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Cholangiocarcinoma: risk factors and clinical presentation

M. GATTO, D. ALVARO

Department of Clinical Medicine, Division of Gastroenterology, "Sapienza" University of Rome, Polo Pontino, Rome (Italy)

Abstract. – Cholangiocarcinoma (CCA), a cancer originating from the neoplastic transformation of the biliary epithelium, is characterized by a progressive increase in incidence and prevalence. A number of risk factors have been identified including primary sclerosing cholangitis, liver fluke infestation, and hepatolithiasis. More recently, hepatitis viruses (HCV, HBV) have been taken into consideration as risk factors for the intrahepatic CCA and this could explain the increased incidence seen in the last two decades. All these risk factors induce chronic inflammation in the biliary epithelium together with partial bile obstruction. These two conditions are considered the background (chronic inflammation) favouring the cancer development. The only effective treatment is the radical surgical resection but, this is applicable in less than 40% of the patients since CCA is mostly diagnosed at an advanced stage. This mainly occurs because, in the majority of the cases, CCA is clinically silent, with symptoms only developing at an advanced stage but also for the lack of effective biomarkers to be used for a screening purpose. A number of serum and bile biomarkers have been recently proposed for the diagnosis of CCA but, their impact on the early diagnosis is still under the evaluation.

Key Words:

Cholangiocarcinoma; Cholangiocytes; Proliferation; Apoptosis; Growth factors.

Introduction

Cholangiocarcinoma (CCA) is a malignant tumor arising from the malignant transformation of cholangiocytes, the epithelial cells lining the biliary tree. CCA is the second most common primary hepatic malignancy whose recent epidemiologic studies suggest a progressive increasing incidence in Western countries[1]. CCA is characterized by a bad prognosis, with a median survival of less than 24 months[2] and a scarce response to chemotherapy[3-9]. From the anatomic point of view, CCA is classified as intrahepatic (IH-CCA) or extra-hepatic (EH-CCA), the latter being further divided into proximal or perihilar and distal depending on the location of the cancer within the extra-hepatic biliary system. Perihilar CCA is also known as Klatskin tumor. Three different growth patterns of EH-CCA can be observed: (1) periductal infiltrating, (2) papillary or intraductal, and (3) mass forming[10]. IH-CCA typically presents as an intrahepatic mass. The only curative therapy is surgical resection or liver transplantation but, unfortunately, the majority of the patients were diagnosed at an advanced stage, when the surgical therapies are excluded. This should stimulate researches on the identification of effective surveillance strategies that would permit detection of early CCA or, better yet, premalignant lesions in patients at increased risk, particularly patients with primary sclerosis cholangitis (PSC). Serum and bile tumor markers, non invasive and endoscopic-based imaging modalities, and histology and cytology have been attempted with varying success[11].

This review deals with the most recent advances on the risk factors and clinical presentation of CCA.

Risk Factors

A number of different risk factors have been definitively identified. Primary sclerosing cholangitis (PSC) is the major risk factor for CCA in the Western society[12-15]. Different cohort and multicentric studies have demonstrated that, in 50% of CCA, the diagnosis occurs together with the identification of PSC or detected during the first two years of follow-up, with an annual incidence rate of 0.6-1.5%[12-15]. In 30-42% of PSC cases, CCA is often found incidentally at autopsy or in the explanted livers of patients submitted to transplantation.

