Chapter 10
Proximal Biliary Strictures Mimicking Hilar Cholangiocarcinoma

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Synopsis

This chapter addresses basic biliary tract anatomy and the clinical manifestation and diagnostic workup of patients with benign tumors and pseudotumors of the biliary tract that can masquerade as hilar cholangiocarcinoma. These benign neoplasms or conditions may present as localized masses or strictures resulting in biliary obstruction. They can be classified in the following broad categories: (1) Papilloma and adenoma, (2) Granular cell tumor, (3) Neuroendocrine tumors, (4) Neural tumors, and (5) Pseudotumors.

Basic Anatomy

The gallbladder is located in a fossa on the inferior surface of the liver. It is divided into four anatomical areas: fundus, body, infundibulum, and neck. Histologically, it is distinct from the remainder of the gastrointestinal tract, as it lacks a muscularis mucosa and a submucosa [1]. The extrahepatic biliary system consists of the right and left hepatic ducts, the common hepatic duct (CHD), the cystic duct, and the common bile duct (CBD), as illustrated in Fig. 10.1. Most commonly, the right and

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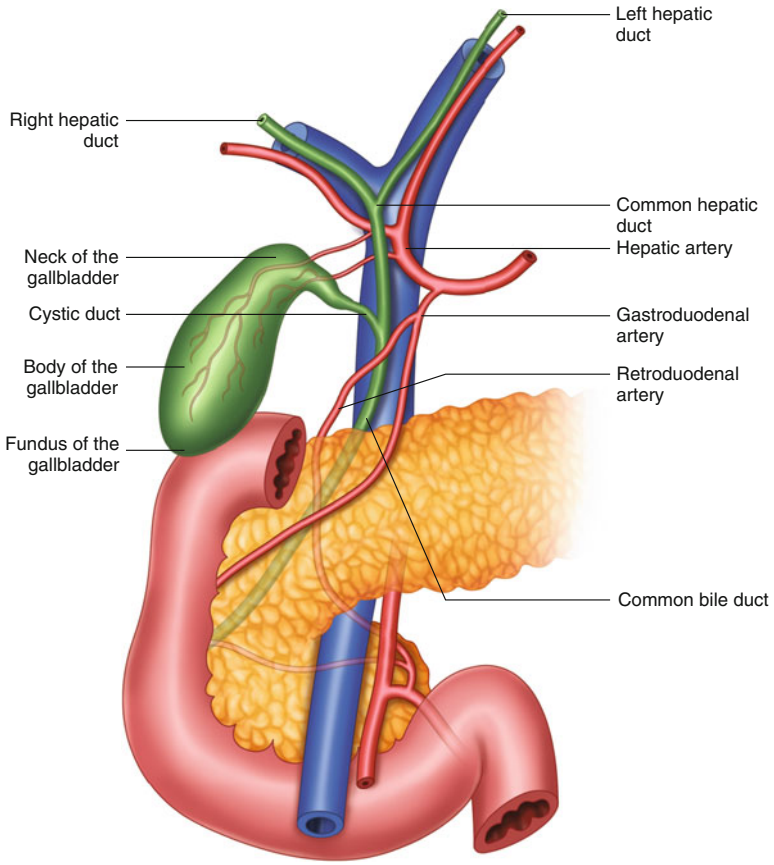

Fig. 10.1 Anatomy of the biliary tree. Shown is the standard anatomy of the biliary tree and the anterior aspect of biliary anatomy related to the pancreas, right hepatic duct (a), left hepatic duct (b), common hepatic duct (c), hepatic artery (d), gastroduodenal artery (e), cystic duct (f), retroduodenal artery (g), common bile duct (h), neck of the gallbladder (i), body of the gallbladder (j), fundus of the gallbladder (k). Note particularly the position of the hepatic bile duct confluence anterior to the right branch of the portal vein, the posterior course of the cystic artery behind the common hepatic duct, and the relationship of the neck of the gallbladder to the right branch of the hepatic artery. Note also the relationship of the major vessels (portal vein, superior mesenteric vein, and artery) to the head of the pancreas

left hepatic ducts join to form the common hepatic duct, although there are several important anatomical variations that must be recognized. Within the porta hepatis, the common hepatic duct usually lies anatomically anterior to the portal vein and to the right of the hepatic artery [1]. The cystic duct typically joins the common hepatic duct acutely forming the common bile duct. Extrahepatic bile duct walls are lined by a single layer of columnar epithelium with minimal smooth muscle [2]. The supraduodenal portion of the common bile duct runs inferiorly in the hepatoduodenal ligament anterior to the portal vein and to the right of the hepatic artery. By the

middle third of the CBD (retroduodenal portion), it deviates laterally from the other vasculature and curves behind the first portion of the duodenum. In roughly 70 % of patients, the main pancreatic duct joins the pancreatic portion of the CBD outside the second portion of the duodenum and they traverse the duodenal wall as a single unit [1]. On the other hand, in 20 % of people, the pancreatic duct and CBD unite inside the duodenal wall itself and in 10 %, the two ducts enter the duodenum separately through two distinct openings [1, 2]. The intraduodenal segment of the duct is termed the ampulla of Vater. It is roughly 10 cm distal to the pylorus and is encircled by the Sphincter of Oddi, which helps control bile outflow.

