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Case report

A case of Mixed Hepatocellular Carcinoma and Cholangiocarcinoma in a 27-year-old female patient with ulcerative colitis

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SUMMARY

We report the case of a 27-year-old female patient, with 8-year history of ulcerative colitis (UC), admitted to our department because of exacerbation of the disease. Hematology and blood chemistry results confirmed the diagnosis of UC exacerbation. Abdominal CT detected a left liver lobe mass. Needle biopsy histological examination demonstrated adenocarcinoma. The patient was treated with left hepatic lobectomy. Histopathology of the resected lobe revealed the presence of Mixed Hepatocellular Carcinoma and Cholangiocarcinoma (MHCC) and changes characteristic of sclerosing cholangitis of small bile ducts at a distance from the carcinomatous areas. Our patient had no previous history of liver disease. Liver function tests were normal, except for mild increase in γ-GT and alkaline phosphatase. Serum values of CEA and CA19-9 were quite elevated, while AFP was normal. The association of cholangiocarcinoma with UC is well established, while MHCC is reported in a few case reports. Primary sclerosing cholangitis (PSC) of intrahepatic (pericholangitis) or extrahepatic (classic PSC) bile ducts usually precedes the development of cholangiocarcinoma, occasionally asymptomatic. MHCC is a rare hepatobiliary complication of UC, probably in pre-existing, asymptomatic PSC of small bile ducts. The issue of liver manifestations in patients with UC is discussed here.

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INTRODUCTION

Hepatobiliary complications may affect as many as 10% of patients with ulcerative colitis (UC), with primary sclerosing cholangitis (PSC) being the most common.[1,2] The primary cholangiocarcinoma and the hepatocellular carcinoma are rare complications of UC, with the former being ten times more frequent than that of the general population.[1-5] It is assumed that the primary cholangiocarcinoma in UC patients may be developed in pre-existing pericholangitis or PSC. The latter, occasionally, may be asymptomatic, prior to the development of the neoplasm.[1-5] Furthermore, few studies of mixed hepatocellular carcinoma and cholangiocarcinoma (MHCC) in UC, have been published.[3] We present the rare case of a female patient, admitted with UC exacerbation who was found to have primary mixed hepatocellular carcinoma and cholangiocarcinoma of the left liver lobe.

CASE REPORT

A 27-year-old female patient was admitted to our department because of high fever, up to 38,8°C, rigor, diffuse abdominal pain and 15-day period of bloody diarrheas, 8 to 11 per day. She also reported headache, backache and weight loss, about 5 Kg the last 2 months. The patient had suffered from UC, affecting the whole large bowel for the last 8 years. She had been hospitalized 3 times in a general hospital because of exacerbation of UC. She had to be admitted to a general hospital for severe attacks three times over this period. For the

last two years she had been on maintenance therapy with 5-ASA preparations.

Personal history: She reported no smoking, no alcohol abuse or contraceptives.

Physical examination: The patient was a pale, thin, moderately ill person. A painless mass was palpated in the epigastrium, extended to the left subcostal area, 4-5 cm under the left subcostal margin. The rectal examination was painful, positive for blood and mucus.

Other systems: Normal findings.

Laboratory examination: Ht 30.8%, Hb 9.5 g/dl, WBC 10.500/μl with normal differentiation, PLT 624.000/μl, ESR 83mm/1h, glucose 95 mg/dl, urea 26 mg/dl, K^+ 3.9 meq/dl, $N\alpha^+$ 142 meq/dl, Ca^{++} 9.56 mg/dl, P 2.9 mg/dl, total bilirubin 0.2 mg/dl, transaminases (SGOT, SGPT) normal, alkaline phosphatase 155 IU/L (normal 39-117 IU/L), γ-GT 108 IU/L (normal 7-32 UI/L), LDH 248 IU/L, total proteins 7.4 g/dl (albumine 3.8 g/dl, globulines 3.6 g/dl), clolesterol 125 mg/dl, triglycerides 51 mg/dl, CRP: 7.11 g/dl (normal < 0.8 g/dl). Alkaline phosphatase and γ-GT were increased (serum values twice as normal).

Immunological examination: ANA, ASMA and p-ANCA were positive, while AMA and anti-DNA were negative.

Serum tumor markers: CEA 216.7 U/ml (normal 0-5 U/ml), CA19-9 479,9 U/ml (normal 0-37 U/ml). AFP was normal.

Cultures: The blood and stool cultures were negative. The stool parasitological examination was also negative.

Radiological examination: The chest and abdomen roentgenograms were normal. The abdomen CT revealed a left liver lobe 'mass' of abnormal density with the radiological features of hepatoma. Enlarged lymph nodes were detected in the liver hilum and around the aorta. The cecum and the ascending colon wall were found to be thickened.

Endoscopy: Gastroscopy was normal. Colonoscopy showed findings of exacerbated UC (spontaneous haemorrhage, edema, friability, erythema, ulcerations of the mucosa and multiple pseudopolyps). The terminal ileum was slightly oedematous. Multiple biopsies were obtained from different sites of the whole bowel. Histopathology confirmed relapse of chronic UC.