Corresponding Author: Domenico Alvaro, MD; e-mail: domenico.alvaro@uniroma1.it

An European multicenter study[14], including 394 PSC patients from five European countries with a median follow-up of 18 years, have demonstrated that the majority of CCA cases (50%) was diagnosed within the first year after the diagnosis of PSC and in 27% of the cases at intended liver transplantation. There was no correlation between the incidence of CCA and the duration of PSC. The coexistence of inflammatory bowel diseases and their duration confer an additional risk of CCA development in PSC patients. In an onother study conducted at the Mayo Clinic[12], 161 patients with PSC who did not have CCA at study entry were followed for a median of 11.5 years and 6.8% of patients developed CCA. The rate of CCA development was approximately 0.6% per year. Compared with the incidence rates of CCA in the general population, the relative risk of CCA in PSC was significantly increased. In contrast with the European multicenter study, no association was found between CCA incidence in PSC patient and coexistence of ulcerative colitis or with its duration. Also in this study, the majority of CCA cases were diagnosed during the first 2.5 years after the initial PSC diagnosis[12]. Therefore, patients who present with their first diagnosis of PSC should be carefully screened and regularly followed-up for CCA development mainly during the first two years after PSC diagnosis. Unfortunately, no follow-up strategy of patients at risk have been yet validated. Recently, an algorithm based on Ca19-9 serum levels combined with cross-sectional liver imaging was proposed by Charatcharoenwitthaya et al[16], for screening and surveillance of patients with PSC. In this research, the combination of serum CA 19-9 with either CT, MRI, MRCP or ERCP show the best sensitivity (~100%) but a low specificity (~40%) in diagnosing CCA occurring in PSC patients. In contrast, the combination of serum CA19-9 and ultrasonography (US) had intermediate specificity (62%) with a good sensitivity (91%) for detecting CCA. On the basis of test properties, cost and availability, combination of serum CA 19-9 (cut-off value of 20 U/mL) and abdominal US at 12-month intervals was proposed as useful strategy for the screening/surveillance of CCA in PSC[16]. In PSC patients[12-15], older age at PSC diagnosis, history of colorectal dysplasia or carcinoma, smoking, and current or former alcohol use (>80 g/die), have all been suggested as additional risk factors for CCA development.

Liver fluke infestation is one of the most important risk factor for CCA in east countries. Both epidemiologic and experimental data strongly support the role of parassitary[17,18] or bacterial infections (i.e., *Opisthorchis Viverrini*, *Clonorchis Sinensis*, *Schistosomiasis Japonica* and *Salmonella Typhi*) as risk factors for CCA development in endemic regions of Asia. Certain xenobiotics may lead to increased risk of CCA. Iatrogenic exposure to thorotrast (thorium dioxide), a radiocontrast agent used in the 1950s and 1960s, first led to reports of CCA in the 1970s[21,22]. Since that time, hundreds of cases of CCA (as well as other primary hepatic malignancies) owing to thorotrast exposure have been described.

Caroli disease, congenital choledocal cist[23-26], Vater ampulla adenoma, intra-hepatic lithiasis[27-29] and abnormal biliary-pancreatic junction are additional risk factors for CCA. Recent retrospective study has suggested that an abnormal pancreatic-bile duct junction, with a common channel length of 8-15 mm, can influence the degree of pancreatic fluid regurgitation, resulting in an increased incidence of biliary tract malignancy. The abnormal junction was found in 44.8% of CCA respect to 6.2% of controls ($p<0.01$)[30]. From a pathogenetic point of view, it has been considered that lysolecithin, formed as consequence of the mixing between pancreatic juice and bile, acts as detergent on the biliary epithelium favoring chronic inflammation[31]. This mechanism has been also considered for the patients submitted to bilio-enteric surgical drainage for benign diseases which represent another well recognized category at risk. In contrast to this latter category, patients submitted to endoscopic sphinterotomy during Endoscopic retrograde cholangiopancreatography (ERCP) do not express increasing risk of CCA and this has been definitively demonstrated in three different studies performed in large series of patients with long follow-up[32-34].

Several case-control studies have described an increased risk of CCA in patients with chronic hepatitis C virus (HCV) infection[35,36], and HCV RNA has been detected in the biliary epithelium of resected CCA[37]. A prospective study of 600 HCV-infected individuals in Japan between 1980 and 1997 (median follow-up 7.2 years), detected a 2.3% incidence of CCA, which is well above the baseline population incidence[38]. Although hepatitis B virus nucleic acids have been detected in selected cases of CCA[39], an association between hepatitis B virus infection and CCA is less well established[17,35,38,40,41]. Multiple case-control

analyses have reported an association between CCA and alcohol use[35]. More recently, obesity, diabetes[28,42] and smoking have been taken into consideration especially for intra-hepatic CCA but further confirmation is need.