In clinical practice, this classic picture of biliary anatomy only exists in less than half of patients. A number of anatomic variations are relatively common, making awareness of them essential in order to prevent significant intraoperative complications. Variants of the hepatic and cystic arteries are of the more frequently encountered, as seen in roughly 50 % of patients [1]. The main arterial supply to the bile ducts is the gastroduodenal artery (GDA) and the right hepatic artery (RHA), whose trunks run along the medial and lateral duct walls. Most commonly, the RHA branches from hepatic artery proper, a branch of the common hepatic artery. However, significant anatomic RHA variants exist, such as a replaced RHA (20 %), which instead comes off the superior mesenteric artery (SMA), or an accessory RHA (5 %), where two RHAs are present, one from the SMA and from the common hepatic [1]. Specifically in patients with a replaced RHA, the RHA may course anterior to the CHD in the porta hepatis, making it easily susceptible to injury if not properly identified. In regard to the cystic artery, 80–90 % branch from the RHA. However, variants can occur and can branch from a replaced RHA, an accessory RHA, left hepatic artery, SMA, GDA, or common hepatic artery [1].

Benign Tumors

Accounting for roughly 6 % of neoplasms that occur in the biliary tract, biliary obstruction secondary to benign biliary tumors is significantly less common when compared to other inflammatory, iatrogenic, or malignant etiologies. However, despite the rarity of these benign neoplasms, it is important to include them in the differential diagnosis when a patient presents with obstructive jaundice or evident biliary stricture. A complete list of benign tumors and pseudotumors of the biliary tract can be seen in Table 10.1.

The clinical presentation of patients with benign biliary tumors often parallels those with an underlying biliary malignancy, as both commonly present with signs of obstruction, such as jaundice, scleral icterus, and pruritus [3]. Regarding symptoms, either group may present with associated colicky epigastric pain, nausea, and vomiting, while others may remain relatively asymptomatic. Rarely is significant weight loss or anorexia present in patients with benign disease, in comparison to those with a malignant stricture etiology [4]. Ultimately, however, no clinical symptoms or physical exam findings have been found to be specific enough to differentiate

Table 10.1 Benign biliary tumors

Benign tumors and pseudotumors that can cause biliary obstruction
Epithelial tumors
Adenoma
Papilloma
Cystadenoma
Nonepithelial tumors
Leiomyoma
Lipoma
Hemangioma
Lymphangioma
Granular cell tumor
Neural tumors
Neurofibroma
Schwannoma
Neuroendocrine tumors
Pseudotumors
Idiopathic benign focal stricture
Lymphoplasmacytic focal stricture
Sclerosing cholangitis
Heterotopic tissue

Adapted (with permission) from Linehan DC, Jarnagin WR, Blumgart LH. Benign Tumors and Pseudotumors of the Biliary Tract. 2012; 50:751–763

a benign biliary tumor from malignancy or inflammatory pseudotumors. Because of the lack of characteristic symptoms and physical findings, benign biliary tumors are not generally diagnosed preoperatively.

Papilloma and Adenoma

The most common type of benign tumor of the extrahepatic biliary tree is that developing from the glandular epithelium lining the ducts themselves [2, 5]. The majority of these neoplasms fall into the category of polyps, papillomas, adenomas, or cystadenomas. This is evident in the historic review of benign extrahepatic biliary tumors by Chu (1950), which referenced a total of 55 documented cases with the following type and frequency: 24 biliary papilloma/polyp (44 %); 18 bile duct adenoma (33 %); 3 neuroma, lipoma, and fibroma; 2 granuloma; 1 melanoma and 1 carcinoid [2, 5, 6].

In regard to biliary cystadenomas, extrahepatic cases are exceptionally rare, as they predominantly tend to occur within the intrahepatic bile ducts [7]. Soochan et al. (2012) reported a unique case of a 62-year-old woman ultimately found to

have an intra- and extrahepatic biliary cystadenoma. The clinical manifestation was obstructive jaundice and the initial radiologic workup included contrast-enhanced CT and MRCP, which revealed significant atrophy of the left lobe of the liver, as well as dilatation of the common bile duct (CBD), common hepatic duct, and left intrahepatic duct [7]. ERCP with brush cytology sampling was negative. Unable to definitively rule out malignancy, the patient underwent an extended left hepatectomy with CBD excision and Roux-en-Y anastomosis. Macroscopically, the specimen appeared to be a mucin-containing mass, which arose from the left hepatic duct and prolapsed into the CBD [7]. Microscopic examination confirmed the diagnosis of biliary cystadenoma, as it displayed the classic findings of a cyst lined with mucinous columnar or cuboidal epithelium [7].

