Digestive organs: Liver: Combined hepatocellular and cholangiocarcinoma

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Identity

Other names: Hepatoccholangiocellular carcinoma

Note: Defined as an intrahepatic tumor nodule that contains both hepatocellular carcinoma and cholangiocarcinoma.

Classification

Note: Tumor staging is separated by TNM classification.

TNM classifications for hepatocellular and cholangiocarcinomas of the liver.

Clinics and pathology

Disease

Combined hepatocellular and cholangiocarcinoma is a more aggressive malignancy with a poorer prognosis than ordinary hepatocellular carcinoma (HCC).

Etiology

The reported frequency of combined hepatocellular and cholangiocarcinoma (combined tumors) varies widely; 1.0-6.5% among patients with primary liver cancer. Statistical data indicate that combined tumors occur predominantly in men (reported ratio is ranged from 14:1 to 2:1). The mean age of onset is in the sixth decade. In Asian cases, a high incidence of hepatitis B or C virus infection and frequent association of chronic liver disease/cirrhosis have been reported. Conversely, in Western countries, these features are less common. Combined tumors exhibit an invasive character with frequent venous permeation and tumor microsatellite formation, features that are seen more frequently than in ordinary HCC.

Epidemiology

A rare subtype of primary liver cancer.

Clinics

The typical clinical symptom is abdominal pain. Complaints of fatigue and weakness are mostly attributable to compromised liver function. Jaundice is found in a much lower percentage of patients than of those with intrahepatic cholangiocarcinoma (CC). Chills and fever appear rarely.

In combined tumors, HCC and CC areas rarely can be identified using imaging techniques such as ultrasonography, helical CT, and dynamic MRI. In many cases, even in tumor biopsy samples, the two components are not included or discriminated. Generally, final diagnosis is entrusted to pathological findings of surgically resected or autopsy samples.

Pathology

The histopathological classification reported by Goodman et al. is popular:
- type I, in which HCC and CC occur coincidentally and no transitional forms are observed;
- type II, in which there are areas of apparent transition between HCC and CC;
- type III, in which tumor cells resemble the fibrolamellar subtype of HCC but contain mucin-producing glands.

Other classifications, reported by Allen and Lisa, and by Kojiro et al., are known.
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(A and B) Gross feature and schematic illustration of combined hepatocellular and cholangiocarcinoma. HCC: hepatocellular carcinoma, CC: cholangiocarcinoma. (C-E) Border zone between HCC and CC. Moderately differentiated HCC (right) with vague granular component (left). The granular tumor cells were positive for CK19 and HCC component was positive for Hep par-1.

**Treatment**
Surgical resection, chemotherapy, radiofrequency ablation, microwave coagulation, ethanol injection, transarterial embolization.

**Evolution**
Intrahepatic recurrence is common. Combined tumors have been reported to be more aggressive than HCC, with widespread metastasis and regional lymph node involvement.

**Prognosis**
The prognosis of combined tumors is poorer than that of HCC because of relatively frequent lymph node metastasis and vascular invasion. Survival rates of patients with combined tumors are generally poorer than those of patients with HCC.

**Cytogenetics**

**Note:** Loss of heterozygosity (LOH) at 4q, 8p, 13q, 16q, and 17p is seen frequently in combined hepatocellular and cholangiocarcinoma similar to in HCC. LOH at 3p and 14q are reported to be specific in CC and combined hepatocellular-cholangiocarcinoma in contrast to HCC.

**Genes involved and Proteins**

**Genes**

**K-RAS**

**Location:** 12p12.1

**DNA/RNA**

4 exons.

**Protein**
Proto-oncogene. GTP-GDP binding protein with GTPase activity. The K-ras proto-oncogene is thought to exert control over some of the mechanisms of cell growth and differentiation. This gene is converted to an active oncogene by point mutations concentrated significantly in codons 12, 13, and 61. Mutations of the K-ras gene have been reported to be common (67-75%) in intrahepatic CC. Conversely, the mutations rarely have been found in HCC. K-ras mutations in combined hepatocellular and cholangiocarcinoma have been analyzed in Japanese cases and it has been reported that the mutations were found rarely, as in the case for HCC. This observation may reflect the background of Japanese patients; specifically, chronic hepatitis C infection and evidence
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