Pathogenesis of Cholangiocarcinoma

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The pathogenesis of cholangiocarcinoma is poorly understood. The cancer, previously regarded as rare, has an increasing trend in its incidence and mortality.[1,2] It is often diagnosed late and survival is poor.

INCIDENCE

Approximately 20,000 new cases of liver and biliary tract cancer are diagnosed annually in the United States of America. Liver and biliary tract malignancies account for more than 12,000 deaths per year in the United States of America (US). Between 15-25% of these cancers are bile duct tumors or cholangiocarcinomas. Like gallbladder cancers, the incidence of cholangiocarcinoma increases with age. However, bile duct malignancies have a more even distribution between men and women. Overall, the incidence of cholangiocarcinoma in the US is approximately 0.8 per 100,000 people per year.[1] The annual frequency per 100,000 population is 7.3 in Israel, 6.5 in American Indians, and 5.5 amongst the Japanese.[3] In autopsy series, the incidence of cholangiocarcinoma varies from 0.01% to 0.46%.[4] Biliary tract cancers have traditionally been divided into cancers of the gallbladder, the intrahepatic and extrahepatic bile ducts, and the ampulla of Vater. The term cholangiocarcinoma was originally intended to refer only to primary tumors of the intrahepatic bile ducts and was not used for tumors of the extrahepatic bile ducts. Lately, however, the term has been used to include intrahepatic, perihilar, and distal extrahepatic tumors of the bile ducts. Perihilar tumors involving the bifurcation of the hepatic duct are also called Klatskin tumors, from Klatskin's original description in 1965.[5] In this review, the term cholangiocarcinoma is used for primary tumors of the bile ducts, including intrahepatic, perihilar, and distal extrahepatic tumors.

The perihilar bile duct tumors were further classified by Bismuth et al. as tumors below the confluence of the left and right hepatic ducts (type I), tumors reaching the confluence (type II), tumors occluding the common hepatic duct and either the right or left hepatic duct (types IIIa and IIIb, respectively), and tumors that are multicentric or that involve the confluence and both the right and left hepatic ducts (type IV).[6] Even more detailed classifications have been proposed, but they are

not used in daily practice. Most cholangiocarcinomas involve the perihilar and distal extrahepatic bile ducts.

Although the numbers vary among countries and regions, about two thirds of all cases of cholangiocarcinoma are perihilar tumors, about one fourth are distal extrahepatic tumors, and the remainder are intrahepatic. Except for embryonal rhabdomyosarcoma, the frequency of all types of biliary tract cancers increases with age. Gallbladder cancers are more frequent in women, and cholangiocarcinomas are slightly more common in men. These sex differences are probably related to the higher incidence of gallstones in women and of primary sclerosing cholangitis in men. These are known risk factors for gallbladder cancer and cholangiocarcinoma, respectively.

RISK FACTORS[7]

A number etiologic factors have been linked to cholangiocarcinoma in man. Factors common to a number of these etiologic parameters include stones, biliary stasis, and infection. Strong associations have been found between cholangiocarcinoma and hepatolithiasis, liver flukes, biliary cystic disease, sclerosing cholangitis, ulcerative colitis, and the radiocontrast agent Thorotrast. Associations have also been reported between cholangiocarcinoma and radionuclides, chemical carcinogens, and drugs.

1. Hepatolithiasis

Cholelithiasis has been observed in up to one third of patients with cholangiocarcinoma. This figure, however, is not dramatically different from what might be expected in an elderly population. Thus, although there may be an association between gallstones and cholangiocarcinoma, a definitive cause-and-effect relationship has not been established. In contrast to cholelithiasis, hepatolithiasis is a definite risk factor for cholangiocarcinoma. In certain parts of East Asia, intrahepatic stones are endemic. Cholangiocarcinoma will develop in between 5% and 10% of these patients with hepatolithiasis. This cancer risk is apparent with hepatolithiasis even in the absence of secondary infestation with liver flukes.

2. Liver Flukes

For more than three decades, an association has been recognized between infection with the liver fluke *Clonorchis sinensis* and cholangiocarcinoma. Clonorchiasis is common in Asia, where the ingestion of infected raw fish is common. The parasite gains entry through the host's duodenum. The preferred habitats in the human host are the intrahepatic and, less commonly, the extrahepatic biliary ducts. The adult trematodes measure up to 25 mm long, and they can obstruct the flow of bile and cause periductal fibrosis and hyperplasia, which are believed to be forerunners of cholangiocarcinoma. The liver fluke *Opisthorchis viverrini* has also been proposed as a risk factor for cholangiocarcinomas. This parasite is endemic in certain regions of Thailand that also have a very high incidence of cholangiocarcinoma. Dietary habits, such as a high ingestion of nitrosamines, may

also play a role in the high incidence of cholangiocarcinoma in this region.

