Cholangiocarcinoma in patients with primary sclerosing cholangitis

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Abstract
Primary sclerosing cholangitis (PSC) is an uncommon inflammatory disease that affects the bile ducts to produce cholestasis. Currently, the only treatment available is management of symptoms with ursodeoxycholic acid and liver transplantation. In addition to its relation to long-term cirrhosis, its natural history has an important association with cholangiocarcinoma (CCA), an aggressive neoplasia which is almost exclusive to this group of patients. Today CCA is the main cause of death of these patients, primarily due to the difficulty of diagnosis and the very limited treatment options.

This article discusses current ideas about this pathology and emphasizes the importance of appropriate screening with effective diagnostic tests (CA 19-9 and magnetic resonance cholangiopancreatography (MRC)) that help differentiate CCA from benign processes and can detect it in early stages when the probability of curative treatment is much greater.

Keywords
Primary sclerosing cholangitis, cholangiocarcinoma.

INTRODUCTION

Primary sclerosing cholangitis (PSC), first described in the 1850s, is a chronic, progressive, fibrosing and inflammatory disease that mainly affects the biliary epithelium. It produces stenosis, multifocal dilatations and destruction of the ducts of the entire biliary tree but especially of the medium and long ducts. This leads to cholestasis. (1-4)

Usually, patients are asymptomatic, but clinical manifestations commonly reported at the time of diagnosis include fatigue, fever, jaundice, pruritus and vague upper abdominal discomfort. (5) This pathology’s natural history can vary a great deal, but affected individuals eventually develop complications such as biliary cirrhosis and intra-abdominal malignancies. (1, 2, 4, 5) Currently there is no effective therapy, so the only treatment used is symptomatic management with ursodeoxycholic acid and liver transplantation. Nevertheless, the pathology recurs in 30% to 50% of patients within 10 years of transplantation which is a poor prognosis. (2, 5)

In the pre-transplant era, the main cause of death of PSC patients was liver failure, but currently it is cholangiocarcinoma (CCC). This aggressive and malignant neoplasm originates in cholangiocytes that may have intrahepatic, extrahepatic or hilar locations. The latter is also known as Klatskin’s tumor and is the most common accounting for approximately two thirds of all cases reported. (6-8)

Patients with PSC have a 5% to 10% lifetime risk of developing CCC: 398 times higher than the risk of the general population: (6, 9) While CCC is a rare gastrointestinal malignant tumor for the general population, for patients with PSC this comorbidity is of great importance and is the main cause of death. (6, 10)
EPIDEMIOLOGY

Although epidemiological data for PSC have significant geographical variation, recent studies of the general populations of the Netherlands, the USA, and the United Kingdom have reported prevalences ranging from 3.85 to 6 cases per 100,000 inhabitants and incidences ranging from 0.1 to 0.5 cases per 100,000 inhabitants. This suggests that the geographical variation initially described was skewed because data came from studies carried out in health centers that specialized in liver diseases. (6, 11, 12)

The association of PSC with inflammatory bowel disease (IBD) is well known and occurs in 60% to 80% of cases. It usually appears early and almost always manifests as ulcerative colitis on the right side. (5, 11) PSC patients are at four times the risk of death than are people in the general population. The main causes of death for these patients are cholangiocarcinoma (CCC) (32%), liver failure (18%), complications of liver transplantation (9%), and colorectal cancer (CRC) (8%). (13)

PSC is the most common predisposing condition for CCC in the Western world. (9) CCC occurs in 1% to 2% of PSC patients each year after diagnosis. CCC is often detected within the first three years after the initial diagnosis and has a cumulative risk of 20% thirty years later. (5, 13) Approximately 50% of CCC cases are diagnosed jointly with PSC or in the year after PSC is diagnosed. (13, 14) Nevertheless, the incidence of CCC in patients with PSC does not correlate with diagnosis at an early age, since the disease has a less aggressive phenotype in these cases. When PSC is detected later in life, it is more likely to be associated with hepatobiliary malignancies and liver decompensation. (15) Consequently, it is necessary to have a high index of suspicion of CCC once PSC is detected in older people. (6, 15, 16)