Chen and associates reported a patient referred for surgical resection of a suspicious liver nodule found as an incidental finding on CT scan. The patient did not manifest any symptoms of obstructive jaundice nor were his liver function tests abnormal. Suspicious for carcinoma, the decision was made to pursue surgery. Intraoperatively, a hard 1.4 cm mass was identified near the diaphragmatic dome of the left hepatic lobe [8] without evidence of infiltration into the liver capsule. Interestingly, after postoperative microscopic examination, the mass was shown to be a bile duct adenoma. As illustrated in these reports, the clinical presentation and radiographic features of extrahepatic bile duct adenomas remain difficult to distinguish from cholangiocarcinoma, making preoperative diagnosis challenging and surgical resection the mainstay of treatment [2, 7, 8].

Granular Cell Tumors

Granular cell tumors are extremely rare, benign tumors, which occasionally occur in the extrahepatic biliary tree. More commonly occurring in the oral cavity, subcutaneous tissue, or skin, it is believed that less than 1 % of all granular cell tumors arise from the biliary tree [2, 9–11]. First reported in 1952, the majority of cases are found in young, African-American females [11–13]. This is evident in a case report from 2010 describing a 16-year-old, African-American female who underwent orthotopic liver transplant for liver failure secondary to severe biliary tract obstruction from a granular cell tumor [13]. Initially thought to arise from myoblasts, it is now believed that granular cell tumors may indeed originate from Schwann cells. This theory is supported by the positive immunohistochemical staining for the S-100 protein, which is normally found in Schwann cells of the peripheral nervous system [11, 13, 14].

Uniquely, Saito et al. reported the occurrence of a granular cell tumor of the common bile duct in a 36-year-old Japanese woman. The patient initially presented with a sudden elevation of liver and biliary tract enzymes 3 days following delivery of twins by Cesarean section. Scleral icterus was evident within 1 week. Abdominal ultrasound revealed an enlarged gallbladder with associated debris and a common bile duct with a diameter of 7 mm [11]. CT and MRCP were then performed, and

displayed stenosis and wall thickening of the mid-bile duct. ERCP further confirmed the presence of the respective stenosis. Subsequent endoscopic brush cytology and forceps biopsy failed to diagnose the etiology of the identified stricture. Unable to definitively rule out cholangiocarcinoma, the patient underwent a pancreaticoduodenectomy roughly 1 month after her Cesarean section. Gross inspection of the specimen revealed the tumor to be small, ill-defined and located in the distal CBD, with involvement of all three layers of bile duct wall. On microscopic examination, the tumor cells were polygonal with eosinophilic granular cytoplasm that exhibited partial infiltration of the peripheral nerve fibrous tissue of the bile duct wall [11]. Immunohistochemistry revealed cells positive with the periodic acid-Schiff reaction as well as positive for S100. Given these findings, the authors concluded that this was a benign granular cell tumor. The patient was reported as stable, with no complications or recurrences 5 years later [11].

Neural Tumors

Schwannomas are benign tumors that arise from Schwann cells. Schwann cells are the myelin-producing cells that form the inner portion of peripheral nerve sheaths [15]. Madhusudhan and coworkers reported a case of a 46-year-old man who presented with 2-month history of progressive jaundice, dark urine, and pruritis. Physical examination revealed an enlarged yet non-tender liver. Laboratory findings included elevated bilirubin and alkaline phosphatase. Imaging studies performed in the diagnostic workup included ultrasound, CT, and MRI. Contrast-enhanced CT showed a mass extending along the CBD and right and left hepatic ducts beyond the secondary confluence, as well as dilatation of the intrahepatic bile ducts [16]. No abnormalities were visualized in the associated vasculature. MRI exhibited a branching solid mass along the extrahepatic and intrahepatic bile ducts. The working diagnosis was cholangiocarcinoma on the basis of these findings. Further exploration followed with an ultrasound-guided biopsy of the suspicious mass. Immunohistochemistry of the biopsied mass revealed the tumor cells to be positive for S100 and neurofibrin, which are markers consistent with Schwannoma. Schwannomas of the biliary tree are rare, and when they do arise, it is typically from the neural elements present in the wall of the ducts [16, 17]. Patients can present with indistinguishable signs of obstructive jaundice and indistinct imaging, as seen in this patient, which again makes definitive diagnosis difficult without surgical resection. A Schwannoma in a 54-year-old woman with prior diagnoses of melanoma who was found to have liver panel abnormalities undergoing routine surveillance studies is shown in Fig. 10.2. After confirmation that this lesion was not consistent with metastatic melanoma (e.g., negative PET scan), the tumor was resected, noted as a Schwannoma on pathology review and the patient recovered well without issue or further sequelae.