3. Biliary Cystic Disease

A 2.5-28% incidence of cholangiocarcinoma has been noted in patients with cystic abnormalities of the bile duct. Patients with cystic lesions of the bile duct who have cholangiocarcinoma develop usually present two decades earlier than patients with sporadic cholangiocarcinoma. Furthermore, a relationship has been noted between the age of initial symptoms from the choledochal cyst and the incidence of cholangiocarcinoma. If the choledochal cyst became symptomatic in the first decade of life, the risk of cholangiocarcinoma was 0.7%. When the choledochal cyst became symptomatic in the second decade of life, a 6.8% risk of cholangiocarcinoma was observed. In contrast, when the choledochal cyst became symptomatic after the age of 20 years, a 14.3% risk of cholangiocarcinoma was noted. Thus, although three quarters of choledochal cysts present in infancy and childhood, more than 75% of cholangiocarcinomas associated with choledochal cysts have been found in patients presenting with symptoms as adults.

One explanation for the origin of choledochal cysts and subsequent formation of cholangiocarcinoma involves the finding of an anomalous high entry of the pancreatic into the extrahepatic biliary tree in patients with choledochal cysts. This finding of an anomalous pancreatic-bile duct junction (APBDJ) suggests that reflux of pancreatic exocrine secretions into the bile duct epithelium causes malignant transformation of the bile duct. Additional factors that may lead to malignant transformation in the choledochal cysts include bile stasis within the cyst, stone formation within the cyst, and chronic inflammation and bacterial infection within the cyst. These same factors may play a role in the high incidence of cholangiocarcinoma in patients with Caroli's disease.

4. Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is an idiopathic disease characterized by multiple intrahepatic and extrahepatic inflammatory bile duct strictures that cannot be attributed to specific causes such as operative trauma or choledocholithiasis. A strong association exists between sclerosing cholangitis and ulcerative colitis. Between 60-80% of all patients with sclerosing cholangitis have coexisting ulcerative colitis. Autoimmunity has been implicated in the pathogenesis of sclerosing cholangitis, with serum autoantibodies that cross-react with bile ductules being found in 60% of ulcerative colitis patients with sclerosing cholangitis.

Cholangiocarcinoma may develop in patients with sclerosing cholangitis, often manifested by rapid clinical deterioration and progressive jaundice. Previously unrecognized cholangiocarcinoma has been noted at autopsy in up to 40% of patients dying with sclerosing cholangitis and in 9-36% of patients undergoing orthotopic liver transplantation for this disease. Currently, no reliable laboratory or radiographic features indicate the presence of cholangiocarcinoma in patients with sclerosing

cholangitis. The prognosis of patients with sclerosing cholangitis and cholangiocarcinoma is poor, with median survivals averaging less than one year.

The incidence of cholangiocarcinoma in patients with ulcerative colitis ranges from 0.14-1.4%, which represents a 400 to 1000 times increased risk over the general population. Patients with ulcerative colitis who have cholangiocarcinoma develop typically have the cholangiocarcinoma diagnosed in the fifth decade of life, which is approximately 20 years earlier than cholangiocarcinoma patients without ulcerative colitis. Patients with ulcerative colitis and cholangiocarcinoma usually have pancolonic involvement with the inflammatory bowel disease, as well as a long duration of colitis. The medical and/or surgical treatment of ulcerative colitis does not influence the subsequent development of cholangiocarcinoma because many patients have had bile duct carcinoma develop years after total proctocolectomy.

AIDS has also been associated with cancers throughout the entire biliary tract, including the ampulla of Vater.

5. Radionuclides

The most impressive association between a carcinogen and the development of hepatic and bile duct malignancies has been documented with exposure to the radiocontrast agent Thorotrast. Thorotrast in a 25% colliodal solution was first used for radiocontrast studies in 1928 and was widely used in the 1930's and 1940's. Thorotrast emits energy as alpha particles. When Thorotrast is injected intravenously, it is retained within the reticuloendothelial system for life, with a biologic half-life of 200-400 years. Thorium-related cholangiocarcinomas have been diagnosed after a mean latent period of 35 years, and they occur, on average, one decade earlier than nonthorium-related cases. When compared with nonthorium-related cholangiocarcinoma, tumors arising in patients with past thorium exposure tend to be located more peripherally, often within the intrahepatic biliary tree.