In addition, it has been documented that the simultaneous presence of IBD, especially ulcerative colitis, increases the risk of cholangiocarcinoma because the symptoms that are accompanied by Crohn's disease have more benign behavior. (6, 17) In terms of overall mortality, malignant hepatobiliary neoplasms account for 13% of cancer-related deaths. Of these, 10% to 20% are attributed to the CCC. Mean age of diagnosis is 50 years old, and CCC usually occurs before cirrhosis when it is associated with PSC (Figure 1). (13, 18)

PSC's incidence varies widely in different parts of the world depending on local risk factors. Incidence ranges from 0.5 to 1.5 cases per 100,000 inhabitants in the western world where PSC is the most important risk factor, but is 113 cases per 100,000 in Thailand due to the endemic presence of the Opisthorchis viverrini, a trematode parasite that has been recognized as a causative agent of CCC. (16)

Opisthorchis viverrini is a trematode or stave that has been considered to be a human carcinogen by the International Agency for Research on Cancer since a positive direct correlation was found between the incidence of CCC and the prevalence of O. viverrini infections in various regions of Thailand. It infects humans as well as cats and dogs that consume raw or undercooked freshwater fish, especially carp (Cyprinidae family), in their diet (second intermediate host). The metacercariae, the encysted larva, of the parasite contained in the fish flesh is ingested by a person (definitive host) and hatch in the duodenum. They migrate through the ampulla of Vater to the bile duct where they mature and become adults that can live up to 20 years. There they generate asymptomatic chronic infections (20-40 years), advanced periductal fibrosis, cholecystitis and/or CCC (19-21).

Eight million people are infected with this parasite, mainly in Thailand, Laos, Cambodia, Vietnam, China and Korea. Five thousand of them have CCC (figures from Thailand). It develops through three key mechanisms: mechanical damage in the epithelium of the ducts caused

Figure 1. Natural history of primary sclerosing cholangitis. CCC in patients with PSC is often detected within the first one to three years after initial diagnosis at an average age of 50 years. It usually occurs earlier than cirrhosis. PSC: primary sclerosing cholangitis.
Review articles

are probably related to the development of cancer. (9, 18)

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pathways that increase cell proliferation. In addition, muta
and metastasis. (18) Cholestasis also activates signaling
mediator of the stroma which regulates tumor invasion
growth factor which has been postulated as a paracrine
enzymes responsible for DNA repair and hepatocyte
is activation of nitric oxide synthase mediated by inflam
response to the infection which leads to inflammation-rege
ation-fibrosis, and molecules excreted секретed by the
parasite that cause toxic or carcinogenic effects in the host.
One of these substances is granulin, a parasite growth factor
that causes human cells to proliferate. (19-21)

Currently there is no vaccine against infection by this
parasite. However, pharmacological treatment with a single
40 mg/kg dose of praziquantel, an anthelmintic used in pre
ventive chemotherapy, has a cure rate of 96%. Nevertheless,
excessive use of this medication can reduce its efficacy and
induce inflammation of the biliary system. In addition, despit
the fact that the parasite is eliminated from the organ
ism, the hepatobiliary changes generated are not always res
olved in those treated and reinfections occur frequently.
(19-21) This is information of great importance since con
sumption of raw and imported fish in our environment has
increased in recent years. (22)

