Differential Diagnosis

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9.1 Introduction

The differential diagnosis of hilar cholangiocarcinoma (HCCA) that include primary malignancies, metastatic disease and benign lesions is challenging and presents a diagnostic dilemma in surgery. Generally, biliary tumors are accompanied by painless jaundice with evidence of biliary obstruction [1, 2]. Currently, this presentation by itself is usually enough to raise a strong suspicion of neoplastic biliary obstruction. The clinical findings and laboratory values including tumor markers are non-specific and cannot correctly identify the exact cause of the stricture. Thus, preoperative differential diagnosis, which is desirable to confirm surgical indication and to advise patients about the disease and their respective prognosis, is extremely difficult. Although the assessment of patients with obstructive jaundice has greatly improved by the currently available noninvasive, and invasive imaging modalities, all these techniques cannot always be relied upon to provide a definitive diagnosis, in particular in the absence of a visible tumor mass [3]. In addition, it is well known that not all hilar obstructions are due to HCCA and alternative diagnosis that mimic HCCA may count for up to 25 % of all hilar obstructions [4–7]. Benign strictures for example, occasionally manifest as focal areas of wall thickening that obstruct the lumen and, thus, mimic malignant strictures. Approximately 16 % (range, 3.4–58.6 %) of patients initially diagnosed with hilar cholangiocarcinoma proved to have a benign stricture [3–20]. Biopsy is so often nondiagnostic that decisions about therapy are usually made on the basis of the imaging tests and lack of evidence for some other disease [3, 4, 21–26]. Although specific radiographic features, such as absence of tumor mass, smooth concentric pattern or tapering of the bile duct, can be associated with benign lesions, none can unequivocally exclude the presence of malignancy [6]. As a result, differentiating HCCA related biliary obstructions (Fig. 9.1) from obstructions caused by other malignant (Figs. 9.2 and 9.3) and benign (Figs. 9.4 and 9.5) lesions remains a challenge. Because the majority of biliary strictures at the liver hilum in the absence of previous surgery are usually malignant in nature and presumed to be due to HCCA, a reasonable approach is to assume the presence of HCCA until proved otherwise [15, 27–29]. However, surgeons should always be aware of the possibility of other disease particularly a benign disease and advise their patients appropriately. The diagnosis is much less specific than is generally thought, so there is considerable opportunity for mismanaging such patients. Although it has always been clear that basing the diagnosis on indirect evidence would occasionally be incorrect, a 25 % rate of false diagnosis by a team of highly specialized clinicians who encounter many such complicated cases is higher than most would have expected. Alternative diagnosis with proximal biliary obstruction mimicking HCCA is present in such a proportion of patients that it really deserves a place in the differential diagnosis of biliary obstruction. Differentiating HCCA from other causes of obstructive jaundice is important because of the differences in treatment. Curative surgical therapy for HCCA requires bile duct resection with concomitant major hepatectomy and caudate lobe resection or neoadjuvant chemoradiation, followed by liver transplantation in highly selected patients [30, 31]. This type of surgery is generally not necessary for benign conditions and generally not warranted for metastatic

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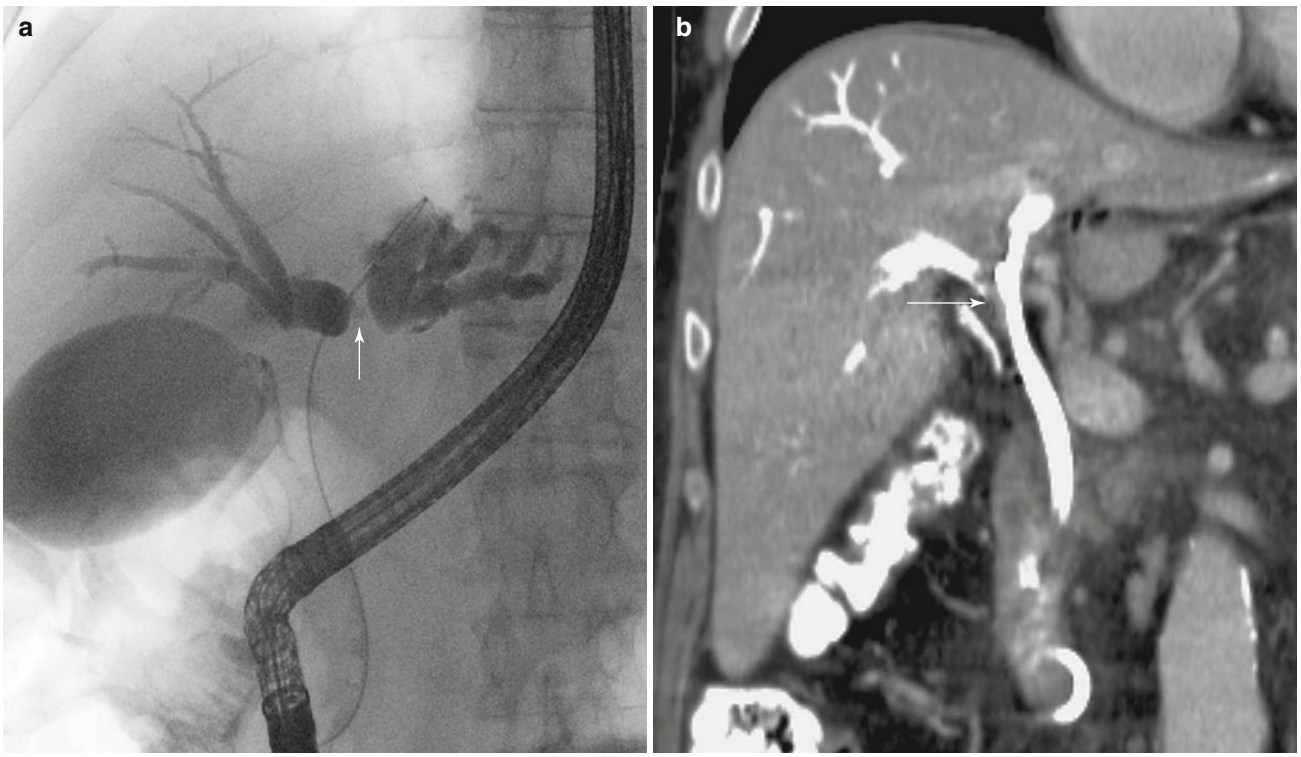

