

A Case of Biliary Cystadenocarcinoma of the Liver

Toshimasa ASAHARA¹⁾, Toshiyuki ITAMOTO¹⁾, Koji KATAYAMA¹⁾, Hideki NAKAHARA¹⁾, Yuzo OKAMOTO¹⁾, Hiroshi HINO¹⁾, Eiji ONO¹⁾, Kiyohiko DOHI¹⁾ and Fumio SHIMAMOTO²⁾

1) Department of Surgery II, Hiroshima University School of Medicine

2) Department of Pathology, Hiroshima University Hospital

ABSTRACT

We describe a case of biliary cystadenocarcinoma of the liver, a very rare malignant tumor, in a 40-year-old man referred to our hospital because of sporadic abdominal pain. A left lobectomy of the liver was performed, and macroscopic examination of the resected specimen revealed prominent papillary projections in a multiloculated cystic tumor containing mucinous material. Histologic examination of the specimen showed a biliary cystadenocarcinoma without mesenchymal stroma, associated with a cystadenoma. Cystadenoma with mesenchymal stroma (CMS), which occurs exclusively in women, is generally regarded as a precancerous lesion, and patients with biliary cystadenocarcinoma with mesenchymal stroma have a good prognosis. Cystadenoma without mesenchymal stroma arises in both men and women. However, the origin and precancerous lesions of cystadenocarcinoma are unknown. Moreover, the prognosis of patients with biliary cystadenocarcinoma without mesenchymal stroma is poor, especially in men. The cystadenoma without mesenchymal stroma in our patient was considered a precancerous lesion. The present patient has shown no evidence of recurrence in the 8 years after hepatic resection. Previously reported cases of cystadenocarcinoma without mesenchymal stroma, especially those in men, have had a poor outcome. A good outcome in men is very rare.

Key words: *Cystadenocarcinoma, Liver, Hepatic resection*

Although cystic lesions of the liver are not uncommon, biliary cystadenocarcinoma is an extremely rare form of primary liver cancer that may arise from pre-existing cystadenomas. About 50 cases have been reported in the English literature^{1,2,5,8,11-13,18)}. Geist⁶⁾ reported that the cystadenomas accounted for only 4.6% of all intrahepatic cysts of bile-duct origin. The prevalence of cystadenoma of the liver estimated mainly on the diagnosis of liver cysts by ultrasonography (US) and computed tomography (CT), appears to be 1,000 times less than that of simple cysts of the liver³⁾. Most cystadenomas of the liver are associated with mesenchymal stroma, and cystadenoma with mesenchymal stroma (CMS), regarded as a precancerous lesion, occurs exclusively in women^{5,8)}. Similarly, cystadenocarcinoma with mesenchymal stroma, which has a good prognosis if resected completely, arises exclusively in women^{5,8)}. In contrast, patients who have cystadenocarcinoma without mesenchymal stroma have a poorer outcome and are more likely to die because of their tumors⁵⁾.

We describe our experience with a man who had biliary cystadenocarcinoma without mesenchymal stroma of the liver. The tumor was associated with

cystadenoma without mesenchymal stroma, suggesting that the cystadenocarcinoma might have arisen from the cystadenoma.

CASE REPORT

A 40-year-old man who had had sporadic episodes of mild pain in the upper abdomen during the 2 years before presentation was referred by his physician to the Department of Surgery II, Hiroshima University Hospital, Hiroshima, Japan in October 1990 because of a mass in the liver, detected on US and CT. The patient had undergone an appendectomy in 1970, but had no history of receiving a transfusion. On physical examination, neither the liver nor any abdominal mass could be palpated. On admission, liver function tests and serum levels of alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9 were within normal limits. US revealed dilatation of the left hepatic duct and left lateral posterior segmental duct. An echogenic tumor about 4 cm in diameter projected into the latter duct (Fig. 1). Magnetic resonance imaging (MRI) showed that the tumor was located in the periphery of the left lateral segment and was associated with cystic dilatation of the intrahepatic bile duct

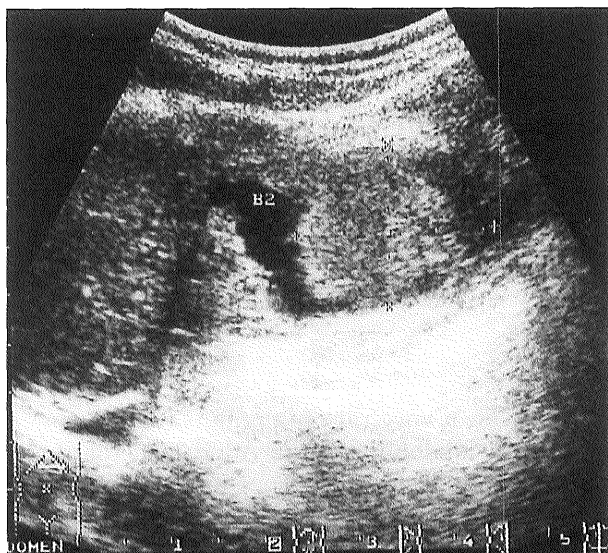


Fig. 1. Ultrasonogram: The left hepatic duct and left lateral posterior segmental duct are dilated, and an echogenic tumor about 4 cm in diameter seems to project into the latter duct.