6. Chemical Carcinogens

In addition to radionuclides, a number of other chemical carcinogens and drugs have been implicated in the pathogenesis of cholangiocarcinoma. Chemicals that may potentially cause bile duct malignancies include asbestos, dioxin, nitrosamines, and polychlorinated biphenyls.

CELLULAR and MOLECULAR ASPECTS[8]

The precise cellular origin of human cholangiocarcinoma remains unknown. However, recent experimental evidence in a rat model using phenotypic analyses combined with morphologic and autoradiographic techniques suggests that carcinogens may induce neoplastic differentiation of pluripotent liver stem cells resulting in cholangiocarcinoma. These studies suggest that cholangiocarcinoma arises from stem cells near the portal triads through several intermediate preneoplastic cellular lesions, including oval cells, nodules, or atypical hyperplastic duct-like

structures. The correlation, however, between these animal studies and human cholangiocarcinoma remains speculative at present. Recently, more than one progenitor cell sub-population has been identified in the liver, each responding to different mechanism of injury by proliferation (9). The process of carcinogenesis of bimorphic (hepotomas and cholangiocarcinomas) tumor types may be related to activation of these stem cell sub-populations.[9]

The evolution of cellular changes most probably can be described as a multi-step, sequential, progression of metaplasia, dysplasia, and finally neoplasia.

Conversion from normal to malignant bile-duct tissue probably requires a number of successive genomic mutations similar to the sequence of events proposed for other gastrointestinal cancers, although our knowledge of biliary tract cancers is less extensive than that of the more common gastrointestinal cancers. A variety of mutations in oncogenes, as well as tumor-suppressor genes, have been described in specimens of biliary tract tumors. These include mutations in the oncogenes K-*ras*, c-*myc*, c-*neu*, c-*erb*-b2, and c-*met* and the tumor-suppressor genes p53 and *bcl*-2. These mutations may lead to detectable phenotypic changes; for instance, biliary epithelial cells switch from expressing MUC-1 apomucin before birth to MUC-3 after birth. Malignant transformation can reverse this process, and as mentioned before, many cholangiocarcinomas show staining with antibody to MUC-1. Similarly, core mucin carbohydrate Tn and sialyl-Tn antigens were expressed in many intrahepatic bile-duct cancers. However, as with other tissue types, mutations and phenotypic changes are also seen under nonmalignant conditions, precluding their routine use in clinical practice. Newer molecular markers and events are being described. Although there is much speculation regarding the factors that induce the various mutations such as chronic inflammation, ethnic background, diet, and exposure to carcinogens, little or nothing is known about how these factors actually cause biliary tract cancer.

FUTURE DIRECTIONS

Cholangiocarcinoma is one of the diseases where the East can teach the West. A description of the pathology, diagnosis, treatment, and prognosis is beyond the scope of this discussion. An improvement in survival of patients with cholangiocarcinomas probably will not result from more aggressive surgical techniques. The Asian countries hold the key to the secret of epidemiology and clinical evolution of the disease. A better understanding of the cellular and molecular events should lead to early detection, and hence treatment and even prevention.

REFERENCES

1. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33:1353-7.
2. Taylor-Robinson SD, Toledano MB, Arora S, Keegan TJ, Hargreaves S, Beck A, Khan SA, Elliot P, Thomas HC. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and

Wales 1968-1998. Gut 2001;48:816-20.
3. Waterhouse JC, Muir P, Correa S. Cancer incidence in five countries. Lyon (France): V03 TARC Scientific Publishers, International Agency for Research in Cancer 1976.
4. Sako S, Seitzinger GL, Garside E. Carcinoma of the extrahepatic bile ducts: review of the literature and report of six cases. Surgery 1957;41:416-22.
5. Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis: an unusual tumor with distinctive clinical and pathological features. Am J Med 1965;38:241-56.
6. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. Ann Surg 1992;215:31-8.
7. Pitt HA, Dooley WC, Yeo CJ, Cameron JL. Malignancies of the biliary tree. Curr Probl Surg 1995;32:1-90.
8. De Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. N Engl J Med 1999;341:1368-78.
9. Sell S. Hetergeneity and plasticity of hepatocyte lineage cells. Hepatology 2001;33:738-50.