Fig. 9.1 (**a**) ERCP image from a patient with obstructive jaundice caused by histologic proved HCCA demonstrating complete obstruction at the hilar confluence level (*arrow*) with upstream ductal dilatation; (**b**) multiplanar reconstructed CT image of the same patient demonstrating intrahepatic biliary dilatation with a mass-forming lesion (*arrow*) at the confluence and stent placed across the lesion

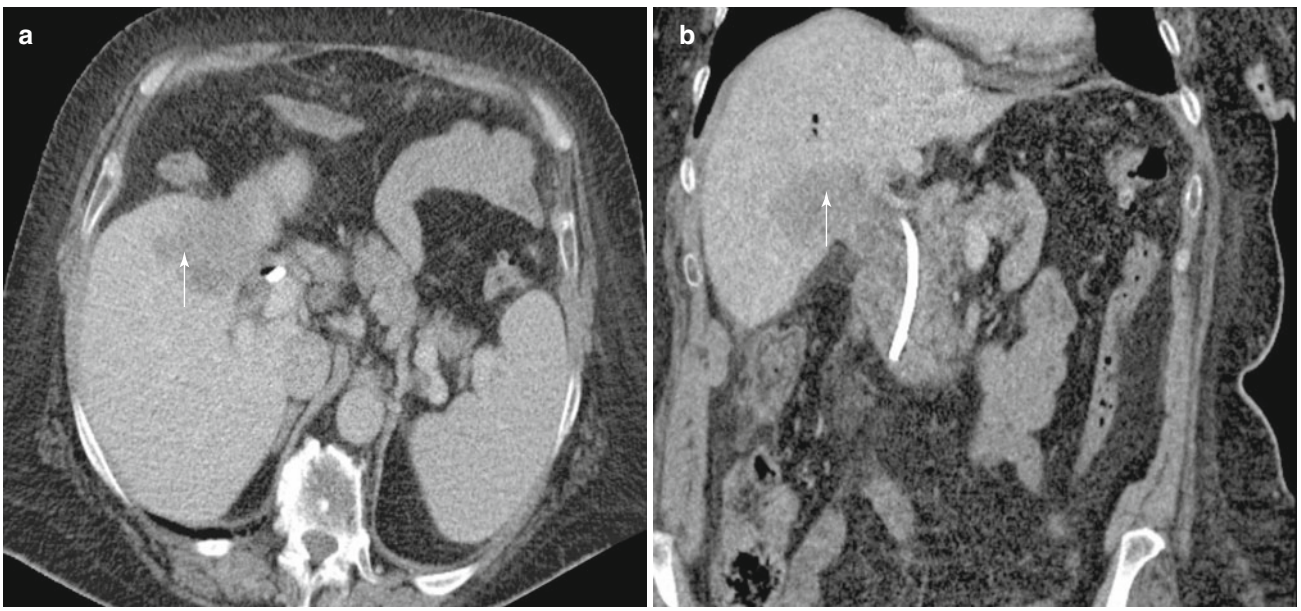

Fig. 9.2 Computed tomographic (CT) scans in the axial (**a**) and multiplanar reconstruction in the coronal plane (**b**) from a patient with carcinoma of the gallbladder (*arrow*) filling the entire gallbladder and invading the liver hilum and adjoining right lobe

or other non-HCCA malignancies. Thus, preoperative precise characterization of obstructive jaundice due to hilar obstruction has important clinical implications. It would potentially improve planning for surgery and may prevent subjecting some patients to major and risky surgical interventions unnecessarily.

