Primary Mucoepidermoid Carcinoma of the Intrahepatic Bile Duct : A Case Report with Review of Literature

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Abstract

A 64-year-old Thai man had a primary mucoepidermoid carcinoma, a variant of the cholangiocarcinoma, of the left lobe of the liver. A 5 x 4 x 3 cm tumor metastasized within the liver and to the porta hepatic and parapancreatic lymph nodes with compression of the head of pancreas and distal part of the common bile duct resulting in obstructive janudice. The patient died within 7 months from massive hemorrhage of a chronic peptic ulcer of the duodenum. Review of the medical literature in the English language disclosed 11 primary mucoepidermoid carcinomas of the bile ducts, including the present instance. Nine tumors were intrahepatic; three were in the right lobe and six in the left lobe. Two neoplasms were extrahepatic; they arose in the common hepatic ducts. There were 6 men and 5 women of 44 to 78 years old; the mean age was 60 years. The size of the tumor ranged from 1.5 to 18 cm in greatest dimension; the average size was 8.4 cm. The tumor metastasized frequently to the regional lymph nodes. Invasion of the portal vein and hepatic artery has also occurred. Ten patients having primary mucoepidermoid carcinoma of the bile duct died within 11 months regardless of treatments. Only one patient was well, 10 months after extensive resection of a 1.5 cm tumor of the common hepatic duct. It is concluded that the prognosis is generally poor for the patient having primary mucoepidermoid carcinoma of the bile duct.

Key word : Liver Tumor, Bile Duct Cancer, Mucoepidermoid Carcinoma, Jaundice

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Primary mucoepidermoid carcinomas have been reported to occur in the major and minor salivary glands, buccal mucosa, esophagus, anal canal, skin breast, lacrimal sac, thymus, thyroid gland, tracheobroncheal tree, lung, uterine cervix, and bile ducts[1-22]. The prevalence of the mucoepidermoid carcinomas, however, is highest in the salivary glands[1-3]. Sites of occurrence other than

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the latter are uncommon. We describe herewith a primary mucoepidermoid carcinoma arising in the left lobe of the liver. A review of the medical literature in the English language is made concerning the primary mucoepidermoid carcinoma of the bile ducts[16-22].

Patient

During 7 months before death, a 64-year-old man, a native of Srisakes province, had intermittent jaundice which disappeared spontaneously without any specific treatment. Two months prior to death, he was investigated in a hospital because of abdominal distention in addition to recurrence of jaundice, and it was found that the jaundice was obstructive in type. One month before death, he developed abdominal pain and fever.

Body temperature was 38°C, pulse rate 100 beats/min, respiratory rate 24/min, and blood pressure 90/60 mm Hg. Abnormal physical findings were severe jaundice, distended and painful abdomen, hepatomegaly, and emaciation.

The following laboratory values were noted: hemoglobin 10-11 g/100 mm^3, 16,300-21,300 leukocytes/mm^3 with 81-83 per cent of granulocytes, and 17-19 per cent of lymphocytes, 150,000-201,000 thrombocytes/mm^3, plasma glucose 111-114 mg/100 ml, BUN 29-60 mg/100 ml, creatinine 1.3-3.8 mg/100 ml, albumin 2 g/100 ml, globulin 4.5 g/100 ml, total bilirubin 22.4 g/100 ml, direct bilirubin 14.3 mg/100 ml, SGOT 146 IU/L, SGPT 43 IU/L, alkaline phosphates 406 IU/L, and prothrombin time 42 seconds (control 31 seconds).

The patient's clinical course was downhill in spite of receiving antibiotics, albumin infusions, and diuretics. He died 7 days after hospitalization. The clinical impression was cholangiocarcinoma.

Pathologic examination

A 1,700 g liver contained a firm and irregular mass, 5 x 4 x 3 cm, in the left lobe. The lump had slimy and gray cut surfaces. Multiple satellite nodules, 0.5 to 1.0 cm across were scattered in the icteric hepatic substance. The porta hepatic and peripancreatic lymph nodes were enlarged, 1 to 1.5 cm across. Some of them compressed upon the head of the pancreas and the distal part of the common bile duct. The proximal portion of the common bile duct above the site of compression was moderately dilated. There was no tumor in the pancreatic substance. About 3,000 ml of yellow serous ascitic fluid filled the peritoneal cavity.