PATHOGENESIS

Although the pathophysiological mechanisms that lead to
the development of PSC are not completely known, it is
recognized that it is a disease caused by environmental tri
gers in genetically susceptible people. (23) To date, exist
ence of a genetic predisposition mainly associated with
some variants of HLA has been reported. Possibly, a bac
terial translocation alters the microenvironment of hepato
cytes occurs. This, plus toxicity caused by retained bile and
the development of an abnormal immune response are crit
ical factors in the genesis of this pathology. (16, 24, 25) All
of these factors lead to the establishment of a continuously inflamed microenvironment that alters many things includ
ing cell division. The sequence of inflammation-dysplasia-
carcinoma is probably the origin of CCC in people with
PSC. Inflammation through DNA damage, evasion of apo
ptosis, promotion of cell proliferation and neoangioge
sall work to create a carcinogenic niche. Recent work has
highlighted inflammatory pathways essential roles not only
in the development of cancer, but also in invasion and
migration of tissues. (18)

Another more specific factor reported in the literature
is activation of nitric oxide synthase mediated by inflam
matory cytokines. This damages DNA and inhibits both
enzymes responsible for DNA repair and hepatocyte
growth factor which has been postulated as a paracrine
mediator of the stroma which regulates tumor invasion
and metastasis. (18) Cholestasis also activates signaling
pathways that increase cell proliferation. In addition, muta
tions in isocitrate dehydrogenase have been associated with
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DIAGNOSIS

Early diagnosis of CCC is the fundamental pillar of com
prehensive management of PSC patients because, as described in
this article, its aggressive behavior is the main cause of death
in this group of patients. Nevertheless, diagnosis is currently a
challenge for the treating medical team because CCC can be
easily confused with benign alterations of the bile duct. As a
result, it is often diagnosed in late stages after neoplastic inva
sion has already occurred. This limits therapeutic possibilities
even more and casts a shadow over the prognosis. (26)

Various studies have reported that factors such as smo
king, alcoholism and certain genetic variants increase the
risk of suffering from CCC. (16, 27) However, the clinical
usefulness of this is low due to the high incidence of this neoplasm in all patients with PSC. For this reason, routine
screening is recommended in all cases regardless of the pre
sence or absence of other risk factors. (16)

Currently there is no fully sensitive and specific test for
diagnosis of CCC, nor are there guidelines that propose
an evidence-based approach to monitoring these patients.
(28) However, the literature discusses several proposals for
this purpose that combine different modalities of diagno
stic tests to increase their diagnostic yield (Figure 2).

Monitoring should begin with noninvasive measures
such as imaging studies at regular intervals. Hepatobiliary
ultrasound or magnetic resonance cholangiopancreatogra
phy (MRCP) are useful methods although MRCP is better
for identifying small lesions. In addition, it provides infor
mation on the intensity and enhancement of lesions which
may help differential diagnosis. This is why it is considered
the ideal study. (29) In statistical terms, MRCP’s sensitivity
is 89%, and its specificity is 75%. Hepatobiliary ultrasound’s
sensitivity is 53%, and its specificity is 94% according to a
study published in 2008. (30)

Either of these strategies can show whether or not there
is a dominant mass, polyp, or stenosis of the biliary tree
(defined as a narrowing of the diameter of the common
bile duct to 1.5 mm or less, and/or narrowing of the diame
ter of hepatic ducts to 1 mm or less). Any of these findings
increase the suspicion of CCC, but do not confirm it. (31)
In these cases it is useful to perform endoscopic retrograde
cholangiopancreatography (ERCP) accompanied by brush
cytology of the stenotic parts to clarify the diagnosis. (32)

A metaanalysis covering 747 subjects with PSC that was
published in 2014 showed that positive results of brush
cytology for CCC had a sensitivity of 43% and specificity of
93%. Nevertheless, it is important to note that this proce
dure may yield indefinite findings of atypical cells or other
suspicous characteristics rather than definitive malignancy.
When this happens there are no established guidelines for
management. (32)
Currently, the most widely used strategy to increase the yield and accuracy of cytology is fluorescence in-situ hybridization (FISH). This tool is based on the ability of nucleic acids to hybridize with complementary strands and works by making probes that bind to specific sequences of the chromosome and emit fluorescence. (33) Among its applications is identification of aneuploidies in the cells of the sample which may suggest the presence of CCC. It was shown that the use of cytology and FISH together for detection of CCC has a sensitivity of 46% and a specificity of 88% when chromosomal polysomy was found. (26, 34)