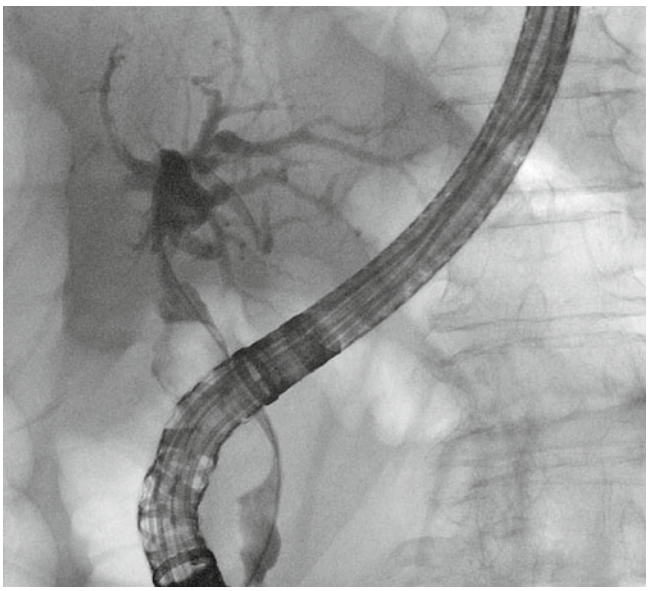

Fig. 9.3 ERCP of the same patient shows intrahepatic ductal dilatation indicating invasion of the common bile duct und thus resembles HCCA. An ERCP stent is placed across the lesion in to the left duct as this provides drainage of the future remnant liver following resection

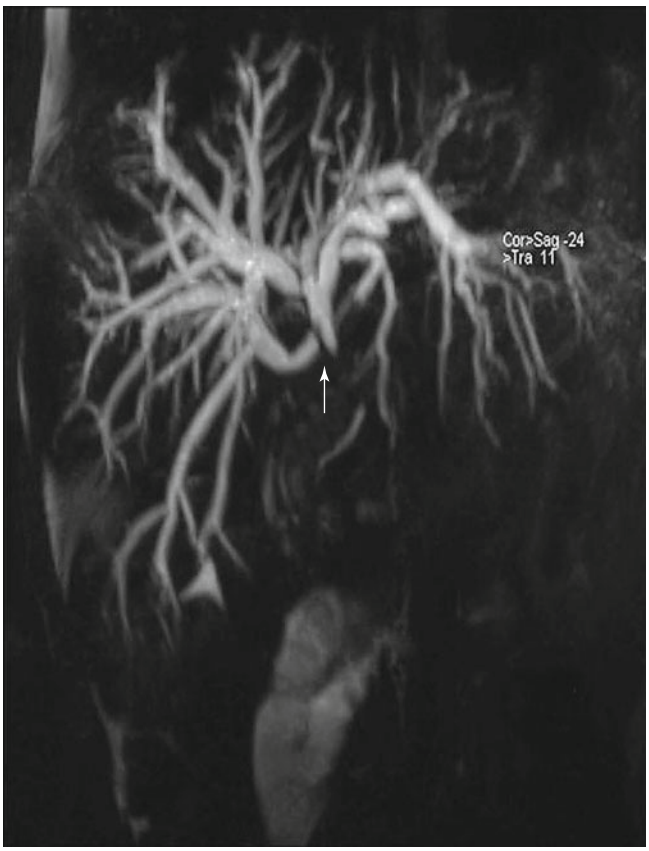

Fig. 9.4 Coronal image from color-coded 3D T2-weighted MRCP image from a 22-year-old patient with progressive jaundice demonstrating complete obstruction at the hilar confluence (*arrow*) with intrahepatic biliary dilatation in both the left and right lobes of the liver. Hilar cholangiocarcinoma was suspected. The patient was treated with extended right hepatic lobectomy with removal of the biliary confluence. Histology revealed a chronic inflammatory stricture of the Confluence including the right duct with no evidence of malignancy

9.2 Type of Malignant Lesions Mimicking Hilar Cholangiocarcinoma (HCCA)

9.2.1 Carcinoma of the Gallbladder

Because of the intimate anatomic relationship of the biliary confluence to the gallbladder, carcinoma of the gallbladder in some cases involves the hepatic hilum, either through direct extension or from metastatic spread. In some studies it was the most common non-HCCA malignancy involving the biliary confluence, accounting for more than 50 % of alternative diagnosis [15]. While 45 % of patients with carcinoma of the gallbladder present with jaundice as a marker of advanced disease [32], the number of patients with HCCA that develop jaundice exceeds 90 % [33]. Normally, the presence of a mass on imaging originating from the gallbladder wall and invading the liver with or without involvement of the biliary tree indicates toward gallbladder cancer. In addition, gallbladder cancer-related stricture of the biliary tree is localized mostly at a more distal location below the biliary confluence. Unfortunately, such clear-cut diagnostic findings are not uniformly present. Thus, clinical features, laboratory values and imaging studies including ERCP are helpful in only a small proportion of patients differentiating advanced stage gallbladder cancer from HCCA.