Microscopically, the hepatic main mass was composed of both malignant squamous cells and mucin-producing cells. They were supported by fibrous stroma. The squamous cells were often arranged in sheets. They showed occasional intercellular bridges, pale acidophilic and homogeneous perikaryon, and pleomorphic vesicular nuclei with distinct nucleoli in hematoxylin and eosin (H & E) stain (Fig. 1). They were nonreactive in Mayer's mucicarmine stain. A few keratin pearles were observed.

The mucin-producing tumor cells were less numerous than the squamous neoplastic cells (Fig. 1). They often demonstrated vacuolar cytoplasm which was positive in Mayer's mucicarnine stain. Incompletely formed glands with mucin production were also encountered. Mingling of mucin-producing cells and squamous cells was infrequently noted (Fig. 2). The tumor cells exhibited strong positivity to cytokeratin in immunohistochemical study.

The intrahepatic satellite nodules showed the same microscopic features as in the intrahepatic main mass. Metastatic carcinoma was detected in lymph nodes from the porta hepatic and peripancreatic regions.

The rest of the liver showed portal and periductal fibroses and many inflammatory infiltrates especially mononuclear cells, indicating chronic nonspecific cholangitis. There was severe cholestasis of the liver. Parasitic infestation such as opisthorchiasis was not observed.

Additionally, the duodenal mucosa demonstrated a 2 cm hemorrhagic peptic ulcer which penetrated into the head of the pancreas (Fig. 3). About 1,000 ml of altered blood filled the lumen of the small bowel. The kidneys showed numerous bile casts and acute tubular necrosis.

The pathologic diagnoses, then, were moderately differentiated mucoepidermoid carcinoma of the bile duct of the hepatic left lobe with intrahepatic dissemination and extrahepatic metastasis to porta hepatic and peripancreatic lymph nodes, and chronic peptic ulcer of duodenum with massive bleeding. The latter finding was considered as the patient's immediate cause of death.

DISCUSSION

Primary mucoepidermoid carcinoma of the liver has been defined as a variant of cholangiocarcinoma containing malignant squamous cells and