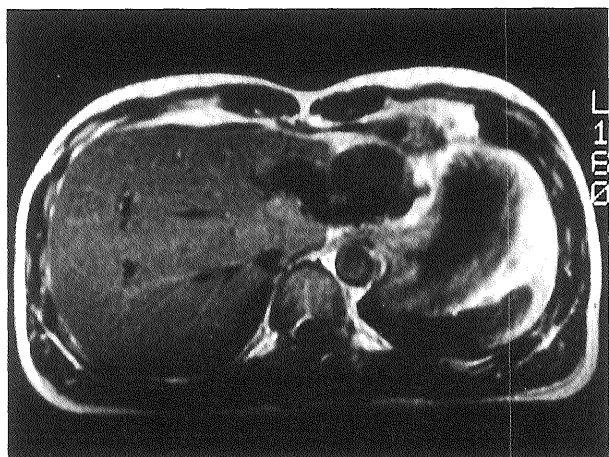


Fig. 2. Magnetic resonance imaging: A tumor can be seen in the periphery of the left lateral segment with cystic dilatation of the intrahepatic bile duct.

(Fig. 2). Hepatic resection was indicated based on these findings. The clinical diagnosis was cystadenoma, cystadenocarcinoma in the left lobe of the liver, or cholangiocellular carcinoma arising in the dilated intrahepatic bile duct. A left lobectomy of the liver with T-tube bile drainage of the common bile duct was carried out on November 20, 1990. There was no evidence of spread to the liver parenchyma or surrounding organs. The resected specimen weighed 230 grams and included a white, soft mucin-producing tumor measuring 5.5 cm in diameter. The tumor was located in the periphery of the left lateral posterior segment. On macroscopic examination of the cut surface of the tumor, prominent papillary projections were seen in a multiloculated cystic tumor. The tumor communicated with the dilated left lateral posterior segmental duct, which contained mucinous mater-



Fig. 3. The multilocular tumor is lined by a complex papillary structure associated with various degrees of atypia and mitotic activity. The underlying layer of connective tissue is not cellular and does not show "mesenchymal stroma".



Fig. 4. In the tumor, areas of mucinous cystadenoma coexist. The lesion is lined by tall columnar cells with basal nuclei and abundant mucin-containing cytoplasm. A papillary configuration without "mesenchymal stroma" can be seen.

ial. Histologically, the lining of the multilocular tumor had a complex papillary architecture, associated with various degrees of atypia and mitotic activity. Stromal infiltration was regionally present. The underlying connective tissue was not cellular and did not show "mesenchymal stroma" (Fig. 3). This mucinous cystadenocarcinoma coexisted with areas of mucinous cystadenoma. The lesions were lined by tall columnar cells with basal nuclei and abundant mucin-containing cytoplasm and showed a papillary configuration without "mesenchymal stroma" (Fig. 4). The histologic diagnosis was a biliary cystadenocarcinoma without mesenchymal stroma, associated with a cystadenoma.

No adjuvant chemotherapy was given to the patient after the curative hepatic resection. The patient remains well and has had no signs of recurrence in the 8 years after operation.

DISCUSSION

Biliary cystadenocarcinoma of the liver is

extremely rare. The term 'cystadenocarcinoma' is sometimes misused to include both carcinomas occurring in a simple cyst of the liver and bile duct carcinomas with intrahepatic bile duct dilatation¹²⁾. Mizumoto et al¹²⁾ reported on 65 Japanese patients with cystic malignant tumors of the liver. Only two of these patients had 'cystadenocarcinoma with cystadenoma'.

Symptoms of biliary cystadenomas or cystadenocarcinomas of the liver are usually nonspecific and may include abdominal discomfort, dull pain in the upper abdomen, nausea, and anorexia^{3,5,8)}. A large hepatic mass is frequently palpated³⁾. However, reports of asymptomatic disease are increasing because of recent advances in diagnostic technology^{1,11)}. The results of liver function tests are usually normal, such as in our patient. He had mild, sporadic upper abdominal pain of 2 years' duration.