Clinical Presentation

CCA patients diagnosed with early bile duct cancer and submitted to radical surgery have a survival >80% after 5 years[43]. This means that an early diagnosis is imperative but, unfortunately, most CCA are diagnosed at advanced stages when radical surgery is not allowed. Late diagnosis is generally caused by the fact that CCA is, in the majority of cases, clinically silent, with symptoms only developing at an advanced stage but also for the lack of effective serum biomarkers to be used for screening purpose[43-45]. Clinical presentation largely differs between extra-hepatic and intra-hepatic CCA and depends on the degree of biliary obstruction (Table I). Patients with extra-hepatic CCA usually present with symptoms of biliary obstruction, including painless jaundice, pale stools, dark urine, and pruritus[3,44,45]. In less than 10% of cases, extra-hepatic CCA presents with the clinical manifestation of acute cholangitis and more rarely with paraneoplastic syndromes including, diabetes, hypoglycemia, hypercalcemia, porphyria cutanea tarda, migratory thrombophlebitis or acantosis nigricans. As far as the intra-hepatic CCA is concerned, the most frequent clinical presentation is related to symptoms typical of hepatic mass, including abdominal pain, malaise, night sweats, and cachexia. In a study summarizing a 7-years experience of a single centre[46], the age at presentation was found to be higher for distal CCA than peri-hilar or intra-hepatic CCA. In addition, as expected, bilirubin serum levels were lower, at presentation, for the intra-hepatic CCA than for the hilar or distal form[46]. A well know clinical manifestation of CCA is the "atrophy-hypertrophy complex" presenting as palpable prominence of one hepatic lobe[47]. Unilobar biliary obstruction with ipsilateral vascular thrombosis has demonstrated to be the cause of this syndrome with vascular thrombosis having a sensitivity of 90% and a specificity of 97% for identification of the syndrome.

Table I. Cholangiocarcinoma clinical presentation.

Extra-Hepatic CCA	Intra-Hepatic CCA
• Painless, jaundice 90% • Cholangitis 10% • Rare: – Paraneoplastic syndromes – Diabetes – Hypoglycemia – Hypercalcemia – Porphyria cutanea tarda – Migratory thrombophlebitis – Acantosis nigricans	• Aspecific symptoms: – Abdominal pain – Diminished appetite – Weight loss – Malaise – Night sweats • Cholestasis • Incidental mass

More detailed information is available for CCA complicating the course of PSC[12-14,48,49]. In these patients, CCA may represent an incidental finding at transplantation or surgery or during radiological or endoscopic follow-up. In other PSC patients, CCA may emerge as unexplained biliary tract stricturing during follow-up or as deterioration of PSC clinical conditions (new fevers, weight loss, worsening of jaundice, persistent upper abdominal pain, intractable pruritus). In a multicenter study[48], including 370 PSC patients followed up to 24 years and with 48 CCA detected, the modality of CCA presentation includes: inoperable tumours (25%), incidental findings at transplant (22%), primary sclerosing cholangitis follow-up (18%, dominant strictures), transplant work-up (10%), transplant waiting list (10%) and incidental finding at cholecystectomy (2%). At the moment of CCA diagnosis, 22/48 CCA patients were candidates to radical treatment (transplantation or radical surgery) but, neither clinical manifestation nor serum markers or biochemistry allowed discrimination of these patients with respect to patients diagnosed at advanced stages during follow-up. Therefore, the message of this study is that clinical manifestations and biochemistry fail to help for early diagnosis of CCA in PSC patients[48].

The "cholangiocarcinoma committee" of Italian Association for the Study of the Liver (AISF) just concluded an Italian survey on CCA clinical presentation, diagnostic modalities and treatment strategies. Approximately 1/3 of CCA cases diagnosed in Italy in a 12 month period (i.e., 180 cases) have been recorded and analyzed. In our proposal, findings of this study should shortly furnish detailed information on important clinical features of this cancer.

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