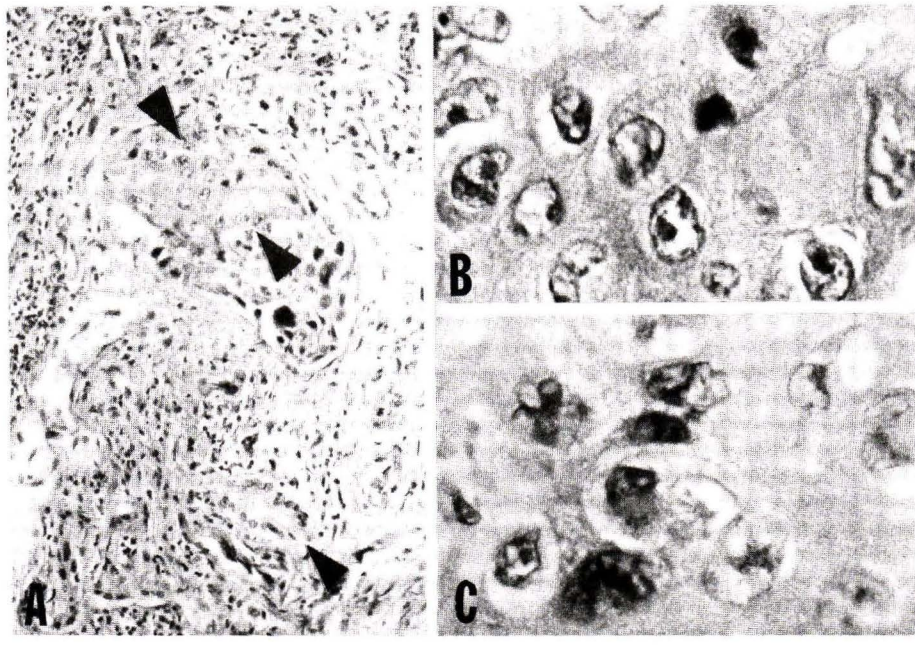

Fig. 1. Mucoepidermoid carcinoma of bile duct.
A. Squamous tumor cells and mucus-producing neoplastic cells are demonstrated. The area between the upper and middle arrowheads is further shown in B. The lower arrowhead points toward a gland formed by mucus-secreting tumor cells. H & E, x 100.
B. Nest of squamous neoplastic cells showing intercellular bridges and vesicular muclei with distinct nucleoli. H & E x 400.
C. Tumor cells exhibiting cytoplasmic vacuoles and bizarre nuclei. H & E, x 400.

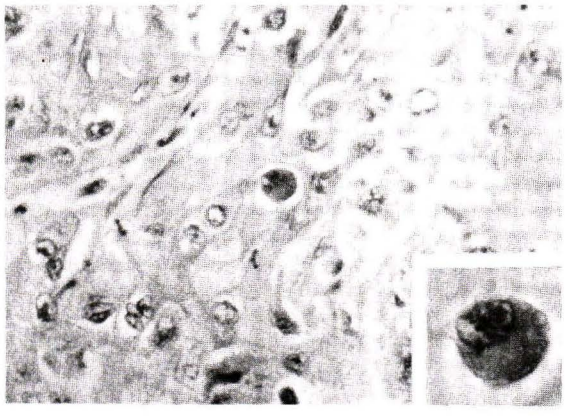

Fig. 2. Mucoepidermoid carcinoma of bile duct showing a mucus-secreting tumor cell among squamous neoplastic cells. Mayer's mucicarmine stain, x 400. Inset demonstrates the globular mucus-secreting cell having bizarre nucleus and cytoplasmic globules of mucin. Mayer's mucicarmine, x 1,000.

Fig. 3. Chronic peptic ulcer of duodenal mucosa with recent hemorrhage is shown. The arrowhead points toward the site of penetration of the ulcer into the head of the pancreas. The latter is underneath the arrowhead. The scale is 1 cm in length.

Table 1. Summary of 11 reported cases of mucoepidermoid carcinoma of bile duct.

Authors (Year)	Pt's age (yrs) & sex	Clinical presentation	Site of tumor	Size of tumor (cm)	Extent of tumor	Treatment	Outcome
1. Pianzola et al (1971)[16]	44 M	Fever, vomiting, R hypochondralgia, weight loss & hepatomegaly	R intrahepatic	15 x 10 x 10	Not stated	R hemihepategtomy	Died 45 days after operation. Residual tumor at autopsy
2. Ho (1980)[17]	65 M	Pyogenic cholangitis, swinging fever, abd pain, obst jaundice & hepatomegaly	R intrahepatic	8 x 6 x 7	Lymph nodes (porta hepatic)	Wedge biopsy	Died 2 wks after operation. Bronchopneumonia at autopsy
3. Ho (1980)[17]	63 F	Abd pain, anorexia, weight loss, obst jaundice & hepatomegaly	L intrahepatic	6	Lymph nodes (porta hepatic & peripancreatic), portal vein	No operation	Died 3 mos after clinical onset or 16 days after admission
4. Koo et al (1982)[18]	44 F	Pyogenic cholangitis, abd pain & distension, fever, weight loss & hepatomegaly	L intrahepatic	12	Not stated	L hemihepatectomy Clonorchis sinensis found	Died 6 mos due to recurrence of disease. No autopsy
5. Koo et al (1982)[18]	66 M	Obst jaundice & hepatomegaly	Extrahepatic (common hepatic duct	4 x 3	Gallbladder, portal lymph nodes & R hepatic artery	Radical en block resection	Died 1 wk after surgery from liver failure. Autopsy: not stated
6. Koo et al (1982)[18]	62 M	Hepatomegaly, anorexia, emaciation & obst jaundice	Extrahepatic (common hepatic duct)	1.5	No description	Radical en block resection	Well 10 mons after operation
7. Katsuda et al (1984)[19]	78 M	Adb discomfort, emaciation & hepatomegaly	L intrahepatic	11 x 10 x 6.5	Lungs, kidneys, peripancreatic lymph nodes & peritoneum	Chemotherapy	Died 3 mos after hospitalization. Autopsy: multiple cysts around & within tumor, cachexia & ascites
8. Lambrianides et al (1986)[20]	59 F	Previous Thorotrast exposure 32 yrs ago R upper quadrant pain, weight loss & jaundice	R intrahepatic	18	Superior pole of R kidney	No specific statement	Died 2 wk after admission Autopsy: Thorotrast deposition in liver, spleen, abd lymph nodes, bone marrow & site of injection of R carotid angiogram
9. Hayashi et al (1987)[21]	46 F	Cyst in liver & R hypochondralgia	L intrahepatic	3 x 3 x 2	No statement	Resection*	Died 11 mos after surgery with recurrence
10. Palma et al (1992)[22]	66 F	L hypochondralgia	L intrahepatic	9 x 5.7 x 4.7	Diaphragm, pericardium & portal vein	Partial resection of liver, diaphragm & pericardium	Died 6 mos after surgery with evidence of spreading. No autopsy
11. Shuangshoti (current case)	64 M	Obst jaundice, abd pain, fever & ascites	L intrahepatic	5 x 4 x 3	Lymph nodes (porta hepatic & peripancreatic) with compression of CBD	No specific treatment	Died 7 mos after onset of jaundice with massive bleeding of chronic DU found at autopsy