9.2.2 Malignant Melanoma of the Biliary Tract

Malignant melanoma of the biliary tract is a rare entity arising primarily from the biliary epithelium [34]. It can also result from systemic dissemination of a primary location elsewhere as it exhibits a remarkable ability to metastasize to diverse locations [35]. When it does occur as a primary or metastatic disease, it usually presents with obstructive jaundice and an intraluminal polypoid soft tissue mass on imaging, thus simulating and further complicating the diagnosis of HCCA [36]. Features at multiple, complimentary imaging techniques such as ultrasonography, CT, MRI and ERCP are nonspecific. Thus, accurate differentiation of obstructive jaundice related to melanoma from that of HCCA is almost impossible.

9.2.3 Neuroendocrine Neoplasia of the Bile Ducts

Neuroendocrine neoplasia of the biliary tract are extremely rare with only few cases being reported to date [34]. These tumors may arise anywhere along the intrahepatic or extrahepatic biliary tree. Approximately 50–60 % of neuroendocrine neoplasia of the biliary tree occur at the common bile duct, and the remainder occur in the perihilar region (28 %), cystic

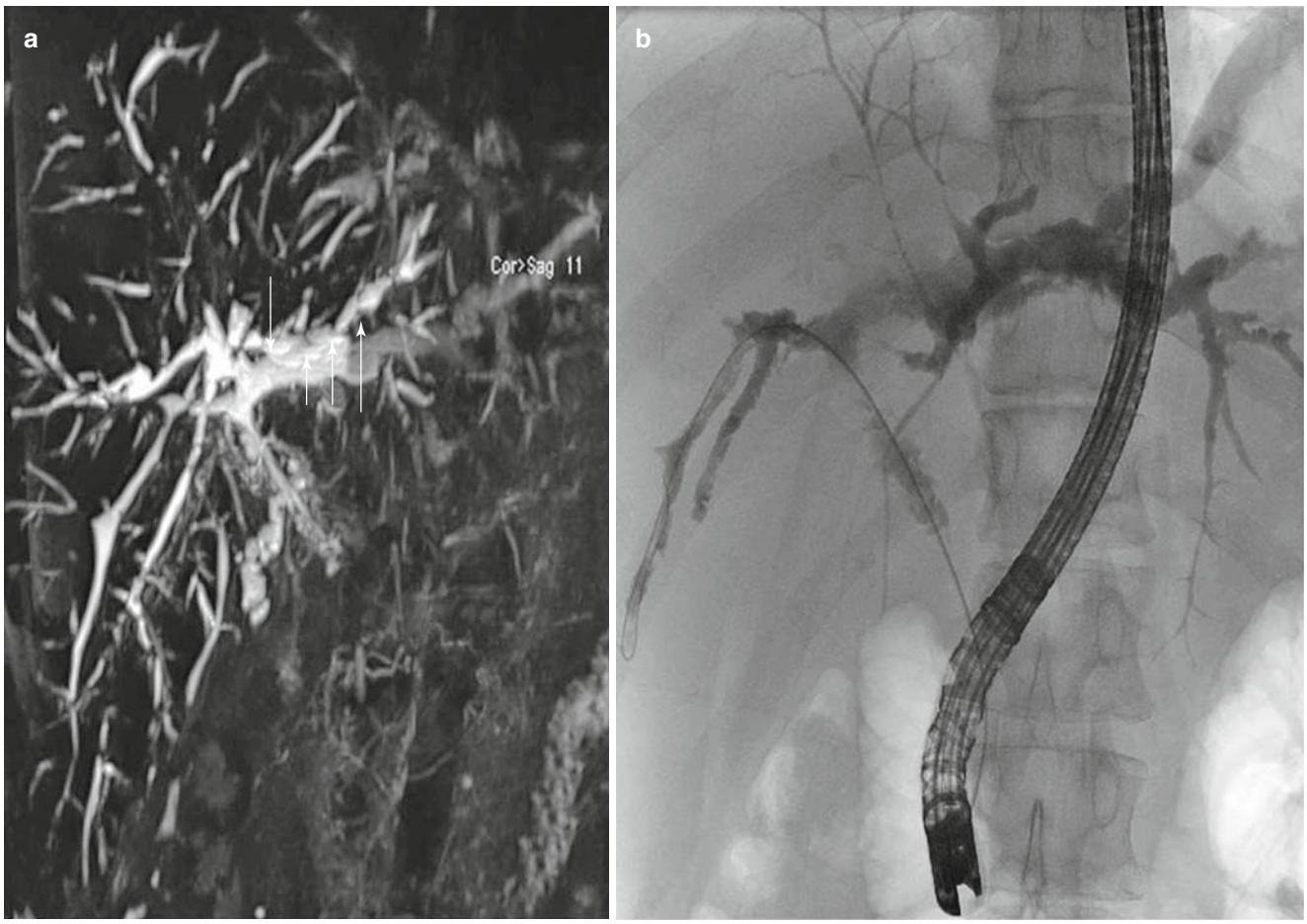

Fig. 9.5 (**a**) Coronal image from color-coded 3D T2-weighted MRCP in a patient with primary sclerosing cholangitis showing segmental strictures (*thin arrows*) and dilatation (*thick arrow*) of the bile ducts as a classic imaging finding; (**b**) ERCP image reveals bile duct strictures with upstream ductal dilatation simulating infiltrating cholangiocarcinoma

