Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Solid Tumour Section

Mini Review

Liver: Intrahepatic cholangiocarcinoma

Munechika Enjoji, Shinichi Aishima

Department of Hepatology and Pancreatology, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan (ME), Department of Pathology, Hamanomachi Hospital, 3-5-27 Maizuru, Chuo-ku, Fukuoka 810-8539, Japan (SA)

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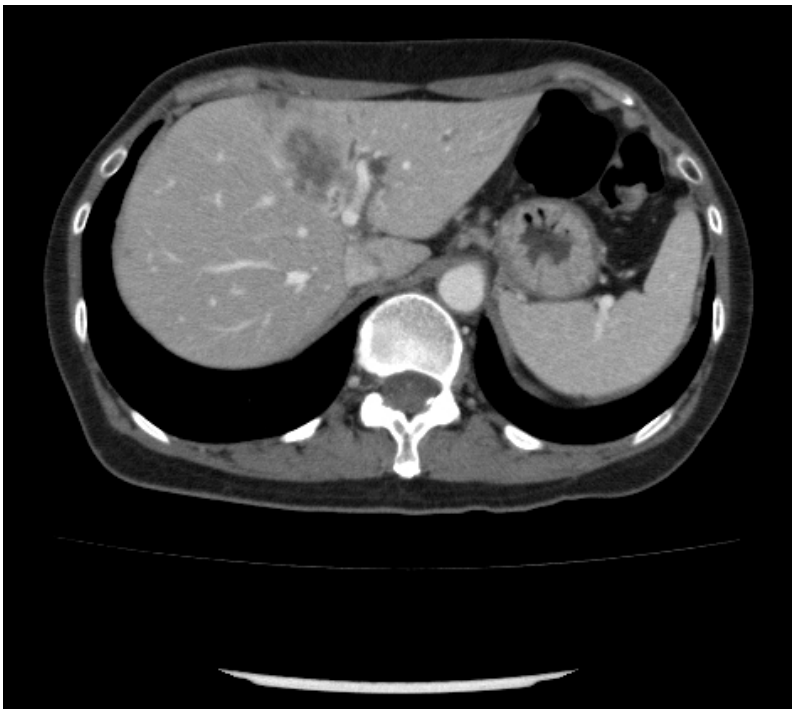
Identity

Alias
Peripheral cholangiocarcinoma
Peripheral bile duct carcinoma
Note
Defined as a malignant tumor arising from the intrahepatic bile duct epithelium. Cholangio-carcinoma arising from the right and left hepatic ducts at or near their junction (hilar cholangio-carcinoma) are considered as carcinoma of the extrahepatic bile ducts.

Classification

Note
Tumor staging is separated by TNM classification.
Classification
TNM classification of tumors of the liver and intrahepatic bile ducts.



Intrahepatic cholangiocarcinoma, CT image. The quadrate robe contains a mass. Peripheral enhancement of the tumor and peripheral bile duct dilatation are shown.

Clinics and pathology

Disease

Intrahepatic cholangiocarcinoma is an aggressive malignancy with poor prognosis. The causes of this disease lethality are not only its rapid growth but also its tendency to invade adjacent organs and metastasize.

Etiology

Intrahepatic cholangiocarcinoma, unlike hepato-cellular carcinoma, is not usually related to liver cirrhosis and is sometimes accompanied by severe fibrosis. This suggests that hepatocellular and cholangiocarcinoma might originate from hepatic precursor cells. Opisthorchis viverrini-induced cholangiocarcinomas are common in Thailand. Liver fluke infection causes chronic inflammation and enhances the susceptibility of bile duct epithelium to carcinogens/free radicals, leading to genetic and epigenetic damage in cells. Increased carcinogenic nitroso-compounds as a result of regional dietary factors are thought to have a synergistic effect on patients with liver fluke infestations.