US, CT, and MRI are useful in the diagnosis of cystadenoma or cystadenocarcinoma. Imaging studies often provide evidence of a single, multilocular low-density cystic mass with internal septations or papillary projections along the cystic wall; septa are sometimes demonstrated. US reveals an anechoic cystic mass with internal echoes representing papillary infoldings or echogenic septations. However, differentiation between cystadenoma and cystadenocarcinoma may be difficult on the basis of radiological findings¹¹⁾, and microscopic examination is often required^{7,8)}. In our patient, the US findings, which were not typical of biliary cystadenoma or cystadenocarcinoma, partially resembled those of intrahepatic bile duct cancer with segmental dilatation of the bile duct. MRI revealed findings similar to those obtained by US. However, macroscopic examination of the cut surface of the resected tumor disclosed a cystic appearance with many papillary projections. Moreover, the cystic tumor communicated with the intrahepatic bile duct.

Etiologically, cystadenocarcinomas of the liver are considered to arise by malignant transformation of preexisting cystadenomas^{2,3,18,19)}, whereas the pathogenesis of cystadenoma is poorly understood. Wheeler and Edmondson¹⁸⁾ proposed that "cystadenoma with mesenchymal stroma" occurs exclusively in women and shows two essential tumor components: (1) a cyst lining of columnar to cuboidal, mucin-secreting epithelium; and (2) a moderately to densely cellular stroma consisting of spindle (rarely oval) cells. Moreover, 4 of 17 cases of CMS showed malignant changes characteristic of cystadenocarcinoma. Akwari et al²⁾ reviewed 44 patients with CMS including 2 of their own patients and reported that all were women with a mean age of 41 years; an additional 7 women with a mean age of 57 years had evidence of malignant transformation with mesenchymal stroma in the cyst wall. They concluded that CMS occurs exclu-

sively in young women and has the potential for malignant transformation. Moreover, they hypothesized that CMS could develop from nests of primitive embryonal cells. Cystadenomas without mesenchymal stroma have been produced experimentally by exposure to aflatoxin⁴⁾ or by induction of hepatic ischemia¹⁴⁾. Such tumors are apparently derived from ductal epithelium. Clinically, cystadenoma without mesenchymal stroma occurs in both men and women. Although it is uncertain whether biliary cystadenocarcinoma without mesenchymal stroma occurs because of the malignant transformation of cystadenoma without mesenchymal stroma, the former is speculated to arise from malignant neoplastic outgrowths of the biliary or cholangiolar duct²⁾. However, microscopic examination of the present case revealed that the cystadenocarcinoma had no mesenchymal stroma, despite its close proximity to the cystadenoma without mesenchymal stroma. These findings suggest that cystadenomas without mesenchymal stroma can give rise to cystadenocarcinomas without mesenchymal stroma.

Patients with biliary cystadenocarcinoma of the liver generally have a better prognosis than those with hepatocellular carcinoma or cholangiocellular carcinoma^{17,19)}. Unsuccessful or incomplete treatment of biliary cystadenocarcinoma, using techniques such as cyst drainage^{8,9)}, marsupialization^{2,8,18)}, and partial resection^{2,11,18)}, have been described. Such treatment has resulted in a poor long-term outcome. Complete resection of biliary cystadenocarcinoma is thus the treatment of choice in patients who have an adequate hepatic functional reserve^{2,15,16,18,19)}. Nakajima et al¹³⁾ classified biliary cystadenocarcinoma into two subtypes, "non-invasive type" and "invasive type," based on clinicopathologic features. Patients with "non-invasive" type disease had cystic neoplasms surrounded by a thick fibrous wall lined with adenocarcinoma cells. These patients had a good outcome after complete resection of their tumors. Patients with "invasive type" disease had carcinomas that extended to adjacent organs or the surrounding liver tissue. Most of these patients, whose carcinomas showed focal anaplastic changes, had a poor outcome, irrespective of whether they had received radical hepatic resection or anticancer chemotherapy. Our patient apparently had "noninvasive" type disease because his tumor was not invasive and has not recurred. Devaney et al⁵⁾ reported that although all 5 patients who had cystadenocarcinoma with mesenchymal stroma were women and survived for 4 to 8 years, 7 of 9 patients who had cystadenocarcinoma without mesenchymal stroma were men and 6 of these men died of their tumors 3 months to 4 years after treatment. Moreover, 6 of 8 Japanese men with cystadenocarcinoma who were described in the literature died of their tumors irrespective of the outcome of complete

resection, although it is unclear whether their lesions were associated with mesenchymal stroma^{10,11,13}. Given these results, our patient, who survived for 8 years after complete resection, is extremely rare among male patients with biliary cystadenocarcinoma. Although the difference in outcome between men and women may be related to the presence or absence of mesenchymal stroma, further studies of this rare neoplasm are required before firm conclusions can be drawn.