duct (11 %) or the hepatic duct bifurcation (3 %) [37]. Patients are usually young and present with painless jaundice from biliary obstruction and related symptoms including clay-colored stools and dark urine. Although radiologic findings of these tumors are diverse and nonspecific, they may appear as long segment biliary stricture with wall thickening with or without mass formation, thus simulating HCCA.

9.2.4 Lymph Node Metastases

Metastatic processes in the liver including the liver hilum, in particular from cancers of the gastrointestinal tract, are responsible for most cancer related deaths in the world [38, 39]. The liver is the most common site of colorectal cancer metastases and frequently the only affected organ. Up to 35 % of patients with colorectal cancer will have hepatic metastases at the time of surgery for the primary lesion, and further, 8–25 % will develop metachronous hepatic metastases after primary resection [40]. Furthermore, colorectal adenocarcinoma, on account of its proclivity to spread along epithelial surfaces, shows an increased predilection to involve the biliary ducts and cause obstructive jaundice as well [41]. Lymph node bearing metastatic deposits at the liver hilum may be enlarged to many times their normal size, often exceeding even the diameter of the primary lesion and causing obstructive jaundice. Therefore, a history of malignancy, cholestasis and a mass lesion at the hepatic hilum should also raise the suspicion of metastatic lymphadenopathy as differential diagnosis of HCCA.

9.2.5 Primary Hematolymphoid Malignancies Involving the Hepatic Hilum

Obstructive jaundice is a common consequence of malignancy but only rarely has been reported as a presenting manifestation of primary hematolymphoid malignancies [42, 43]. The majority of cases involve secondary infiltration of the biliary tree including the hepatic hilum from systemic

dissemination of extrahepatic wide spread disease [44]. However, the existence of primary hematolymphoid malignancies of the biliary tract characterized by obstructive jaundice has been recognized for many years [45, 46]. It includes non-Hodgkin lymphomas, plasmocytomas, non-leukemic granulocytic sarcomas and others. These malignancies of the bile duct are extremely rare and ill defined. Clinical symptoms and signs such as abdominal pain, fever and weight loss are common in those patients. However, these symptoms are nonspecific and patients with HCCA can also present with such symptoms too. In addition, there are no laboratory and radiologic findings that help differentiate these malignancies of the bile duct accurately from HCCA. As a result their exact diagnosis as a cause of cholestasis could only be established with certainty retrospectively. Owing to the above mentioned diagnostic difficulties, and in particular their rarity, this kind of malignancies of the bile duct causing obstructive jaundice often are not included in the differential diagnosis of HCCA and rather mistakenly being attributed to it. On the other hand, differentiating HCCA from primary hematolymphoid malignancies causing obstructive jaundice is important because of the differences in treatment. Extensive surgery, which is the main stay of therapy in HCCA, is rarely indicated in primary hematolymphoid malignancies. Most of these malignancies can be treated safely and effectively with multiple agent chemotherapy alone without the need for extensive and risky surgical procedures [47]. Surgery is indicated only when lesions produce complications, that are not amenable to non-surgical treatment, or chemotherapy fails to eradicate localized disease [43].

9.3 Type of Benign Lesions Mimicking Hilar Cholangiocarcinoma (HCCA)

9.3.1 Primary Sclerosing Cholangitis (PSC)

PSC is an idiopathic, chronic cholestatic disease of possible autoimmune origin characterized by periductal inflammation, resulting in multifocal strictures of the intrahepatic and extrahepatic bile ducts [48, 49]. This disorder is the commonest known predisposing condition for cholangiocarcinoma in the west [50, 51]. Cholangiocarcinoma rates of 8–40 % (follow-up studies, autopsy and explant specimens) have been reported in patients with PSC, making cholangiocarcinoma the most dreaded complication of PSC [50–53]. Cholangiocarcinoma in such patients tends to present earlier, in the fourth or fifth decade, than in sporadic cases [50, 54]. Its natural history is variable, and the true incidence of cholangiocarcinoma is unclear. However, the highest incidence of developing cholangiocarcinoma is reported in the first 2 years of diagnosis of PSC and the risk of cholangiocarcinogenesis seems unrelated to the duration of the inflammatory disease [50, 55]. Distinguishing benign from malignant strictures is challenging in the setting of PSC particularly in the presence of localized bile duct stricture. Pool data composed of 190 patients with obstructing benign lesions of the common bile duct whose initial clinical and imaging diagnosis was hilar cholangiocarcinoma showed 1.6 % PSC at final histology [4–15, 18].