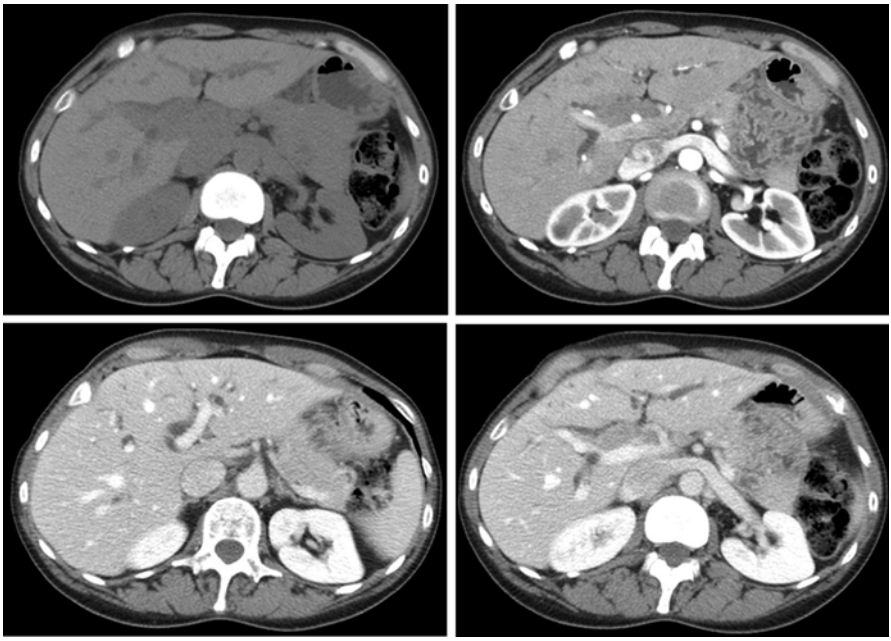

Fig. 10.2 Shown is a CT angiogram of the liver from a 54-year-old woman with abnormal liver enzymes with history of melanoma of the back, upper arm and labia status post definitive resection for all. Physical examination was unremarkable and laboratory examination during surveillance for melanoma yielded a normal total bilirubin, AST = 145 U/l, ALT = 516 U/l, and ALKP = 158 U/l. A PET scan to rule out melanoma was negative for FDG avidity. Fine needle aspiration by referring physician showed a spindle cell neoplasm that was S-100 positive and c-Kit, desmin and synaptophysin negative. At operation, a soft mass was noted arising from the proximal bile duct extending into the base of segment IV. On frozen section, a low grade spindle cell neoplasm consistent with a Schwannoma was noted. Resection of the extrahepatic bile duct ensued and the patient recovered well with normalization of liver enzymes and no further sequelae

De Rosa et al. reported a 70-year-old woman who presented with obstructive jaundice for 1 month. The patient was status post open cholecystectomy 2 years prior to presentation. Laboratory studies were consistent with biliary obstruction and a contrast-enhanced CT identified a stricture at the mid-CBD. There was no evidence of a mass, vascular invasion, or enlarged lymph nodes. The patient underwent exploratory laparotomy with intraoperative frozen section biopsies to confirm clean margins. Excision of the extrahepatic bile duct and subsequent Roux-en-Y hepaticojejunostomy was performed. Postoperative histological findings were consistent with neurofibroma positive for S-100. The authors concluded that while solitary neurofibromas may occur, the majority of neurofibromas are seen more frequently in the setting of Neurofibromatosis [2, 17, 18].

Neuroendocrine Tumors

Neuroendocrine tumors of the extrahepatic bile ducts are particularly uncommon, accounting for 0.2–2 % of all gastrointestinal neuroendocrine tumors [19–21]. When they do occur, the most commonly reported presenting symptom is jaundice and the most common anatomic sites of occurrence are the common bile duct (58 %), perihilar region (28 %), cystic duct (11 %), and the common hepatic duct (3 %) [19, 21, 22]. Most reported biliary neuroendocrine tumors fall into the category of carcinoid, gastrinoma, and somatostatinoma, the majority of which are hormonally nonfunctional [2, 22]. However, in a recent Italian study, 17 patients diagnosed with Multiple Endocrine Neoplasia (MEN) Type 1 affected with Zollinger-Ellison syndrome (ZES) were analyzed and 3 of 17 were found to have functioning ectopic biliary tree gastrinomas [23]. Two of these were incidental findings during pancreaticoduodenectomy for ZES and were removed intraoperatively. The third case was discovered 1 year after pancreaticoduodenectomy for ZES recurrence and was subsequently removed [23].

