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Preneoplastic conditions underlying bile duct cancer

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Abstract

Background—Malignancies arising from the biliary tract can arise from the epithelial lining of the biliary tract and surrounding tissues. Conditions that predispose to malignancy as well as preneoplastic changes in biliary tract epithelia have been identified. In this overview, we discuss preneoplastic conditions of the biliary tract and emphasize their clinical relevance.

Results—Chronic biliary tract inflammation predisposes to cancer in the biliary tract. Biliary tract carcinogenesis involves a multistep process as a consequence of chronic biliary epithelial injury or inflammation. Reminiscent of other gastrointestinal epithelial malignancies such as gastric, colon, and pancreatic cancer, biliary tract cancers may evolve via a multistep progression from epithelial hyperplasia and dysplasia to malignant transformation. The potential role of initiating cells is also becoming recognized.

Conclusions—In spite of improved risk factor recognition, and advances in diagnostic tools, the early diagnosis of pre-malignant or malignant biliary tract conditions is extremely challenging, and there is a paucity of evidence on which to base their management. As a result, the role of pre-emptive surgery remains largely undefined.

Keywords

cholangiocarcinoma; liver cancers; dysplasia; primary sclerosing cholangitis; hepatolithiasis

Introduction

Cholangiocarcinoma are a heterogeneous group of malignant tumors arising from the biliary tract epithelium of both the intrahepatic and extrahepatic bile ducts.[1–3] These tumors are relatively uncommon, and have a low incidence in the West. Collectively, these tumors account for less than five percent of all gastrointestinal cancers. However, there are marked regional variations and an extremely high prevalence in some parts of the world such as South East Asia.[4–6] The incidence is slightly higher in men with the peak age in the seventh decade [7], although the average age of onset varies with etiology and the tumor can develop at an earlier age in patients with primary sclerosing cholangitis (PSC). [8,9]

Cancers involving the perihilar region or the confluence of the right and left hepatic ducts account for about half of all cholangiocarcinoma cases.[10] Other distinct phenotypes include tumors arising within the liver, or intrahepatic cholangiocarcinoma, as well as tumors arising within the large extrahepatic ducts, or ductal cholangiocarcinoma.[11,12] More than 90 % of all cholangiocarcinomas are adenocarcinomas.[12] Although the different phenotypes vary in their clinical presentation, natural history and biological behavior, these tumors as a group are often difficult to diagnose and have a poor prognosis with limited effective treatment options. The identification of individuals who are at higher

risk of these cancers may enable early diagnosis with subsequent improvement in outcomes if curative resection is possible. Similarly, recognition and optimal management of individuals with premalignant lesions may reduce the occurrence of these cancers.

Risk Factors/Pathogenesis

Although the majority of cases of cholangiocarcinoma occur in patients without identifiable predisposing factors, several risk factors have been recognized.[13] These include PSC, bile duct cysts, parasitic infections, hepatolithiasis, biliary malformations, such as Caroli's disease, toxic exposures, such as thorotrast and dioxins, genetic conditions, including Lynch syndrome and multiple biliary papillomatosis, chronic hepatitis B and chronic hepatitis C viral infections.[2,3,14–17] The risk of cholangiocarcinoma is increased in patients with cirrhosis, as well as with diabetes, obesity, alcohol and tobacco use.[6,14,18–20]

Precursor lesions

Many patients who develop this cancer have underlying long standing chronic inflammation of bile ducts and chronic injury of the biliary epithelium. Although the key steps of cholangiocarcinogenesis are poorly understood, they are believed to proceed in a multistep process. Thus, precursor lesions result from biliary tract epithelial cell hyperplasia leading to dysplasia and eventually adenocarcinoma. These changes are associated with molecular changes such as alterations in oncogenes and tumor-suppressor genes.[21]

Biliary intraepithelial neoplasia (BilIN)

BilIN is a premalignant condition that was originally described by Zen et al. in 2005. The criteria for BilIN were subsequently refined based on an international interobserver agreement study in 2007.[22,23] BilIN is a microscopic epithelial lesion that is characterized by cuboidal or columnar cells showing variable degrees of cellular and nuclear atypia, loss of polarity and mitotic figures. Based on the degree of cellular and structural atypia, BilIN is classified into 3 grades namely BilIN-1, BilIN-2, and BilIN-3 indicating low-grade dysplasia, high-grade dysplasia, and carcinoma in situ respectively.