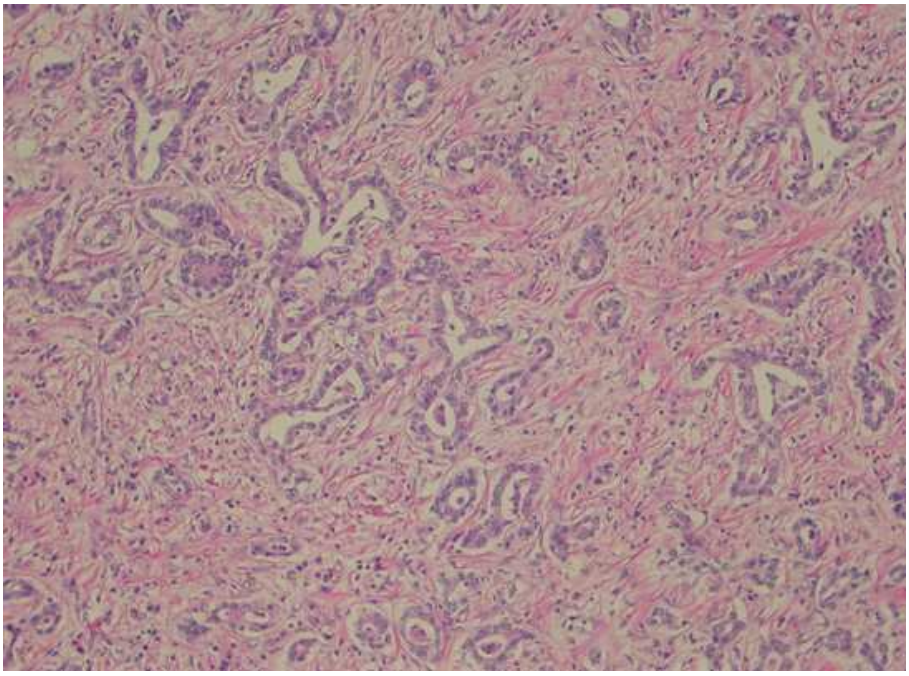
Hepatolithiasis represents a high-risk state for intrahepatic cholangiocarcinoma because of recurrent bacterial infections and bile stasis. Hepatitis C virus (HCV) infection has also been reported as a risk factor for cholangiocarcinoma; however, the relationship between HCV and cholangiocarcinoma formation is not unequivocally established. Patients with primary sclerosing cholangitis have a tendency to develop bile duct carcinoma including intrahepatic cholangiocarcinoma. However, most intrahepatic cholangiocarcinomas arise in the absence of known etiological factors.

Epidemiology

Intrahepatic cholangiocarcinoma is the second most prevalent intrahepatic primary cancer. It occurs in the middle-aged and elderly with no obvious sex differences. Its incidence reveals wide geographic variations: the highest incidence is reported in Southeast Asia especially in Laos and Northeast Thailand, areas suffering from endemic infection with the liver fluke, Opisthorchis viverrini. Hepatolithiasis, another risk-factor, is also more frequently seen in East Asian than in Western countries.

Clinics

The clinical features of intrahepatic cholangiocarcinoma are primarily governed by its anatomical location and growth pattern. Biliary obstructive symptoms are rare. Generally, early stages of intrahepatic cholangiocarcinoma do not produce specific clinical symptoms that are recognized by affected persons, and there is no specific or practical laboratory method for the diagnosis in early stages. Hence, diagnosis of tumors is frequently made when malignancies have progressed to an advanced stage with poor prognosis. In an advanced stage, abdominal pain, fever, general malaise, and weight loss can occur. On ultrasound imaging, there are no specific features for intrahepatic cholangiocarcinomas to distinguish them from other intrahepatic tumors. On magnetic resonance imaging, intrahepatic cholangiocarcinomas appear hypointense on T1-weighted images and hyperintense on T2-weighted images. On computed tomography, typical intrahepatic cholangiocarcinomas present as mass lesions with irregular margins though significant enhancement is not shown in the central portion of the lesion.



Intrahepatic cholangiocarcinoma. Well differentiated tubular adenocarcinoma.

For staging the disease, computed tomography and magnetic resonance imaging are effective.
Percutaneous tumor biopsy is available for qualitative diagnosis but there is the possibility of tumor seeding. As tumor-associated markers, CA19-9, CEA, and CA125 are well studied, and CA19-9 is most useful.

