Best Practice & Research Clinical Gastroenterology 29 (2015) 245–252

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

3

Clinical presentation, risk factors and staging systems of cholangiocarcinoma

Ruben R. Plentz, MD, PD *, Nisar P. Malek, MD, Prof.

Department of Internal Medicine I, Medical University Hospital, Otfried-Müller-Str. 10, 72076 Tübingen, Germany

Keywords:
Cholangiocarcinoma
Risks
Staging systems
Symptoms

A B S T R A C T

Cholangiocarcinoma (CCA) is the second most common primary liver tumour. Intra-hepatic CCA develops within the liver parenchyma while extrahepatic CCA involves the biliary tree within the hepatoduodenal ligament. Hilar CCA are also called Klatskin tumour. The CCA incidence has increased worldwide over the last years, but there are also geographic differences, with focus in Asian countries. Known risk factors are primary sclerosing cholangitis (PSC), hepatolithiasis, Caroli's disease, hepatitis B and C infection, liver flukes, cirrhosis, diabetes, obesity, alcohol consumption and probably tobacco smoking. Patients with early CCA have only little discomfort, but can later show episodes with jaundice and other non-specific tumour symptoms. For the staging of the disease different classifications are available, which consider various factors like tumour size, location, regional lymph nodes, metastasis, vascular involvement and tumour marker.

Cholangiocarcinoma (CCA) represents the second most common primary hepatobiliary cancer [1]. Most CCA tumours are adenocarcinomas arising from epithelial cells lining the intra- and extrahepatic biliary tract system [2]. Hilar CCA are also called Klatskin tumour and they are located within 2 cm from the bifurcation of the common duct [3]. Worldwide epidemiological data have shown an increasing incidence of CCA, most of the increase occurred after 1985, but the reasons for this are only poorly

* Corresponding author. Medizinische Universitätsklinik, Department of Internal Medicine I, Otfried-Müller-Str. 10, 72076 Tübingen, Germany. Tel.: +49 7071 29 82701; fax: +49 7071 29 2095.
E-mail address: Ruben.Plentz@med.uni-tuebingen.de (R.R. Plentz).

http://dx.doi.org/10.1016/j.bpg.2015.02.001
1521-6918/

understood [4]. In the following section we would like to summarize in detail the leading clinical symptoms of patients with CCA, we will discuss possible risk factors and will give an overview about the current staging systems for this deadly disease.

Clinical presentation

Patients with early onset of CCA have no or no typical symptoms. However, during the course of the disease patients with extrahepatic CCA develop jaundice. Often other non-specific symptoms like weight loss, abdominal pain, night sweats, fatigue, emesis, vomiting, loss of appetite, pruritus and increase of cholestasis related lab parameters (ALT, AST, GGT, Bilirubin) are recognized [5,6].

Risk factors

Many risk factors have been identified and they are quite variable in different areas of the world, but nearly 70% of all cases are sporadic [7,8]. One of the most striking risk factors is primary sclerosing cholangitis (PSC) with or without ulcerative colitis (UC) [9]. PSC is an autoimmune disease which involves both the intra- and extrahepatic bile duct system [10]. PSC can cause bile duct strictures, dilatations and can develop malignancies of the bile duct system [9,10]. In populations based series the life-time incidence to develop CCA ranges from 6 to 36% and the cumulative incidence is between 7 and 14% [11–15]. In a prospective study by Rosen et al. 70 patients were recorded for 30 months with PSC on average 42% of the autopsies and thus at least 7% of all patients developed a CCA [16]. Approximately 50% of CCA are diagnosed within the first year of diagnosis of PSC, but the CCA incidence decreases over time [12,13,17]. PSC develops mainly tumours in the hilar area of the bile duct system [10]. CCA complicates PSC in ca. 10% of all cases, possible risk factors for this subgroup are: high bilirubin, variceal bleeding, smoking, alcohol and inflammatory bowel disease like ulcerative colitis (UC) or Crohn's disease (CD) [9,18]. It still remains unclear how the coexistence of inflammatory bowel diseases with PSC increases the CCA risk compared to PSC alone. CCA occurred nearly twice as frequently in patients with UC as in CD [17]. Interestingly, persistent biliary candidiasis in patients with PSC was recently discovered as a new risk factor for CCA development [19]. However, further possible subgroup risk factors for PSC and CCA are still likely but not identified yet.

More than 50 years ago it was also reported that intrahepatic CCA development is strongly associated with hepatolithiasis [7,20,21]. Hepatolithiasis are calculi or concretions often located at the confluence of the right and left hepatic ducts. Hepatolithiasis was found in 5–65% of patients with CCA, but they are rare in Western countries (incidence to 1.3%) [22,23]. The incidence of intrahepatic CCA in patients with hepatolithiasis is reported to be 4–11% [24]. CCA development is very likely caused by chronic inflammation of the bile duct system [25]. Studies from Korea and China showed significant associations between hepatolithiasis and intrahepatic CCA [26,27]. In addition, Asian patients with hepatolithiasis are co-infected with parasites like *Clonorchis sinensis* and *Ascaris lumbricoides* [28]. Liu et al showed that significant risk factors for developing CCA in hepatolithiasis were smoking, family history of cancer, appendectomy in childhood and duration of symptoms longer than ten years [29]. Also patients with gallstones have an increased risk to develop CCA. The risk of extrahepatic CCA increases with the size of gallstones, calcification of epithelium and duration of disease [30]. An Italian study group described that, among 161 patients with hepatolithiasis, 23 developed CCA during the observation period of 14 years [23]. Welzel et al showed a significant association between choledocholithiasis, cholangitis and intrahepatic CCA development in a Danish patient cohort [31]. However, this study did not exclude patients with PSC and therefore provides only incomplete information.

Caroli's disease is a congenital disorder and was first described 1958 and is characterized by segmental communicating saccular dilation of the large intrahepatic bile ducts. Caroli's disease generally starts with bacterial cholangitis and is associated with hepatolithiasis [32,33]. Caroli's disease must be distinguished from the Caroli-Syndrome. The latter is a combination of cystic bile duct disease with congenital hepatic fibrosis [34]. In a German cohort of 33 patients with Caroli's disease, CCA was detected in three patients [35]. A study from Argentina showed that one patient out of 24 patients had CCA and Caroli's disease [36]. Besides these, other case reports with a significant