BilIN occurs in the setting of biliary tract as well as non-biliary tract diseases. Originally, BilIN lesions were described in conditions with chronic biliary inflammation: PSC, hepatolithiasis, and choledochal cysts.[22,23] BilIN is a precursor lesion of hilar cholangiocarcinoma.[21] More recently, several studies have reported BilIN lesions in nonbiliary liver disease such as HCV and alcohol cirrhosis.[24,25] Low grade biliary intraepithelial neoplastic lesions occurred in the bile ducts in 15/226 explant livers from patients with alcoholic, HCV and non-alcoholic liver disease.[26] Similarly, BilIN lesions were identified in 34 of 310 livers from patients with HCV, HBV, alcoholic or cryptogenic cirrhosis.

Genetic changes (e.g. REG1) as well as epigenetic changes occur during the progression of BilIN to carcinoma. An increased number of methylated genes such as TMEFF2, HOXA1, NEUROG1 and RUNX3 are seen with the progression from normal to BilIN to carcinoma. The identification of altered CpG island hypermethylation in BilIN demonstrates that epigenetic changes occur at an early stage in cholangiocarcinogenesis. Altered expression of several cancer-associated proteins are also recognized in progression of BilIN to carcinoma. These include overexpression of matrix metalloproteinases, MMP 7 and MT1-MMP, implicated in tumor invasiveness and progression [27], and alterations in cell cycle-related proteins p16 and p21. Claudin-18 expression is also frequently noted in BilIN.[28] Although some differences in protein expression such as MUC5AC and Ki67 are more often seen in

BilIN associated with biliary tract disease than with non-biliary tract cirrhosis [29] the pathophysiological relevance of these differences is not known.

The recognition of these changes is challenging. Whereas high grade lesions can be readily recognized, the differentiation of low grade changes from reactive inflammatory changes is not always possible. Thus, the diagnostic use of these morphological changes in the identification of preneoplastic changes within the biliary tract is not established.

Intraductal papillary neoplasm of the bile ducts (IPN-B)

IPN-B has been proposed as a counterpart to pancreatic intraductal papillary mucinous neoplasm.[27] These uncommon lesions are grossly discernable and identified by prominent papillary proliferation of dysplastic epithelium with intestinal metaplasia and mucin hypersecretion.[30] IPN-B can have three phenotypes, pancreaticobiliary, intestinal or gastric. IPN-B development has been associated with inactivation of p16INK4A and deregulated expression of MUC1 and MUC2.

In both the BilIN and IPNB lineages, histological progression is associated with over-expression of cyclin D1 (a proto-oncogene, a regulator of cell-cycle progression), p21 (a cyclin-dependent kinase inhibitor involved in cell-cycle progression), p53 (a tumor suppressor gene), and c-myc (a transcription factor that induces proliferation), whereas the expression of Dpc4 (a tumor suppressor gene) is lost. Reduced expression of E – cadherin (a tumor suppressor gene involved in epithelial cell adhesion) is associated with increased invasiveness of carcinoma cells.[31]

Preneoplastic conditions

Chronic biliary tract inflammation is linked to the development of carcinogenesis, and tumor formation may result from alterations in oncogenic processes and pathways induced by inflammatory mediators or processes, or tissue responses.

Primary sclerosing cholangitis (PSC)

This chronic inflammatory condition can affect the intrahepatic or extrahepatic bile ducts and is a well-characterized risk factor for cholangiocarcinoma. Indeed, patients with PSC have a significantly higher relative risk (>160 times) for the development of cholangiocarcinoma compared with the general population.[32–34] Although the development of cholangiocarcinoma in PSC can occur at any stage throughout the disease course, many patients may be diagnosed within a few months of the diagnosis of PSC. In one study, 40–50% of the cholangiocarcinomas were diagnosed during the first year following the diagnosis of PSC but the risk is unrelated to the disease duration.[35,36] The annual incidence of cholangiocarcinoma during follow-up has been estimated to be 0.5–1.5% per year with the lifetime risk of 10–15%.[32,37,38] There is an enormous difficulty in predicting cholangiocarcinoma in patients with PSC.