Pathology

The Liver Cancer Study Group of Japan has proposed a classification of intrahepatic cholangio-carcinoma based on macroscopic features; mass-forming, periductal infiltrating, and intraductal, or mixed mass-forming and periductal infiltrating. The histopathological classification of biliary tract carcinoma follows the WHO classification:
adenocarcinoma,
adenosquamous carcinoma,
squamous carcinoma,
cholangiolocellular carcinoma,
mucinous carcinoma,
signet-ring cell carcinoma,
sarcomatous carcinoma,
lymphoepithelioma-like carcinoma,
clear cell variant,
mucoepidermoid carcinosarcoma.
The most common histology of intrahepatic cholangiocarcinoma is that of an adenocarcinoma showing tubular and/or papillary structures with a variable fibrous stroma.

Treatment

Surgical resection, chemotherapy, radiation therapy, and radiofrequency ablation.

Evolution

Recurrence should be given careful attention.

Prognosis

Surgical resection improves prognosis, but complete removal of cancer at an advanced stage is hardly possible. Chemotherapy, radiotherapy, and immunotherapy show little benefits. Therefore, the prognosis of patients with intrahepatic cholangiocarcinoma remains poor.

Cytogenetics

Note
In intrahepatic cholangiocarcinoma, losses of heterozygosity at chromosomal loci 3p13-p21, 5q35-qter, 8p22, 17p13, and 18q have been reported.

Genes involved and proteins

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 significantly concentrated in codons 12, 13, or 61. The reported rates of K-ras mutations in intrahepatic cholangiocarcinomas vary widely. Variations are caused by racial and geographic variations, the use of different assay techniques; for example, a mutation rate of 50%-56% in Japanese patients versus 0%-8% in Thai patients. It has been reported that mutation rates are higher in periductal and spicular-forming tumors than mass-forming ones.

p53

Location
17p13
DNA / RNA
11 exons.
Protein
Tumor suppressor gene. Wild-type p53 plays an important role in the regulation of the cell cycle process, cell growth, and apoptosis in the event of DNA damage. Inactivation of the p53 gene by missense or nonsense mutations and by loss of chromosome 17p, the chromosomal location of the p53 gene, induces disruption of critical growth-regulating mechanisms and may have a crucial role in carcinogenesis. The reported incidence of p53 mutation is 11-37% in intrahepatic cholangiocarci-nomas. It has been reported that loss of chromosome 17p was present in 38% of intra-hepatic cholangiocarcinomas.

p16 INK4A

Location
9p21
DNA / RNA
3 exons.
Protein
A regulatory protein in the cell cycle and a cyclin-dependent kinase (cdk4/cdk6) inhibitor. The tumor suppressor gene p16 is commonly inactivated in many neoplasms. Three distinct mechanisms of p16 inactivation have been reported in biliary neoplasms: deletion and point mutations of the p16 gene, and hypermethylation of 5' regulatory regions of p16. A study of intrahepatic cholangiocarci-nomas reports that no p16 gene mutations are present but alterations of p16 gene are frequent: methylation of CpG island is present in the 5' region of the gene (54%), allelic loss at the p16 locus on chromosome 9p21 (20%), and homozygous deletion (5%). Therefore, the p16 gene may possibly be crucial for intrahepatic biliary carcinogenesis and progression.

c-erbB-2

Location
17q21.1
DNA / RNA
7 exons
Protein
Proto-oncogene, a member of the family of tyrosine kinase growth factor receptors (epidermal growth factor receptor subfamily). Amplification and overexpression of c-erbB-2 are frequently seen in cancers of the biliary tract. It has been reported that, a high incidence of cholangiocarcinomas (intra-hepatic and extrahepatic) and gallbladder cancers develop in transgenic mice overexpressing ErbB-2. Reported values of the frequency of tumors overexpressing ErbB-2 varies from 0% to 73%.

c-erbB-1 (epidermal growth factor receptor: EGFR)

Location
7p11.2
DNA / RNA
14 exons
Protein
Proto-oncogene; type I tyrosine kinase receptors. ErbB-1 can bind EGF and TGF-a. ErbB-1 and ErbB-2 share approximately 40% homology in their extracellular binding domains. It has been reported in intrahepatic cholangiocarcinoma that 44 % of cases are ErbB-1-positive cases and that ErbB-1 expression is correlated with grade and proliferative index.

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