902 (monoclonal, 1:50; Enzo Diagnostics, New York, NY; USA), anti-cytokeratin 903 (monoclonal, 1:50; Enzo Diagnostics); anti-vimentin (monoclonal, 1:25; Dakopatts, Glostrup, Denmark); anti-S-100 protein (polyclonal, 1:400; Dakopatts); anti-HHF 35 (monoclonal, 1:20; Enzo Diagnostics); anti-smooth muscle α-actin (α-SMA) (monoclonal, 1:5000; Sigma, St. Louis, MO, USA); anti-myoglobin (polyclonal, 1:500; Dako, Glostrup, Denmark); anti-HAM 56 (monoclonal, 1:20, Enzo Diagnostics); anti-lysozyme (polyclonal, 1:500; Dako); anti-MAC 387 (monoclonal, 1:100; Dako); anti-macrophage CD68 (monoclonal, 1:300; Dako); anti-QB end/10 (monoclonal, 1:50; Novocastera, Newcastle, UK); anti-factor VIII RA (polyclonal, 1:1000; Dako); *Ulex europaeus* I (Vector Laboratories, Burlingame, CA, USA).

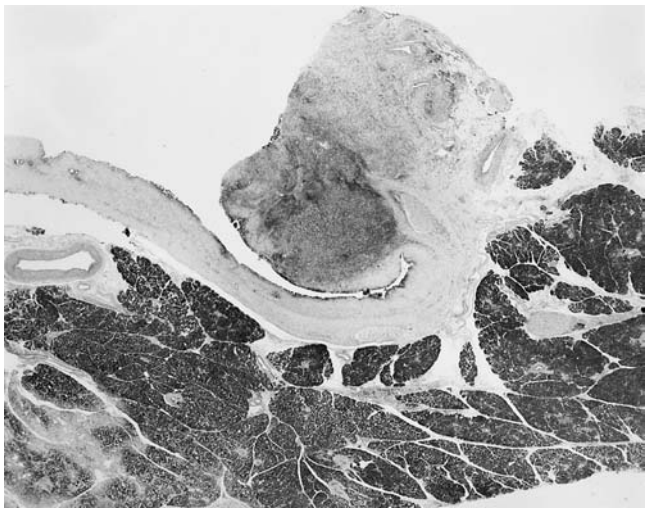

Fig. 2. Cross section of the tumor showing plypoid growth. (H&E, ×10)

Results

Upon gross examination, the common bile duct was found to be obstructed by a nodule measuring 10 × 10 mm, and the bile duct proximal to the lesion was dilated. The cut surface of the tumor showed polypoid growth (Fig. 2) and was homogeneously white without necrosis. Microscopically, the lesion was ill-defined and composed of atypical spindle-shaped and pleomorphic tumor cells (Fig. 3). The former cells proliferated in a whirled or interlacing pattern simulating a sarcoma, and the latter cells had relatively abundant eosinophilic cytoplasm and uncharacteristic nuclei. Numerous neutrophils were admixed with pleomorphic tumor cells. Uncharacteristic mitotic figures were also observed. Neither glandular structures formed by carcinoma cells nor squamoid differentiation was found. No osteoclast-like multinucleated giant cells were observed. In addition, no cartilaginous, osseous, or rhabdomyosarcomatous component was observed. Tumor cells were localized mainly within the bile duct wall. All of the regional lymph nodes examined were free of tumor cells.

Histochemically, a few tumor cells within the nodule contained cytoplasmic mucosubstances that stained with either the AB or PAS method. Immunohistochemically, the tumor cells showed diffusely positive staining for such anti-cytokeratin antibodies as CAM 5.2 (CK 8 and 18) and AE1/AE3 (Fig. 4). A few tumor cells were positive for vimentin. All other markers examined were negative. The histologic diagnosis was undifferentiated carcinoma (spindle cell carcinoma) of the common bile duct.