Several studies have been conducted to identify the risk factors associated with the development of cholangiocarcinoma. Some of the identified risk factors include alcohol consumption,[39] smoking,[40] longstanding inflammatory bowel disease,[35] variceal bleeding,[32] and older age[9] [33,41]. Polymorphism of natural killer cell receptor G2D gene has been suggested to increase the risk of cholangiocarcinoma.[42]

Recent investigations support a sequential hyperplasia-dysplasia-carcinoma model of cholangiocarcinoma development in PSC. Lewis et al demonstrated that liver explants of patients with PSC and cholangiocarcinoma were significantly more likely to have bile duct dysplasia (83%), and high-grade dysplasia (60%) than were livers of patients with PSC who

did not have cholangiocarcinoma. Low-grade dysplasia was a significant predictor of both high-grade dysplasia and cancer, and high-grade dysplasia was closely associated with the presence of cancer.[21] Genetic mutations, such as E-cadherin, K-ras (80–100%), p53 (40%), epidermal growth factor receptor and vascular endothelial growth factor have all been identified.[9]

Liver flukes

Fluke infestation plays a role in development of cholangiocarcinoma in certain geographic regions, particularly in the East. Liver flukes such as *Opisthorchis viverrini* are endemic in several regions in South East Asia, whereas *Clonorchis sinensis* is common in Korea and China.[43] Both of these liver flukes are recognized as carcinogens. In Thailand case series have shown elevated serum antibodies to *O. viverrini* correlate with a nearly 30-fold increase in risk of cholangiocarcinoma. Humans are infected by consuming uncooked cyprinoid fish. The fluke cause biliary tree ulcerations with eggs migrating through the ulcerations and causing the granulomatous inflammation. Infection leads to marked infiltration of bile ducts with inflammatory cells that once activated release free radicals including nitric oxide. These free radicals induce oxidative DNA damage and promote carcinogenesis.[44,45]

Hepatolithiasis

Hepatolithiasis is endemic in certain parts of the Far East with an incidence of 4% to 52% in East Asia, but is uncommon in the West with incidence ranging from 0.6% to 1.3%.[46] This condition is associated with recurrent pyogenic cholangitis and pigmented calcium bilirubinate stones within intrahepatic bile ducts. Distal common hepatic ducts feature chronic inflammation with epithelial cell death and increased proliferation.[47] Mucosal hyperplasia is frequently observed in hepatolithiasis. The incidence of cholangiocarcinoma in hepatolithiasis is reported to be 10%, and presentation occurs after several decades of repeated episodes of recurrent cholangitis, typically occurring after age 50 years. Tumor growth occurs along the stone-bearing bile ducts. It can take several years for the identified dysplastic lesions defined as BilIN mainly found in stone bearing bile ducts to progress to cholangiocarcinoma.[23,22]

Congenital lesions

Choledochal cysts are relatively uncommon. This congenital disorder is characterized by extrahepatic and /or intrahepatic bile duct dilatation. The biliary cysts are separated into 5 types based on Todani's classification.[48] Disease strictly limited to the intrahepatic ducts without involvement of the extrahepatic bile ducts is known as Type V or Caroli's disease. The incidence of bile duct cysts in this condition is ~1 in 13,000. The majority of cases are diagnosed in the first decade of life.[49,50] The incidence of malignancy is age-related and was reported to be 0.35% in children compared to 15.6% in adults with this condition.[51] Cancer occurs in the extrahepatic bile duct, in 50–62% of patients, gallbladder in 38–46%, and intrahepatic ducts in 2.5% of patient, with a small number in the liver and pancreas. 68% of cancers are reported to be associated with Type-I cysts, defined by dilatation of the extrahepatic ducts, and 21% with Type IV, defined by the combination of intrahepatic and extrahepatic bile duct dilatation. 7–15% of patients with Caroli's disease, Type V, develop cancer. [52,53]