A CT-guided liver biopsy from the 'mass' followed. The diagnosis of liver carcinoma, with morphological and immunohistochemical characteristics of adenocarcinoma was established.

Management: The patient was treated effectively with mesalazine and prezolone for the UC exacerbation. After remission was achieved she was referred to surgical department. A left hepatic lobectomy and regional lymph node resection was performed.

Histology: The study of multiple sections of the resected tumor revealed a primary malignant neoplastic process, with morphological and immunohistochemical characteristics of mixed hapatocellular-cholangiocellular carcinoma, poorly differentiated. A group of neoplastic cells (Figure 1) was found immunohistochemically to be focally positive to AFP (Figure 2) and negative to keratins cocteil, EMA, CEA, CA19-9 and CA50. On the other hand, the majority of neoplastic tubular-glandular structures of the tumor (Figure 3), were negative to AFP and positive to the remaining above-mentioned markers (Fig-

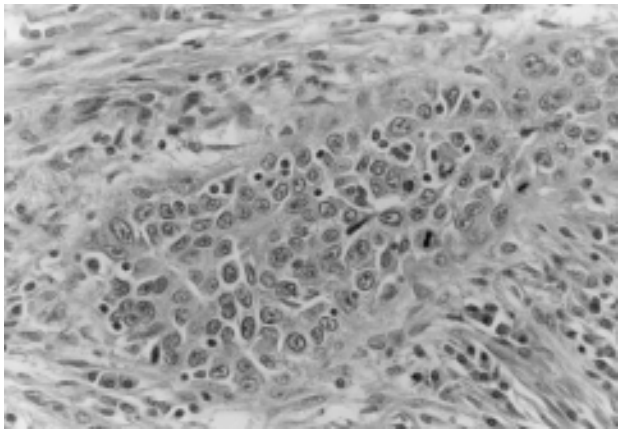

Figure 1. Group of neoplasmatic liver cells with precense of mitoses. AEx200.

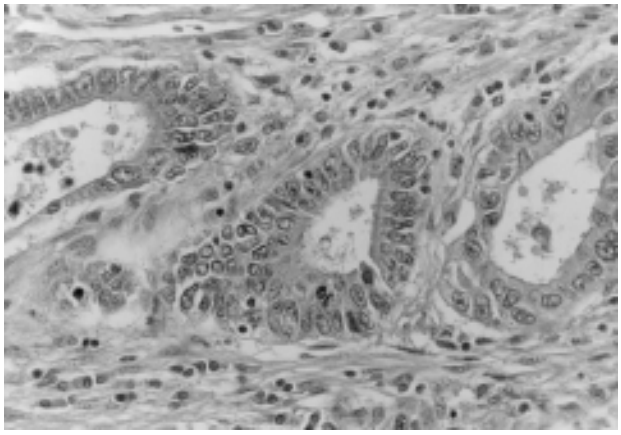

Figure 2. Neoplastic cells positive to AFP. PAPx400

ure 4). Furthermore, histological lesions suitable of sclerosing cholangitis of small bile ducts were found at a distance from the carcinomatous areas. The patient was discharged from the surgical department in good condition.

Follow-up: One month after the operation the patient complained of heavy headache and bone pain. The X-rays of head, spinal column and pelvis showed bone metastases. The bone scintigram and the pelvic bones MRI detected bone metastases. She was initially treated with common analgesics (nimesulid, paracetamol plus codeine), with good response for six months and when the pain deteriorated, she was treated palliatively with external radiotherapy on bone and brain metastases by $Co,^{60}$ in combination with pamidronate and ^{186}Rhenium HEDP isotope injection, with good response. So far, 18 months after the operation, the abdomen CT shows neither signs of local relapse nor metastases in the right lobe of the liver or other abnormal lymph nodes and the patient is in good WHO performance status.

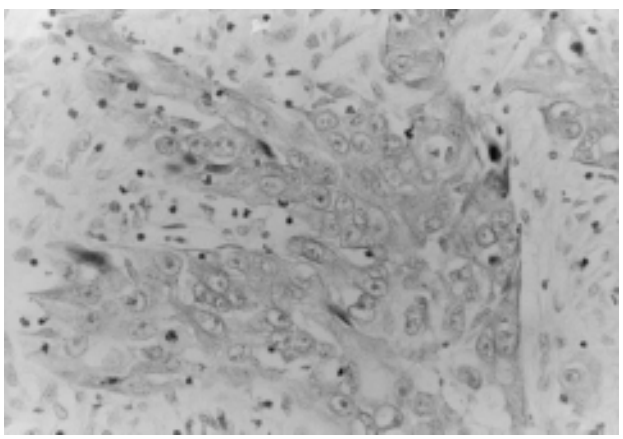

Figure 3. Neoplastic glandular structures-bile ducts. AEx200.