Most carcinoid tumors occur in the gastrointestinal tract, particularly in the ileum (45 %), the rectum (20 %), or the appendix (16 %) [24]. As previously mentioned, carcinoid tumors arising from the extrahepatic biliary tract are rare [21]. Since first depicted by Pilz in 1961, only 70 documented carcinoid cases of biliary origin have been reported [22, 25, 26]. Carcinoids are derived from enterochromaffin cells (or Kulchitsky's cells), which are located at the base of the crypts of Lieberkühn [21, 27]. Since the biliary tree naturally contains a paucity of enterochromaffin cells, it has been hypothesized that biliary inflammation may serve as a template for biliary carcinoid development [2, 27]. The reasoning behind this theory is that persistent inflammation can lead to intestinal metaplasia of the biliary tree, resulting in an increased number of enterochromaffin cells [27]. Recently, Khuroo and associates reported a 56-year-old woman with a history of right upper quadrant pain and progressive jaundice. The patient's past surgical history was significant for cholecystectomy 7 years prior for symptomatic cholelithiasis. Based on preoperative imaging, the patient was presumed to have hilar cholangiocarcinoma (Klatskin tumor) and subsequently underwent surgery. Histological analysis of the surgical specimen revealed small round argyrophilic cells that stained positive for chromogranin A and serotonin [21, 22]. Based upon these findings they concluded that the hilar mass was in fact a carcinoid tumor. Carcinoid tumors of the biliary tree are considered to be of low malignant potential with a favorable 5-year prognosis of 60–100 % following complete resection [21, 22]. Although slow growing, if left untreated, these tumors still have the ability to metastasize. Figure 10.3 depicts gross photos of a resected biliary carcinoid originally noted due to hepatic transaminase elevation noted in the course of routine blood work [21]. This lesion was subsequently resected after preoperative imaging was concerning for hilar cholangiocarcinoma [21]. Therefore, these data illustrate that albeit rare, neuroendocrine tumors can be the etiology of a suspected malignancy in roughly 2 % of cases and should therefore not be ignored as part of the differential diagnosis.