An abnormal pancreatic-biliary junction is proposed as a contributor.[51] Cystic degeneration of the bile ducts results from the reflux of the pancreatic secretions leading to inflammation and structural damage of the bile duct wall which subsequently results in carcinogenic transformation. Due to inflammation the wall of the bile ducts is mostly replaced by fibrous tissue. Choledochal cysts are typically considered to be premalignant

lesions, and the entire biliary epithelium, even if not involved in cystic transformation, is considered at risk for malignant transformation.[52]

Genetic conditions

Lynch syndrome, also referred to as hereditary nonpolyposis colorectal cancer, has been associated with increased risk of cholangiocarcinoma. [54] Multiple biliary papillomatosis is another genetic disorder characterized by multicentric mucosal papillomatous lesions at various stages in the adenoma-carcinoma sequence. It affects extrahepatic and/or intrahepatic bile ducts. Because of the severe dysplasia often present in these lesions, it predisposes patients to significant risk of malignant transformation.[55]

Surveillance and screening

Early diagnosis of cholangiocarcinoma is difficult because signs and symptoms are often nonspecific. In patients with PSC, the clinical presentation of patients with early cancer may be indistinguishable from that of the underlying disease, and differentiating biliary dysplasia and reactive epithelial atypia caused by inflammation or by mechanical irritation due to stenting can be challenging. Unfortunately, many patients are diagnosed with advanced unresectable disease that carries a dismal prognosis.

Investigations for cholangiocarcinoma can include tumor markers and radiologic assessment of the biliary tree, including ultrasonography (US), computed tomography (CT), magnetic resonance imaging and cholangiopancreatography (MRI/MRCP), and endoscopic retrograde cholangiopancreatography (ERCP) along with biliary cytology.[9,56,41,57]

The most commonly used serum marker is serum carbohydrate antigen (CA)19-9. Charatcharoenwittaya et al. showed that a cutoff value of 20U/mL yielded sensitivity of 78% and specificity of 67% for detecting cholangiocarcinoma in patients with PSC. Increasing the cutoff value to 200U/mL improved specificity to 100% but decreased sensitivity to 13%. Thus, increasing the cutoff value allowed identification of cancer only at the advanced stages, while earlier stages of cancer could be identified when a lower value of 20U/ml was used.[37]

Contrast-enhanced magnetic resonance imaging with MRCP is the imaging method of choice if a ductal cholangiocarcinoma is suspected.[58,59] This test is able to depict infiltrative lesions with a higher sensitivity than US, and avoids the radiation and contrast exposure associated with CT scans. ERCP has potential morbidity related to complications such as pancreatitis and therefore is not recommended for surveillance testing. However, ERCP may be invaluable for investigation of worrisome findings such as dominant biliary stricture that are identified on noninvasive imaging. A dominant stricture in PSC occurs in 45–58% of patients with PSC.[60,61] These patients are noted to have tight stenosis either in the common bile duct or common hepatic duct. Such strictures often pose a diagnostic dilemma, as it can be difficult to differentiate benign strictures from cholangiocarcinoma. In order to exclude superimposed malignancy ERCP with brushings for cytology and targeted biopsies may be needed.

A cellular diagnosis of cholangiocarcinoma is often confounded by reactive changes in cytological studies from patients with PSC. This limits the sensitivity of ERCP with brush cytology for the diagnosis of cholangiocarcinoma, and results in a sensitivity of 8% for positive results alone and 46% for both positive and suspicious for malignancy results).[41] Fluorescence in situ hybridization (FISH) analysis can increase the diagnostic sensitivity over conventional cytology.[62] This involves the use of fluorescently labeled DNA probes that hybridize to chromosome 3, chromosome 7, chromosome 17, and the p16 gene on

chromosome 9. Nuclei with abnormal probe signal numbers (representing gain or loss of chromosomal loci) can be visualized by fluorescence microscopy. Detection of polysomy improves sensitivity to 38% for detection of malignancy and improves specificity to 98%. [41] There remains an unmet need for more effective tests for the detection of malignancy in patients with PSC.