9.3.2 Secondary Sclerosing Cholangitis Syndromes (SSCS)

Secondary sclerosing cholangitis syndromes are a heterogeneous group of chronic cholestatic disorders that are morphologically similar to PSC but differ in pathological processes [56, 57]. The clinical and cholangiographic features of these disorders may mimic PSC and HCC, yet its natural history may be more favourable if recognition is prompt and appropriate treatment is introduced. The wide spectrum of these entities includes inflammatory pseudotumor (IPT), autoimmune pancreatocholangitis (AIP), recurrent pyogenic cholangitis (RPC), portal biliopathy, AIDS cholangiopathy, eosinophilic cholangitis, mast cell cholangitis, ischemic cholangitis and other conditions.

9.3.3 Inflammatory Pseudotumor (IPT)

Inflammatory pseudotumor is an idiopathic entity that regroups benign lesions of the extrahepatic bile duct with inflammatory components [56, 57]. At histologic analysis, a heterogeneous population of inflammatory cells-predominantly plasma cells, eosinophils, macrophags, and fibroblasts-as well as areas of fibrosis and/or necrosis characterizes this disorder [4–7, 11, 13, 15, 58, 59]. Associations with PSC, Crohn's disease and phlebitis have been described [60–62]. Next to the lungs of young adults the hepatobiliary system is the second most common target location of IPT [34, 63]. Its aetiology remains obscure and there are neither specific signs on imaging, nor conclusive diagnostic biochemical tests. Although its incidence is not exactly known, about 4–20 % of bile duct strictures mimicking hilar cholangiocarcinoma are IPT [4–11, 13]. These lesions appear on imaging as masses that may show delayed and persistent enhancement due to the fibrous content; and biliary strictures of intra- or extrahepatic ducts on cholangiography, findings remarkably similar to those of cholangiocarcinoma [64, 65]. Furthermore, associations between IPT and RPC that leads to biliary stricture formation and thus mimic HCCA have been described [60]. There is also evidence that its histologic findings are quite similar to autoimmune pancreatocholangitis (AIP) and feature many IgG4-positive plasma cells, thereby suggesting a shared pathogenic mechanism [66].

9.3.4 Recurrent Pyogenic Cholangitis

Recurrent pyogenic cholangitis (RPC) also known as Hong Kong disease and oriental cholangiohepatitis, is a condition that most commonly affects patients with East Asian descent [67]. Although most prevalent in the East, it is seen increasing in the West mainly owing to immigration [68]. This disorder is characterized by recurrent episodes of bacterial cholangitis that occur in association with biliary obstruction from strictures and pigmented stones [69, 70]. RPC peaks in the third and fifth decades of life with no specific sex predilection. Patients most often present with abdominal pain, fever and jaundice [71]. It is thought to occur in patients suffering from chronic infestation of the biliary tree by Ascaris lumbricoides, Clonorchis sinensis, Opisthorchis viverrini, Fasciola hepatica and Opisthorchis felineus that may obstruct the biliary tract with resultant bile stasis, pigment stone formation and bacterial super infection [69, 72]. Although sepsis is the major threat to life in these patients, approximately 10 % will develop cholangiocarcinoma [73, 74]. Imaging may identify biliary strictures, ductal wall thickening secondary to fibrosis, and hepatolithiasis [75, 76]. The ductal wall thickening and enhancement may not be distinguished from cholangiocarcinoma with imaging studies alone [34].

9.3.5 AIDS Cholangiopathy

AIDS cholangiopathy is a syndrome of biliary duct obstruction caused by infection-related strictures [77–79]. The clinical spectrum of disease includes papillary stenosis, sclerosing cholangitis, combined sclerosis of the duct and papillary stenosis, and long strictures of the extrahepatic bile ducts [56, 80]. The large intrahepatic ducts are preferentially affected [56]. It typically manifests as biliary strictures associated with wall thickening and mural stenosis [81]. Among those four distinct cholangiographic abnormalities, which have been demonstrated by endoscopic retrograde cholangiopancreatography (ERCP), the combination of sclerosing cholangitis and papillary stenosis is the most common and occurs in 50 % of patients [82]. This disorder, once considered to have extremely poor prognosis, is now rarely fatal, in part due to the wide spread use of antiretroviral drugs. The current incidence is not known but remains significant in areas where access to retroviral drugs is limited. Its aetiology is multifactorial. Opportunistic infections such as Cryptosporidium and Cytomegalovirus are the most common causes of AIDS cholangiopathy [83]. However, no definite organism is identified in up to 50 % of patients [34]. Patients typically present in the advanced stage of the HIV spectrum, when their CD4 counts are below 135/mm^3 [84]. The presentation of AIDS cholangiopathy varies from features of cholangitis to isolated right upper quadrant abdominal pain. Sometimes the only abnormality is an elevated serum alkaline phosphatase, generally five to seven times above the normal limit [80, 83].