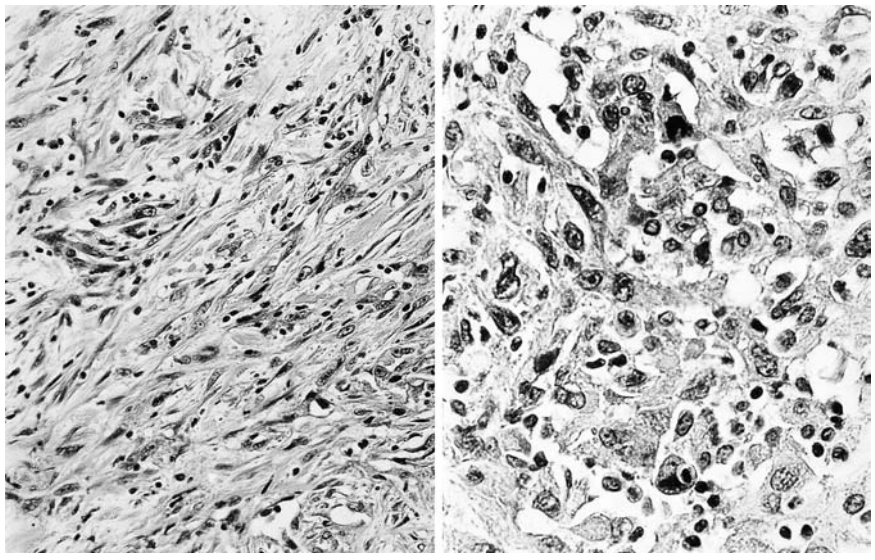

Fig. 3. Microscopic findings. **a** Spindle-shaped tumor cells proliferating in an interlacing pattern. (H&E, ×230) **b** Large polygonal or pleomorphic tumor cells with uncharacteristic nuclei can be seen in some areas admixed with inflammatory cells. (H&E, ×450)

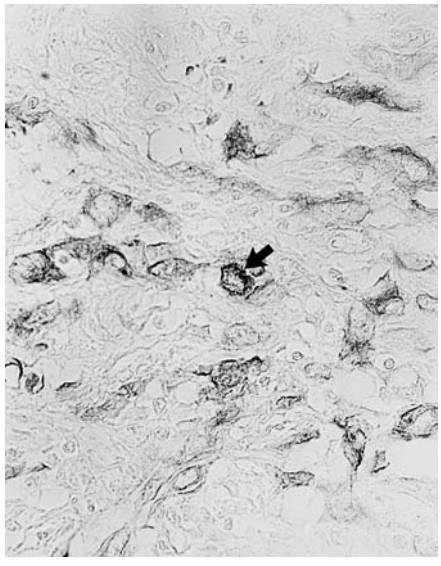

Fig. 4. Immunohistochemical analysis shows immunoreactivity for cytokeratin (AE1/AE3) (*arrow*) of the tumor cells. (×400)

Discussion

Undifferentiated carcinoma is a rare but well recognized neoplasm occurring in the upper respiratory tract,[1,2] alimentary tract,[3,4] skin,[5] breast,[6] and female genital tract.[7] Undifferentiated carcinomas also affect the biliary tract.[12–17] The reported incidence is 0.38% of all extrahepatic bile duct cancers.[18] According to the World Health Organization (WHO) classification of tumors of the gallbladder and extrahepatic bile ducts, undifferentiated carcinoma is defined as a malignant epithelial tumor that resembles a sarcoma and consists of varying proportions of spindle, polygonal, and giant cells.[19] This tumor has previously been reported under a wide variety of names, including pleomorphic spindle cell carcinoma,[20] carcinoma with spindle cell features,[17] pseudosarcoma,[9] and sarcomatoid carcinoma.[21] Spindle-shaped tumor cells usually predominate in undifferentiated carcinomas, as is seen in the present case. Therefore, it may be appropriate to use the term "spindle cell carcinoma" to represent these morphological features. Undifferentiated carcinomas are more common in the gallbladder than in the bile ducts. Moreover, in addition to our patient, only four cases of undifferentiated carcinoma in the extrahepatic ducts have been reported.[8–11] The four previously described patients consisted of two men and two women ranging in age from 52 to 82 years (mean 67.3 years). One of the four cases was complicated by a congenital choledochal cyst, and the other three patients presented with jaundice (Table 1).