So far, the only biomarker routinely recommended is carbohydrate antigen (CA) 19-9. This serves as an alternative or complement to imaging, but its yield is not the best because in the presence of CCC it may be normal, or in cases of cholangitis it may increase. (26) Various measurements have been proposed as cut-off points for screening tests: values greater than 20 IU/mL report a sensitivity of 78% and a specificity of 67%, while those greater than 130 have a specificity of 100% but a sensitivity of only 13%. (26, 34) However, it should be kept in mind that approximately 7% of patients with PSC present a polymorphism in the FUT3 gene so that they do not express the epitope of CA 19-9. (35)

These screening procedures should be performed throughout the course of the disease but especially during the first two years. This is when the incidence of CCC is greatest, when symptoms worsen, and when there are changes in serum cholestatic parameters and rapid or persistent increases in CA 19-9. (26, 28)

**TREATMENT**

Available therapy for CCC can be classified as either curative or palliative. Curative therapy is based on surgical resection, but this is only viable in 25% to 35% of cases since it is only useful for local tumors which have not metastasized to lymph nodes. Liver function should also be preserved since cirrhosis and portal hypertension are markers of a poor prognosis. (36, 37)

Studies show that 5-year survival rates for resection of well-selected CCC patients range from 27% to 44%. In addition, complementing surgical intervention with adju-
vant chemotherapy or radiation therapy to improve the yield of surgery has been postulated. (38)

The second curative intervention is liver transplantation although CCC was considered to be an absolute contraindication for transplantation in the past. Now patients with early stages of the disease, especially with perianal CCC of less than 3 cm can receive a transplant. When transplantation is supplemented with adjuvant therapy the rate of survival free of recurrence is 65%. (39, 40)

There are also local therapeutic strategies such as photodynamic ablation by, external radiation therapy, radioembolization, and high doses of brachytherapy. Nevertheless, most evaluations have been based on small samples of patients or have been retrospective studies that have not allowed for high quality information that could support their use and provides information on possible short and long term adverse effects. (38)

Palliative therapy seeks to improve patients’ general conditions and/or lengthen life expectancy. A clinical trial in 2010 showed that systemic chemotherapy, consisting of the combination of cisplatin and gemcitabine, increase life expectancy by three to six months. These results were later reproduced in a Japanese study. (41, 42) For patients with renal failure, it has been proposed that oxaliplatin replace cisplatin in this scheme. (43) Similarly, gemcitabine monotherapy is recommended in elderly patients whose general health is compromised. A reviewing the use of second-line drugs has found a proposal to use fluoropyrimidines, but currently there is not enough information to validate this application. (44)

Finally, malignant obstruction of the bile duct is a late complication of different types of neoplasms including CCC. Nowadays, endoscopic stenting is recommended for temporary improvement of jaundice and pruritus secondary to obstructions of the bile duct. (26)

PERSPECTIVES

Bearing in mind that the success of curative therapy depends on the stage at which CCC is diagnosed, current research focuses on the development of efficient and minimally invasive diagnostic methods. These include proteomic studies of urine, serum and bile that detect specific peptide panels correlated with CCC, use of non-coding microRNAs as biliary biomarkers of malignancy, and analysis of extracellular microvesicles in bile samples to differentiate benign from malignant stenoses. (10, 45)

It has been found that treatment using molecules such as epithelial growth factor and vascular endothelial growth factor has not provided positive results. (44) Consequently, the need to conduct studies that offer better possibilities for patients with PSC and CCC is recognized, and it is hoped that there will be further progress in this or other areas of research.

REFERENCES

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