9.3.6 Autoimmune Sclerosing Pancreatocholangitis

Autoimmune pancreatitis (AIP) is a type of chronic pancreatitis characterized by an autoimmune inflammatory process in which prominent lymphocyte infiltration with associated fibrosis of the pancreas causes organ dysfunction [85]. In addition to findings specific to the pancreas, about 49 % of patients with this disorder can have extrapancreatic manifestations including sclerosing inflammation of the intrahepatic or extrahepatic bile duct system or the gallbladder [86]. It can mimic malignancy and is commonly named autoimmune pancreatocholangitis [87]. The pathogenesis of AIP is uncertain, and no gold standard exists for its diagnosis. The estimated prevalence of AIP is 5–11 % of all patients with chronic pancreatitis [88, 89]. It is twice as common in men as in women, and most patients are older than 50 years, an age at which pancreatic carcinoma occurs [88, 90]. Immunohistochemical studies demonstrate prominent lymphocyte and Immunglobulin G4-positive plasma cell infiltration and fibrosis [91]. Imaging studies show diffuse or homogeneous enlargement of the pancreas with a moderate enhancement, and a peripheral rim of hypoattenuation [85]. Regarding ductal structures, it is characterized by focal or diffuse strictures of the pancreatic and bile ducts. Narrowing of the intrahepatic bile duct and bile duct strictures with upstream ductal dilatation can also be seen, which may mimic the periductal infiltrating type of cholangiocarcinoma [85].

9.3.7 Portal Biliopathy

The term portal biliopathy (PB) refers to the morphologic abnormalities of the entire biliary tract including extrahepatic and intrahepatic bile ducts in patients with portal hypertension [92]. Chronic thrombotic obstruction of the extrahepatic portal vein is usually followed by the formation of bridging hepatopetal collaterals which drain splanchnic venous blood from the splenic, superior mesenteric and coronary veins to the porta hepatis in an attempt to bypass the obstruction. This results in the formation of a venous network known as portal cavernoma or cavernous transformation [93, 94]. Although extrahepatic portal vein thrombosis is the most common cause of PB, liver cirrhosis, portal vein fibrosis without cirrhosis and congenital hepatic fibrosis can also cause the disorder [92]. Mechanical protrusion of the paracholedochal veins in the lumen of the bile duct and a

secondary ischemic vascular bile duct injury with or without cholangitis is believed to lead to the development of significant strictures. It may lead to asymptomatic cholestasis in more than 50 % of patients; and rarely, it can cause symptomatic biliary obstruction [95]. Symptomatic patients are usually adults, indicating that PB is a slowly progressive disease, because most are thought to have acquired their portal vein thrombosis in early childhood [56]. Direct cholangiographic findings include segmental upstream dilation, calibre irregularity, filling defects that may be interpreted as common bile duct calculi, stricture and extrinsic impression on the bile duct due to collaterals [96]. These cholangiographic appearances may mimic bile duct cancer, with the cavernoma appearing as a solid tumor, the so-called "pseudocholangiocarcinoma sign" [97].

9.3.8 Mirizzi Syndrome

Mirizzi described in 1948 a functional hepatic syndrome that consisted of a common hepatic duct obstruction secondary to compression by a gallstone impacted at the gallbladder neck or cystic duct [98]. The current definition of this syndrome that now bears his name includes four components [99–101]: anatomic arrangement of the cystic duct at the gallbladder neck such that it runs parallel to the common hepatic duct; impaction of a stone in the cystic duct or neck of the gallbladder; mechanical obstruction of the common hepatic duct by a stone itself or by secondary inflammation; and intermittent or constant jaundice causing possible recurrent cholangitis and, if long-standing, secondary biliary cirrhosis. Based on the severity of the disease Csendes et al. classified this syndrome into four types [99]. Type I lesion is a simple pressure on the common hepatic duct due to an extrinsic stone impacted at the neck of the gallbladder or at the cystic duct. Type II lesion is a more severe disease with cholecystobiliary fistula that involves less than one-third of the circumference of the common bile duct. Type III lesion is a cholecystobiliary fistula with erosion of the wall of the common duct that involves two-thirds of the ductal wall. Type IV lesion is a more severe disease with cholecystobiliary fistula, which involves the entire circumference of the ductal wall. This syndrome is rare and occurs in 0.3–3 % of all cholecystectomies performed [100–102].

Recently, a number of methods for the diagnosis of biliary tract disease have been introduced. Ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), magnetic resonance cholangiopancreatography (MRCP), magnetic resonance imaging (MRI), and computed tomography (CT) are all useful. Despite these advances in medical technology the diagnosis of Mirizzi's syndrome is still difficult. The imaging findings are not always specific [103]. For example, gallstones are not always visible at CT, thereby making conclusive diagnosis difficult. Obstruction of the common bile duct leads to chronic, recurrent episodes of cholangitis and stricture formation which may resemble the periductal-infiltrating type of cholangiocarcinoma.