The spindle cell carcinoma presented in this case exhibited polypoid growth. Diebold-Berger et al.[22] suggested that the proliferative activity (revealed by the mitotic index), which was significantly higher in the spindle cell component than in the glandular component, was probably responsible for the gross polypoid appearance of these tumors. Mitotic figures were observed in the present case, and the high proliferative activity may be related to polypoid growth. Moreover, polypoid growth induces obstructive jaundice even in the presence of small tumors.

Undifferentiated carcinoma displays either a biphasic (epithelial and sarcomatous) or monophasic (sarcomatous) proliferative pattern. Considerable controversy remains regarding the histogenesis of the spindle cell component. Three theories have been postulated to account for its histogenesis: (1) mesenchymal reaction; (2)

Table 1. Reported cases of undifferentiated carcinoma of the extrahepatic bile duct

Case no.	Reference	Year	Age (years)	Sex	Symptom	Size (cm)	Outcome
1	8	1990	73	F	Jaundice	?	?
2	9	1994	82	M	Jaundice, loss of appetite	?	Died
3[a]	10	1994	52	F	Abdominal pain, abdominal fullness	4.0 × 2.5	Well at 15 months
4	11	1995	62	M	Jaundice, abdominal pain	3.5 × 2.0	Died 10 days later from surgical complications
5	Present case	2001	78	M	Jaundice, fever	1.0 × 1.0	Well at 15 months

[a] Complicated with a choledochal cyst

true sarcoma; (3) malignant proliferation of epithelial origin. Guo et al.[12] reported that the epithelial nature of the spindle cell component had been described based on histochemical and immunohistochemical studies, and malignant behavior was thus thought to be due to both invasive and metastatic features. Other reports[3,15] have supported the third theory based on immunohistochemical and ultrastructural studies. The strong immunohistochemical staining of cytokeratin and the existence of mucosubstances in tumor cells suggest an epithelial origin of this tumor. Conversely, spindle cell carcinomas sometimes contain immunoreactive products of vimentin. In our case, vimentin-positive spindle cells were observed. The expression of vimentin alone does not rule out that a tumor is of epithelial origin because vimentin has been found to be expressed in carcinomas when the carcinoma demonstrated dedifferentiation or sarcomatous changes.[23] Malignant neoplasms with vimentin-positive tumor cells are not always sarcomas. Microscopically, epithelial elements such as glandular or squamous features were absent, and only sarcomatous elements, comprising spindle or pleomorphic cells, were observed in our case. Tumor cells generally demonstrate immunoreactivity for cytokeratins such as CAM 5.2 and AE1/AE3. Moreover, only a few malignant cells express mucin. The sarcomatous elements are therefore thought to be derived from epithelial cells rather than mesenchymal cells. Despite the lack of any glandular or tubular structures in our case, the neoplasm was consistent with a malignant epithelial tumor originating in the extrahepatic bile duct. To the best of our knowledge, there have been no previous reports concerning spindle cell carcinomas displaying a monophasic proliferative pattern and spindle cell features in the bile duct.

The prognosis of patients with spindle cell-type undifferentiated carcinoma of the gallbladder and the intrahepatic bile ducts has been reported to be poor.[12,16] The outcome of the patients with this tumor originating in the CBD cannot be estimated because of the limited number of reported cases. Only one of the four previous reports included follow-up studies. In our case, a favorable prognosis is expected because of the small size of the tumor, the lack of any nodal involvement, and the lack of any venous or lymphatic permeation.