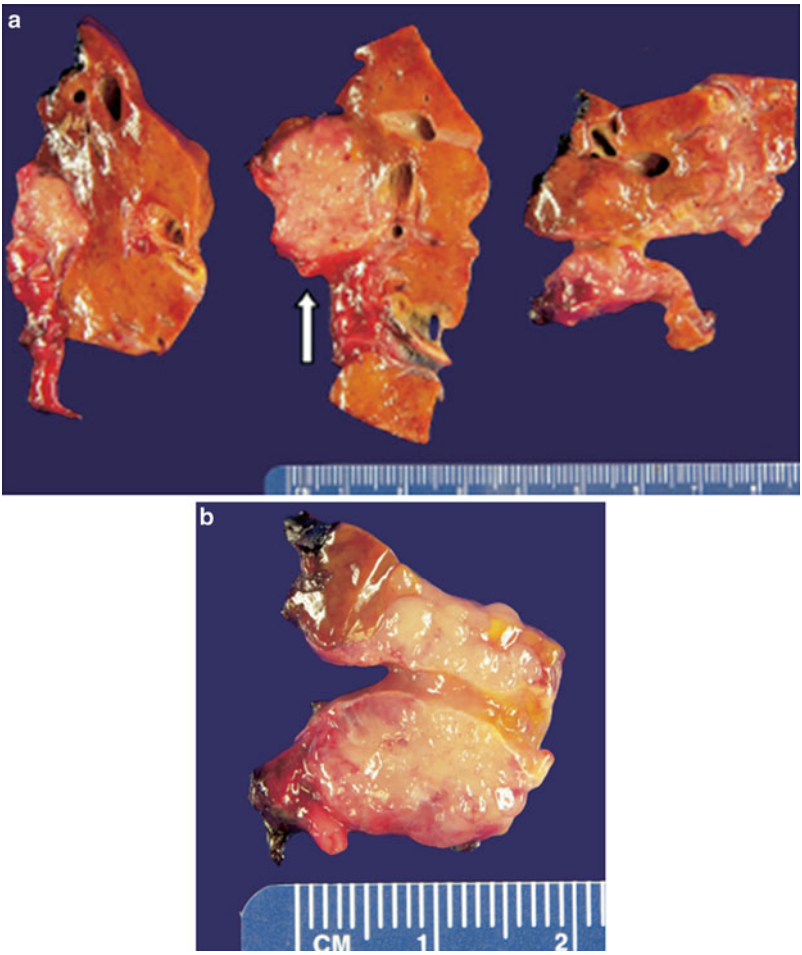

Fig. 10.3 Shown are photos of a right trisegmentectomy with biliary carcinoid (**a**) involving the bile duct with extension to periductal soft tissue (**b**); adapted with permission from [21]. The patient is a 52-year-old male with coronary artery disease s/p coronary artery bypass in 1999 noted to have elevated liver function tests on routine blood work, including an alkaline phosphatase of 289 U/L (33–88 U/L), an aspartate aminotransferase of 67 U/L (10–37 U/L), and an alanine aminotransferase of 85 U/L (5–37 U/L). Physical examination was unremarkable. Liver ultrasonography demonstrated right-sided biliary dilation terminating in a mass arising from the right hepatic duct, consistent with a papillary cholangiocarcinoma. A magnetic resonance cholangiopancreatogram confirmed this finding and showed no evidence of metastatic disease. Additionally, there was no evidence of portal vein involvement or hepatic lobar atrophy. Endoscopic retrograde cholangiogram, performed before referral, demonstrated a mass completely obstructing the right hepatic duct, with a normal left biliary system and common bile duct. Clinically, the patient was well, had no jaundice or pruritus, and denied any symptoms related to the biliary tumor. The patient was taken to the operating room in June 2006 with a presumptive diagnosis of hilar cholangiocarcinoma. The operative findings were consistent with a proximal biliary cancer, confirming the preoperative imaging data. A right trisegmentectomy, common bile duct resection, and portal lymph node dissection were performed. Macroscopically, the tumor appeared as a 2.2-cm homogeneous tan lesion arising from the right hepatic duct and extending into the hilar soft tissue and hepatic parenchyma as shown in panels **a** and **b**

Pseudotumors

Nonmalignant lesions that cause obstruction of the extrahepatic biliary ductal system may closely resemble hepatobiliary malignancies. It has been reported that 5.2–24.5% of biliary strictures prove to be benign after histological examination of the resected specimen [3, 28–30]. Some of the causes of obstruction in these benign cases are listed in Table 10.2. These benign conditions occur frequently enough to be carefully considered in the differential diagnosis of any lesion suspicious for a bile duct tumor. This is evident in a large series in which 5 of the 153 patients (3.3 %) who underwent surgical resection for a suspected biliary malignancy had postoperative histopathologically proven benign disease [30]. Those proven benign were further diagnosed as immunoglobulin G4-related sclerosing cholangitis ($n=3$) and nonspecific fibrosis ($n=2$) [30]. Erdogan and colleagues investigated 185 patients, who underwent resection of proximal bile

Table 10.2 Malignant masquerade. The table highlights recent reports of biliary strictures that were proven to be of benign etiologies following surgical resection or antituberculosis therapy

Reference	Number of patients	Location	Etiology	Treatment
Wakai et al. [30]	3	–	Sclerosing cholangitis	Hemihepatectomy
	2		Fibrosis	Hemihepatectomy
Oh et al. [40]	16	Hilus	Sclerosing cholangitis	–
Khan et al. [43]	1	CBD	Mirizzi syndrome	Cholecystectomy
Deng et al. [38]	1	Hilus	Inflammatory tumor	–
Kanhere et al. [44]	1	Cystic duct, CBD	Atypical mycobacterium	Roux-en-Y hepaticojejunostomy
Corvera et al. [32]	22	Hilus	Lymphocytic sclerosing cholangitis (2) Primary sclerosing cholangitis (3) Granulomatous (3) Stone disease (6) Idiopathic benign biliary strictures (8)	Resection
Vasiliadis et al. [37]	1	CBD	Inflammatory tumor	Resection
Dutta et al. [45]	1	Hilus	Biliary tuberculosis	EUS-FNAC, antituberculosis therapy
Fukuda et al. [51]	1	Hilus	Heterotopic gastric mucosa	Hepatectomy, caudate lobe and extrahepatic bile duct resection
Erdogan et al. [31]	32		Benign proximal biliary strictures	Resection
Ferrone et al. [21]	1	RHD	Neuroendocrine tumor	R trisegmentectomy, CBD resection, portal lymph dissection

Adapted from (with permission) Linehan DC, Jarnagin WR, Blumgart LH. Benign Tumors and Pseudotumors of the Biliary Tract. 2012; 50:751–763

ducts for preoperative diagnosis of cholangiocarcinoma between January 1984 and June 2005. Following postoperative histological examination, 32 (17.3 %) were found to be benign biliary strictures [32]. These data indicate that while suspicion of malignancy is initially high, a minority of patients will eventually be found to have benign disease on final pathologic examination.