In summary, although there are no formal recommendations, annual follow-up for cholangiocarcinoma surveillance in patients with PSC including a combination of MRI/MRCP plus serum CA 19-9 evaluation is suggested.[63] Patients with PSC who are found to have a dominant stricture, elevated CA 19-9, or change in clinical status or laboratory findings should undergo ERCP with biopsies, cytology and FISH analysis of the cytological specimens. Newer techniques such as immunohistochemistry for cell adhesion molecules P-cadherin and CD 24, molecules that are not expressed in normal or inflamed epithelium but are identified in dysplastic and cancerous tissue, are promising but require further validation. [64]

Role of Preemptive Surgery or Transplantation

Choledochal cysts and Caroli's disease

Several surgical options have been practiced in the past, including cyst marsupialization, internal cyst drainage via cystenterostomy with anastomosis to the either duodenum or jejunum. Hepaticojejunostomy is currently preferred since the complete excision of the cyst theoretically eliminates the exposed epithelium and decreases the lifetime risk of cholangiocarcinoma.[65] [66] In addition, the biliary tree is separated from the pancreatic duct thus, preventing the reflux of the pancreatic secretions into the biliary tree. Unfortunately, the risk of carcinogenesis is increased along the entire biliary tree and there is approximately 1% chance of developing cancer after the cyst excision. [67,52] Therefore life-long follow up of patients with choledochal cysts with radiologic imaging and laboratory testing. Segmental hepatectomy is performed in patients with symptomatic localized Caroli's disease.[68] Orthotopic liver transplantation is reserved for patients who develop cirrhosis, portal hypertension, and recurrent cholangitis.[53,68]

Primary sclerosing cholangitis

The only effective therapy for patients with end-stage liver disease due to PSC is liver transplantation.[69] Thus, PSC patients with cirrhosis, portal hypertension, or recurrent episodes of cholangitis should be referred for liver transplantation. The outcomes for liver transplantation are very good and comparable to other indications such as PSC and alcohol with 76% and 66% patient survival at 5 and 10 years.[70] This is in contrast to a dramatic drop in a 5-year survival post transplantation to 35% reported by Brandsaeter et al if cholangiocarcinoma was identified at the time of transplant.[71] Because of the challenges in timely diagnosis of cholangiocarcinoma in PSC patients and dismal outcomes Boberg et al recommended liver transplantation for patients who are found to have low and high-grade dysplasia identified on ERCP and cytology analysis.[72] Unfortunately, there is variable sensitivity in current testing and no risk factors or diagnostic tests that can reliably identify individuals at high risk for developing cholangiocarcinoma. As a consequence preemptive liver transplantation in PSC remains controversial and is limited by the scarcity of donor organs.[73–76]

Until recently, cholangiocarcinoma was regarded as a contraindication for liver transplantation. To date liver transplantation is reserved as a potential cure only for a very small highly selective group of patients who have malignant disease localized to the hilum and demonstrate lack of metastasis.[77] [78,79] In the Mayo Clinic experience with cholangiocarcinoma and underlying PSC were reported to have 73% five-year survival after

undergoing an established protocol of chemotherapy, radiotherapy followed by transplantation.[80]

The goal of future investigations is to identify molecular markers that would better define a group of people with PSC at risk of developing cancer that would lead to optimal timing and results of liver transplantation.

Conclusion

Biliary tract malignancies have a high mortality due to their refractoriness to conventional treatments and an inability to define preneoplastic states for early diagnosis. Several risk factors and conditions predisposing to cancer are known but the majority of these cancers occur sporadically, in the absence of known risk factors and early diagnosis remains elusive. Surgical intervention for treatment or prevention is extremely limited due to the absence of detectable preneoplastic lesions that be readily defined. An improved knowledge of the genetic and molecular changes that occurs during the formation of these cancers is needed and essential in order to improve the early diagnosis and treatment of these aggressive tumors.

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Abbreviations

BiIIN	Biliary intra-epithelial neoplasia
ERCP	Endoscopic retrograde cholangiopancreatography
FISH	Fluorescence in situ hybridization
IPN-B	Intraductal papillary neoplasm of the bile ducts
MRI/MRCP	magnetic resonance imaging / cholangiopancreatography
PSC	Primary sclerosing cholangitis

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