*The patient also had resection of signet ring cell carcinoma of stomach, about 2.5 years earlier.

Pt = patient, M = male, F = female, R = right, L = left, Abd = abdomen or abdominal, wk = week, mo = month, yr = year, CBD = common bile duct, Obst = Obstructive, DU = Duodenal ulcer

glandular epithelium intimately mixed in nests[23]. The current hepatic mucoepidermoid carcinoma, thus, is well fit to this definition when malignant squamous epithelial cells and glandular epithelial cells with mucin production are mingled in clusters. Moreover, this intermingling feature of the squamous and mucus-secreting malignant cells separates the current primary mucoepidermoid carcinoma from the primary adenosquamous cell carcinoma. In the latter, foci of pure epidermoid component with keratin and intercellular bridges are clearly delineated from the glandular areas[24].

To our knowledge, 11 primary mucoepidermoid carcinomas of the bile duct have been recorded, including the current instance (Table 1). The tumor affected 6 men and 5 women between 44 and 78 years old with the mean age of 60 years. Nine tumors arose in the intrahepatic bile ducts. Three of them were in the right lobe of the liver [16,17,20]. Six were in the left lobe, including the present one[17-19,21,22]. The remaining two neoplasms originated in the extrahepatic bile ducts (common hepatic ducts). The size of the tumor ranged from 1.5 cm in the common hepatic duct to 18 cm in the right lobe of the liver[18,20]. The average size was 8.4 cm in greatest dimension.

Metastasis or extension of the tumors was described in 7 examples, including our case[17-20, 22]. Regional lymph nodes were the most common site of metastases (5 cases). The kidney, gallbladder, and lung were uncommon sites of dissemination. Invasion of the portal vein and hepatic artery was also encountered[17,18].

The associated conditions include hepatic cysts in two cases[19,21]. One of these two examples has also signet ring cell carcinoma of the stomach[21]. Chronic cholangitis was found in three patients, including the current one[17,18]. In one of them, there was Clonorchis sinensis infestation[18]. Association with Thorotrast administration was described in a patient[20]. Fatal bleeding of chronic duodenal ulcer, as in our case, has not yet been observed in patients having primary mucoepidermoid carcinoma of the bile duct, but has been noted in relation to a massive spontaneous hemorrhagic glioblastoma multiforme of the cerebellum[25]. However, this event may be fortuitous.