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References

1. Matsui K, Kitagawa M, Miwa A (1992) Lung carcinoma with spindle cell components: sixteen cases examined by immunohistochemistry. Hum Pathol 23:1289–1297
2. Suster S, Huszar M, Herczeg E (1987) Spindle cell squamous cell carcinoma of the lung: immunocytochemical and ultrastructural study of a case. Histopathology 11:871–878
3. Zarbo RJ, Crissman JD, Venkat H, Wiss MA (1986) Spindle-cell carcinoma of the upper aerodigestive tract mucosa: an immunohistologic and ultrastructural study of 18 biphasic tumours and comparison with seven monophasic spindle cell tumours. Am J Surg Pathol 10:741–753
4. Orsatti G, Corvalan AH, Sakurai H, Choi HS (1993) Polypoid adenosquamous carcinoma of the esophagus with prominent spindle cells. Arch Pathol Lab Med 117:544–547
5. Evans HL, Smith JL (1980) Spindle cell squamous carcinoma and sarcoma-like tumors of the skin: a comparative study of 38 cases. Cancer 45:2687–2697
6. Gersell DJ, Katzenstein ALA (1981) Spindle cell carcinoma of the breast. Hum Pathol 12:550–561
7. Steeper TA, Piscioli F, Rosai J (1983) Squamous cell carcinoma with sarcoma-like stroma of the female genital tract: clinicopathological study of four cases. Cancer 52:890–898.
8. Sumikawa M, Ogawa H, Kaibara H, Adachi H (1990) A case of pseudosarcoma of the bile duct (in Japanese). Geka 52:177–179
9. Kagami A, Nikaidou T, Miyairi M, Usui T, Kawashima O, Mochizuki S, Sakuyama T, Suzuki M (1994) An autopsy case of pseudosarcoma of the common bile duct. J Gastroenterol 29:525–530
10. Nonomura A, Mizukami Y, Matsubara F, Ueda T (1994) A case of choledochal cyst associated with adenocarcinoma exhibiting sarcomatous features. J Gastroenterol 29:669–675
11. Yuan C, Lo H, Tseng CH, Takasaki T, Hanyu F (1995) A case of spindle cell sarcomatous change of hepatic ducts manifesting as obstructive jaundice. J Gastroenterol 30:264–267
12. Guo KJ, Yamaguchi K, Enjoji M (1988) Undifferentiated carcinoma of the gallbladder: a clinicopathologic, histochemical, and immunohistochemical study of 21 patients with a poor prognosis. Cancer 61:1872–1879

13. Matsunaga H, Nagai E, Hirota I, Ono H, Fujimura T, Tsuneyoshi M (1994) A case of a growing giant undifferentiated carcinoma of the gallbladder with eosinophilia (in Japanese). Rinsyogeka 49:651–654
14. Ng CS, Suen MWM, Mok SD, Li AKC (1988) Spindle cell carcinoma of bile duct origin. Histopathology 12:329–340
15. Sasaki M, Nakanuma Y, Nagai Y, Nonomura A (1991) Intrahepatic cholangiocarcinoma with sarcomatous transformation: an autopsy case. J Clin Gastroenterol 13:220–225
16. Nakajima T, Tajima Y, Sugano I, Nagao K, Kondo Y, Wada K (1993) Intrahepatic cholangiocarcinoma with sarcomatous change: clinicopathologic and immunohistochemical evaluation of seven cases. Cancer 72:1872–1877
17. Suster S, Huszar M, Herczeg E, Bubis JJ (1987) Adenosquamous carcinoma of the gallbladder with spindle cell features: a light microscopic and immunocytochemical study of a case. Histopathology 11:209–214
18. Albores-Saavedra J, Henson DE, Klimstra DS (1998) Tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater. In: Atlas of tumor pathology, third series, fascicle 27. Armed Forces Institutes of Pathology, Washington, DC
19. Albores-Saavedra J, Henson DE, Sobin LH (1991) Histological typing of tumors of the gallbladder and extrahepatic bile ducts. Springer, Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona
20. Appelman HD, Coopersmith N (1970) Pleomorphic spindle cell carcinoma of the gallbladder: relation to sarcoma of the gallbladder. Cancer 25:535–541
21. Lezzoni JC, Mills SE (1993) Sarcomatoid carcinoma (carcinosarcoma) of the gastrointestinal tract: a review. Semin Diagn Pathol 10:176–183
22. Diebold-Berger S, Vaiton J-C, Pache J-C, d'Amore ESG (1995) Undifferentiated carcinoma of the gallbladder: report of a case with immunohistochemical findings. Arch Pathol Lab Med 119: 279–282
23. Ueyama T, Nagai E, Yao T, Tsuneyoshi M (1993) Vimentin-positive gastric carcinoma with rhabdoid features: a clinicopathologic and immunohistochemical study. Am J Surg Pathol 17: 813–819