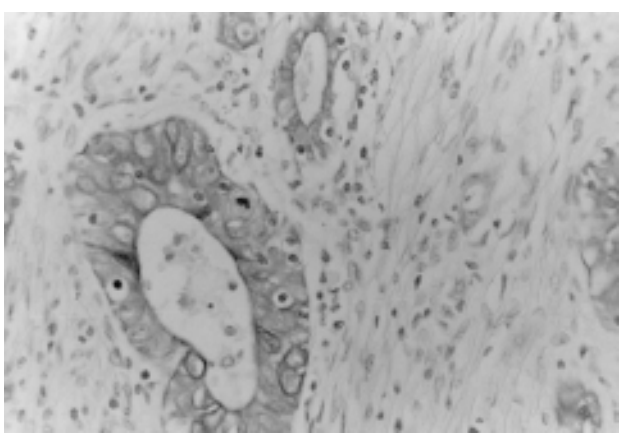

Figure 4. Neoplastic cells positive to AE1 ceratine. PAPx400.

DISCUSSION

The mixed hepatocellular carcinoma and cholangiocarcinoma of the liver (MHCC) is quite rare in the general population, comprising approximately 1% of primary liver cancer in Japan. There are few reports regarding its clinical features and the outcome of treatment remains unclear.[6,7]

The association of cholangiocarcinoma with UC is well established, increasing continuously, while the MHCC is referred to only in a few cases.[1-5] Parker and Kendall reported the first case of biliary tract cancer and UC in 1954.[1] A large study has reported a prevalence rate of 0.5% in UC patients, approximately 20-30 times that of the general population.[4] It is more common in long standing pancolitis. Colectomy does not protect against the development of the tumor, which may occur as long as 20 years after it.[1,2] Furthermore, several studies give sufficient indications that the majority of cholangiocarcinoma in UC patients developed in pre-existing primary sclerosing cholangitis (PSC), either of the small bile ducts (pericholangitis), or the large bile ducts (classic PSC), which may precede the development of the neoplasm.[1-6] The presence of tumor-free PSC, at a distance from the carcinomatous areas, as in our case, would seem to confirm the clinical impression that cholangiocarcinoma may develop in pre-existing PSC.[3] What is more, some studies demonstrate that patients with PSC and UC have a significantly higher risk of developing colorectal neoplasia compared with patients having UC only and also UC patients with PSC and colorectal neoplasia are more prone to develop cholangiocarcinoma as well.[3,8]

It is not known why only some patients with PSC develop cancer of the biliary tract. A possible mechanism is that long standing inflammation, bile stasis and chronic injury of the biliary epithelium may contribute to the development of cholangiocarcinoma, possibly by increasing epithelial cell proliferation and the probability of mutations.[1-6,9-10] PSC, which characterized by stricturing, fibrosis and inflammation of the biliary tree, may precede, even for years (5-10 years), the development of cholangiocarcinoma.[1-3]

The association of Crohn's disease with cholangiocarcinoma is rare and referrs only to Crohn's colitis.[1,2,11,12]

The development of hepatocellular carcinoma in UC patients seems to be associated to pre-existing chronic

hepatobiliary disease (secondary biliary cirrhosis, hepatitis).[1,2,13,14] Also, patients with advanced cirrhotic-stage PSC are at increased risk for developing hepatocellular carcinoma (in one study 2% in PSC patients undergoing orthotopic liver transplantation).[14] Furthermore, the risk of hepatocellular carcinoma increases severalfold in patients with liver cirrhosis, regardless of etiology.[10,14]

MHCC shows histological features of both hepatocellular carcinoma and cholangiocarcinoma present in the same tumor. This is not suprising because hepatocytes and small bile ducts have a common origin and the ability of each cell type to form the other is retained.[10] Its clinical features are intermediate between hepatocellular carcinoma and cholangiocarcinoma and the preoperative diagnosis is difficult, even when a liver biopsy was carried out, as in our case.[1,2] The most prominent clinical sign of the disease is the progressive cholestatic jaundice.[1,2] Endoscopic retrograde cholangiography (ERC) usually reveals bile duct stricture, although the distinction from focal PSC can be difficult or impossible before surgery.[1,2]

In our case, however, there was no previous history of chronic liver disease, the patient had no jaundice and the liver function tests showed a small increase of serum alkaline phosphatase and γ-GT values. This is a common finding in primary cholangiocarcinoma of the small bile ducts.[1,2]

Some studies suggest that increased preoperative serum CEA and CA19-9 levels and a low AFP level, as in our case, may be useful indicators of the diagnosis of the MHCC,[6,7] while other studies support that these tumor markers are of very low diagnostic value[15]. Extensive surgery is considered to be an effective treatment for this disease.[6,7] In our case, the tumor being restricted the left lobe, with no metastases in the right lobe, made surgical resection possible. Histopathology revealed the presence of MHCC poorly differentiated. Furthermore, at a distance from the carcinomatous areas, abnormalities suitable of PSC of the small bile ducts were found.

The prognosis of MHCC is very poor (less than 10% survive more than 2 years[1,2,6]), although the survival rate for resectable tumors is better. In one study from Japan, the 5-year survival rate, after an effective surgery, was 60%.[6,7]

In conclusion, the above mentioned data, in association with the history and the histological (morphological and immunohistochemical) findings of the resected liver tumor, allow us to consider the MHCC of our patient, being a complication of UC, probably in pre-existing asymptomatic, hepatobiliary disease, such as PSC of small bile ducts.

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