Seven patients received surgical treatments such as hemihepatectomy, radical en block resection, and wedge biopsy[16-18,21,22]. The remaining patients did not have specific treatment. Regardless of the method of treatment, 10 patients died within 11 months, including our instance. However, a patient lived well 10 months after resection of a 1.5 cm mucoepidermoid carcinoma of the common hepatic duct[18]. The prognosis of the mucoepidermoid carcinoma of the bile duct, thus, is generally poor.

The etiology of the mucoepidermoid carcinoma of the bile duct has not yet been elucidated. Nevertheless, the coexistence to Clonorchis sinenis infestation, primary cholangitis, Thorotrast administration, and cyst of the liver raises the probable causal relation in some patients[18-21]. Although our patient had also chronic cholangitis we were unable to decide that this pathologic change was the cause of the mucoepidermoid carcinoma or it was the effect of prolonged compression of the common bile duct by lymph nodes containing metastatic mucoepidermoid carcinoma.

In Thailand, cholangiocarcinoma associated with opisthorchiasis of the liver has been noted especially in the Northeastern region with particular reference to Khon Kaen province[26]. However, no primary mucoepidermoid carcinoma of the bile duct has been described before the current instance, to our knowledge. It is probable that primary mucoepidermoid carcinoma of the bile duct has existed but it might have been missed in diagnosis as cholangiocarcinoma with squamous cell metaplasia or as adenosquamous cell carcinoma, as commented by Higushi et al[24].

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มิวโคอีพิเดอร์มอยด์ คาร์ซิโนมา ปฐมภูมิ ของท่อน้ำดีในตับ : รายงานผู้ป่วย 1 ราย พร้อมทบทวนวารสาร

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ได้รายงานผู้ป่วยชายไทยอายุ 64 ปี เป็นมิวโคอีพิเดอร์มอยด์ คาร์ซิโนมา ปฐมภูมิ ของท่อน้ำดีในกลีบซ้ายของตับ และถึงแก่กรรมภายใน 7 เดือน เพราะเกิดตกเลือดรุนแรงจากแผลเปื่อยเรื้อรังของดูโอดีนัม มะเร็งได้แพร่กระจายภายในตับ และไปสู่ต่อมน้ำเหลืองที่ขั้วตับ และรอบ ๆ ตับอ่อน ต่อมน้ำเหลืองที่โตบางก้อนกดท่อร่วมน้ำดีส่วนปลายและหัวตับอ่อน ทำให้เกิดอาการดีซ่านชนิดอุดตันเป็น ๆ หาย ๆ ก่อนเสียชีวิต

จากการทบทวนวารสารพบมีรายงานมิวโคอีพิเดอร์มอยด์ คาร์ซิโนมา ปฐมภูมิ ของท่อน้ำดี 11 ราย รวมทั้งที่รายงานนี้ด้วย เกิดกับท่อน้ำดีภายในกลีบขวาของตับ 3 ราย กลีบซ้าย 6 ราย และกับท่อน้ำดีนอกตับ 2 ราย ผู้ป่วยเป็นชาย 6 ราย หญิง 5 ราย อายุระหว่าง 44–78 ปี เฉลี่ย 60 ปี ขนาดของมะเร็งวัดตามแนวกว้างที่สุดของก้อน 1.5–18 ซม. เฉลี่ย 8.4 ซม. มะเร็งแพร่กระจายไปสู่ต่อมน้ำเหลืองใกล้เคียงบ่อยที่สุด พบแทรกแซงเข้าสู่หลอดเลือดดำพอร์ตัล และหลอดเลือดแดงเฮพาติกได้บ้าง ผู้ป่วย 10 รายตายภายใน 11 เดือน ไม่ว่าจะรักษาด้วยวิธีใดก็ตาม มีผู้ป่วย 1 ราย อยู่ได้อย่างสบาย 10 เดือน หลังผ่าตัด สรุปว่า มิวโคอีพิเดอร์มอยด์ คาร์ซิโนมา ปฐมภูมิ ของท่อน้ำดี มีการพยากรณ์โรคไม่ดี

คำสำคัญ : เนื้องอกของตับ, มะเร็งท่อน้ำดี, มิวโคอีพิเดอร์มอยด์ คาร์ซิโนมา, ดีซ่าน

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