Similarly, in a surgical series of 275 patients with preoperative radiological diagnosis of cholangiocarcinoma, postoperative diagnosis changed after histology in 22 (8 %) of the cases [33]. Again, all 22 patients had undergone surgical resection of the extrahepatic biliary tree for presumptive malignancy, 10 with combined partial hepatectomy. Some of the various etiologies of the benign pseudotumors missed were primary sclerosing cholangitis, granulomatous disease, nonspecific fibrosis/inflammation, and lymphoplasmacytic sclerosing pancreatitis and cholangitis [33]. Corvera et al. (2005) concluded that this "malignant masquerade" of the proximal bile ducts can result from numerous benign processes, often making differentiation from malignancy challenging. Highlighted above is the recurrent fact that preoperative diagnosis of biliary strictures is challenging and usually equivocal. For a presumed malignancy, surgical intervention remains the gold standard, as tissue diagnosis is essential to definitively rule out malignancy [34–37].

Inflammatory Tumors

Inflammatory pseudotumors are rare, idiopathic, benign, mass lesions composed of fibrous tissue with distinct, nonspecific inflammatory infiltrate [34, 38]. This infiltrate typically consists of a combination of inflammatory cells such as lymphocytes, plasma cells, eosinophils, and macrophages [38]. Vasiliadis and associates reported a benign endoluminal inflammatory pseudotumor in a 71-year-old female, who initially presented with jaundice, scleral icterus, and anorexia. Transabdominal ultrasonography revealed dilatation of intra- and extrahepatic bile ducts, proximal to the level of the mid-distal common bile duct (CBD) with no evidence of stones. MRCP and ERCP were performed, which revealed an obstructing mass in the mid-CBD suggestive of neoplasm. Attempts made to biopsy the mass during ERCP were unsuccessful and the patient subsequently underwent surgery. Intraoperatively, the CBD was dilated proximal to a palpable, firm mass in the mid-distal portion. A fibrosing lesion was found surrounding the mass, the adjacent lymph nodes, and the portal vein. Frozen sections of the proximal and distal CBD margins, in conjunction with the regional lymph nodes, were found negative for malignancy. An extrahepatic bile duct resection en-bloc with gallbladder and regional lymph nodes was subsequently performed [38]. Macroscopic examination revealed a 3 cm gray-white pedunculated mass protruding into the CBD. Microscopically, the inner epithelial layer of the CBD exhibited considerable reactive inflammatory changes with no evidence of atypia, dysplasia, or stenosis. The authors concluded that the endoluminal growing mass was consistent with a benign inflammatory

pseudotumor [38]. The patient recovered well with no evidence of recurrence 8 months following treatment. Deng and colleagues published a similar clinical occurrence of a patient in China, with a mass identified by abdominal ultrasound and MRCP to be in the right hepatic duct. The patient underwent surgical resection and the final diagnosis of inflammatory pseudotumor was confirmed following post-operative histopathological examination [39].

Immunoglobulin (IgG4)-associated sclerosing cholangitis (ISC) is another reported benign etiology that can mimic hilar cholangiocarcinoma when localized [32, 40]. Sixteen patients with ISC that manifested as localized hilar strictures were analyzed in attempt to illustrate certain clinical characteristics specific to ISC, as to assist in differentiating this disease from hilar cholangiocarcinoma [41]. Findings noted to be specific to ISC on biliary imaging included prominent bile duct thickening with relatively mild proximal dilatation ($n=11$), multifocal biliary tree involvement ($n=14$), and concentric bile duct thickening with luminal patency ($n=13$) [41]. Liver or endobiliary biopsy revealed significant infiltration of IgG4-positive cells in 11 of 16 patients (69 %), which was not evident in cholangiocarcinoma [41]. Furthermore, all ISC patients expressed significant improvement of respective strictures upon completion of appropriate steroid therapy. Based on these findings, Oh et al. concluded that certain clinical characteristics, such as specific biliary imaging or biopsy findings and improvement following steroids, could help in differentiating hilar strictures secondary to IgG4-associated sclerosing cholangitis from a malignant etiology like cholangiocarcinoma [41]. Even though a limited number of patients were analyzed in this study, the results offer potential new imaging guidelines to consider when diagnosing suspicious hilar strictures. Furthermore, this study highlights that ISC can be a significant cause of biliary stricture and therefore should not be forgotten in the differential diagnosis.

Mirizzi syndrome is a rare cause of biliary obstruction. It is characterized as an impaction of a stone in the cystic duct or neck of the gallbladder, which leads to mechanical or inflammatory compression and obstruction of the common hepatic or common bile duct. As a result, ongoing inflammation transpires, potentially leading to the formation of a cholecystocholedochal or cholecystoenteric fistula [42, 43]. This association between Mirizzi syndrome and fistula development is highlighted in a retrospective review of the 5673 elective or emergent cholecystectomies performed at Hospital De Ovalle in Chile from 1995 to 2006. Out of these 5673 patients, 327 (5.7 %) had Mirizzi syndrome and 105 (1.8 %) had a cholecystoenteric fistula [42]. Furthermore, 94 (89.5 %) of the 105 cholecystoenteric fistulas were found to be in association with Mirizzi syndrome [42]. Numerous variables such as age, sex, duration of gallbladder disease, presence of fistulas, or operations performed were analyzed to identify significant associations with this syndrome. Beltran and associates (2008) concluded that older age, female gender, and the presence of a cholecystoenteric fistula were all significantly associated with the development or presence of Mirizzi syndrome [42].