9.3.9 Biliary Adenomas

These are rare benign epithelial tumors, with few cases reported in the literature. About 90 % of all patients with symptomatic biliary adenomas present with obstructive jaundice as a cardinal presenting sign [104]. Less common symptoms include right upper quadrant abdominal pain, weight loss, fever, and nausea [105]. Most lesions are localized in the common bile duct, particularly in the distal common duct and ampulla of Vater [105]. However, biliary adenomas within the cystic duct have also been described [106]. Although it has been suggested that adenomas of the biliary tract may result from a focal, reactive process to injury, possibly post-inflammatory or post-traumatic, the cause of these lesions in the majority of patients appears to be idiopathic [107]. The radiographic features of these lesions are often difficult to distinguish from cholangiocarcinoma. Small or solitary lesions are usually difficult to detect by CT scan [108]. Sonography indicates a non-shadowing intraluminal mass, occasionally with a pedicle [109]. The occasionally correct preoperative diagnosis of biliary adenomas may be provided by ERCP, cholangiography or cholangioscopy [109, 110]. In addition to mimicking cholangiocarcinoma, these lesions are considered premalignant with a definite risk of recurrence and progression to cholangioncarcinoma if left untreated [111].

9.3.10 Hepatobiliary Sarcoidosis

Sarcoidosis is a chronic, multisystem granulomatous disorder of unknown cause that is pathologically characterized by noncaseating granulomas [112]. It present most frequently in young adults with bilateral hilar adenopathy and pulmonary infiltrates. More than 50 % of patients with sarcoidosis have hepatobiliary involvement, varying from asymptomatic granulomatosis to portal hypertension and severe liver diseases [113]. Most patients with hepatobiliary sarcoidosis are asymptomatic. Although 50–65 % of patients with sarcoidosis show hepatobiliary involvement at liver biopsy, only 5–15 % of patients show signs and symptoms of the disease [113]. The clinical manifestations of hepatobiliary sarcoidosis are protean and include multifocal micronodular granulomas, macronodular granulomas, liver cirrhosis, portal hypertension and granulomatous cholangitis. Granulomatous cholangitis is an extremely rare disease characterized by

insidious onset and chronic progression to biliary cirrhosis [34]. The formation of granulomas in bile ducts in this disorder leads to strictures and ductopenia [114]. This seems to be the underlying mechanism of chronic cholestasis syndrome featuring jaundice, pruritus, hepatomegaly, and marked elevation in serum alkaline phosphatise [115]. In patients with hepatobiliary sarcoidosis featuring biliary strictures and hilar lymphadenopathy, it can be very difficult to exclude a diagnosis of hilar cholangiocarcinoma. The imaging findings are sometimes indistinguishable from those of cholangiocarcinoma [116].

9.3.11 Xanthogranulomatous Cholecystitis and Cholangitis

Xanthogranulomatous cholecystits (XGC) is an unusual and destructive form of severe, chronic cholecystitis characterized by multiple, yellow-brown, intramural nodular formations, proliferative fibrosis, and foamy histiocytes [117, 118]. The incidence of this disease have been reported to range from 1 to 13 %, with a slight predominance in women and almost all patients presenting with gallstones [117–119]. Although the exact pathogenesis of XGC is unknown, study results suggest that XGC may begin as an acute inflammation of the gallbladder and obstruction [118, 120]. Pathologic changes occur primarily in the gallbladder wall and can extend into the surrounding structures. Imaging studies show gallbladder wall thickening associated with extra gallbladder changes such as pericholecystic infiltration, hepatic involvement, biliary obstruction with inflammatory strictures and hilar lymphadenopathy. Thus, there is much overlap between adenocarcinoma of the gallbladder and XGC to reliably differentiate between the two entities [121]. Moreover, xanthogranulomatous cholangitis may occur in isolation or association with XGC [122]. It appears as a biliary stricture with wall thickening and may simulate hilar cholangiocarcinoma [123].

9.3.12 Chemotherapy-Induced Sclerosing Cholangitis

Unlike hepatic parenchyma, which depends on a dual blood supply from the portal vein and hepatic artery, the biliary system drives its vascular supply almost exclusively from branches of the hepatic arteries and is more susceptible to injury if arterial flow is reduced [124]. Arterial occlusion may result in bile duct ischemia and fibrosis without causing significant parenchymal infarction. Possible mechanisms include toxic vasculitis and drug-induced intravascular thrombosis leading to ischemic insult and stricture formation [56]. Chemotherapy-induced sclerosing cholangitis results as a complication of hepatic arterial infusion of chemotherapeutic agents, particularly floxuridine and fluorouracil [56, 125], widely used chemotherapeutic agents for the treatment of liver metastases from colorectal cancer. It has a reported incidence of 8–55 % [126–128]. Floxuridine, fluorouracil and other agents have been used in the last decades as intravenous or intraarterial infusion for both resectable and unresectable disease [129, 130]. It has been suggested that intraarterial application of these agents causes ischemic cholangitis ultimately leading to biliary stricture formation. Ischemic cholangitis is not known to occur from intravenous systemic chemotherapy indicating local vascular inflammation from hepatic arterial chemotherapy but not hepatocellular toxicity of the drug that leads to biliary injury [131].

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