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REFERENCE

1. **Adachi, S., Doy, M., Tsunoda-Shimazu, H. and Ozaki, A.** 1996. A small mucinous cystadenocarcinoma of the liver detected by a fluid-fluid level on ultrasonography. *Surg. Today* **26**: 439–441.
2. **Akwari, O.E., Tucker, A., Seigler, H.F. and Itani, K.M.F.** 1990. Hepatobiliary cystadenoma with mesenchymal stroma. *Ann. Surg.* **211**: 18–27.
3. **Benhamou, J.P. and Menu, Y.** 1994. Non-parasitic cystic diseases of the liver and intrahepatic biliary tree. In L.H. Blumgart (ed.), *Surgery of the liver and biliary tract*. Edinburgh: Churchill Livingstone 1200–1201.
4. **Cruickshank, A.H. and Sparshott, S.M.** 1971. Malignancy in natural and experimental hepatic cysts; experiments with aflatoxin in rats and the malignant transformation of cysts in human livers. *J. Pathol.* **104**: 185–190.
5. **Devaney, K., Goodman, Z.D. and Ishak, K.G.** 1994. Hepatobiliary cystadenoma and cystadenocarcinoma; A light microscopic and immunohistochemical study of 70 patients. *Am. J. Surg. Pathol.* **18**: 1078–1091.
6. **Geist, D.C.** 1955. Solitary nonparasitic cyst of the liver. *Arch. Surg.* **71**: 867–880.
7. **Iemoto, Y., Kondo, Y. and Fukamachi, S.** 1981. Biliary cystadenocarcinoma with peritoneal carcinomatosis. *Cancer* **48**: 1664–1667.
8. **Ishak, K.G., Willis, G.W., Cummins, S.D. and Bullock, A.A.** 1977. Biliary cystadenoma and cystadenocarcinoma; Report of 14 cases and review of the literature. *Cancer* **38**: 322–338.
9. **Kanamori, H., Kawahara, H., Oh, S., Mine, T., Osawa, H., Murakami, T. and Ogata, E.** 1985. A case of biliary cystadenocarcinoma with recurrent jaundice; Diagnostic evaluation of computed tomography. *Cancer* **55**: 2722–2724.
10. **Kawarada, Y., Taoka, H. and Mizumoto, R.** 1991. A report of 5 cases of cystic bile duct carcinoma of the liver and proposal of a new classification. *Gastroenterol. Japon.* **26**: 80–89.
11. **Kosuge, T., Andersson, R., Yamazaki, S., Makuuchi, T., Takayama, T., Mukai, K. and Hasegawa, H.** 1992. Surgical management of biliary cystadenocarcinoma. *Hepatogastroenterol.* **39**: 417–419.
12. **Mizumoto, R., Kawarada, Y. and Taoka, H.** 1991. A new classification of cystic malignant tumors of the liver; Classification of 65 cases reported at the 26th Annual Meeting of the Liver Cancer Society. *J. Gastroenterol. Hepatol.* **6**: 400–407.
13. **Nakajima, T., Sugano, I., Matsuzaki, O., Nagao, K., Kondo, Y., Miyazaki, M. and Wada, K.** 1992. Biliary cystadenocarcinoma of the liver; A clinicopathologic and histochemical evaluation of nine cases. *Cancer* **69**: 2426–2432.
14. **Popovsky, M.A., Costa, J.C. and Doppman, J.L.** 1979. Meyenburg complexes of the liver and bile cysts as a consequence of hepatic ischemia. *Hum. Pathol.* **10**: 425–432.
15. **Shimada, M., Kajiyama, K., Saitoh, A. and Kano, T.** 1996. Cystic neoplasms of the liver: A report of two cases with special reference to cystadenocarcinoma. *Hepatogastroenterol.* **43**: 249–254.
16. **Tsiftsis, D., Christodoulakis, M., Bree, E. and Sanidas, E.** 1997. Primary intrahepatic biliary cystadenomatous tumors. *J. Surg. Oncol.* **64**: 341–346.
17. **Wang, Y.J., Lee, S.D., Lai, K.H., Wang, S.S. and Lo, K.J.** 1993. Primary biliary cystic tumors of the liver. *Am. J. Gastroenterol.* **88**: 599–603.
18. **Wheeler, D.A. and Edmondson, H.A.** 1985. Cystadenoma with mesenchymal stroma (CMS) in the liver and bile ducts; A clinicopathologic study of 17 cases, 4 with malignant change. *Cancer* **56**: 1434–1445.
19. **Woods, G.L.** 1981. Biliary cystadenocarcinoma: case report of hepatic malignancy originating in benign cystadenoma. *Cancer* **47**: 2936–2940.