This established association of Mirizzi and cholecystoenteric fistulas validated the modified Mirizzi classification system developed by Csendes et al. (2007), which included the presence of cholecystoenteric fistula as a distinct type of Mirizzi syndrome, Type V [43]. According to this new classification, there are seven types

of Mirizzi syndrome (I-Vb), which addresses the presence of an associated cholecystobiliary fistula, cholecystoenteric fistula, or gallstone ileus [43]. The type of Mirizzi syndrome a patient has will ultimately dictate their respective treatment.

In addition to the development of fistulas, the chronic inflammation established by Mirizzi syndrome may cause significant biliary strictures that mimic cholangiocarcinoma. Patients with Mirizzi syndrome can manifest with obstructive jaundice, similar to those with malignant biliary etiologies, making definitive preoperative diagnosis challenging, as seen in a case of a 44 year old Asian man with a 2-month history of progressive jaundice. Abdominal ultrasound and ERCP were performed. ERCP demonstrated a stricture of the proximal bile duct, which extended to the confluence of the right and left hepatic ducts [44]. Initially endoscopic stenting was performed but failed. Further workup revealed an elevated CA19-9 level and on abdominal CT: dilated intrahepatic ducts, swelling of the proximal bile duct and gallbladder, and enlarged abdominal lymph nodes [44]. The patient underwent surgical exploration with dissection and delineation of the biliary tract anatomy. Intraoperatively, a thickened gallbladder wall with a large stone impacted in the cystic duct was discovered, resulting in external compression of the common hepatic duct, unveiling a classic picture of Mirizzi syndrome [44]. Subsequently, cholecystectomy with T-tube placement was performed. The patient had an uneventful postoperative course and was identified as stable 18 months later [44].

More recently, there have been reports of biliary tract infections raising a concern for potential malignancy upon initial presentation. Kanhere et al. reported a 45-year-old Caucasian woman who initially presented with obstructive jaundice. The patient had a significant past surgical history of a laparoscopic cholecystectomy 5 years prior with subsequent ERCP exploration and CBD stone extraction. Upon initial workup, the patient had elevated enzymes consistent with obstruction. Subsequent ERCP revealed a stricture at the junction of the cystic duct and CBD with dilatation of the proximal bile duct. No retained stones were visualized. Further workup with CT exhibited multiple hypodense right liver lesions, which ultimately led to the preoperative diagnosis of metastatic cholangiocarcinoma [45]. The shared multidisciplinary plan was to attempt percutaneous biopsy of a liver lesion and initiate systemic chemotherapy [45]. Unsuccessful with percutaneous approach, CT-guided core biopsy of the liver was then performed and a specimen was obtained for analysis. Histological examination of the liver core biopsies revealed a granulomatous process with Langhans giant cells, leading to suspicion of mycobacterial involvement [45]. As a result of the unique findings, Roux-en-Y hepaticojejunostomy was performed to resect the stricture. The final histopathology of the liver lesions was consistent with a multiple granulomas, which grew *Mycobacterium abscessus*, sensitive only to Amikacin [45]. The patient had no previous history of TB exposure, recent travel, or immunodeficiencies. The authors hypothesized that the cause of this unique occurrence may have been the result of minor trauma, which led to inoculation and later hematogenous spread of *Mycobacterium abscessus* to the hepatobiliary system [45].

From India, Dutta et al. reported a similar finding of biliary tuberculosis mimicking hilar cholangiocarcinoma in a 25-year-old male, who presented with 2-month history of intermittent, high-grade fevers, jaundice, and significant weight loss. Comparable to the previous cases mentioned, diagnostic-imaging modalities led to the suspicion of cholangiocarcinoma, which ultimately requires surgery. However, in this particular case, they deemed the mass unresectable as CT revealed encasement of the portal vein, superior mesenteric vein, superior mesenteric artery, and inferior vena cava [46]. As a result, ultrasound-guided fine needle aspiration cytology of the porta hepatis lymph nodes was performed instead for definitive tissue diagnosis. Histological examination revealed granulomatous pathology and the patient was started on antitubercular therapy. Six months following therapy completion, the patient remained asymptomatic with alleviation of obstruction. The authors indicated that biliary tuberculosis is a rare entity that involves the bile duct leading to obstructive jaundice either by enlargement of adjacent lymph nodes or direct tuberculoses involvement of biliary epithelium [46], and that it was extrinsic compression from enlarged infected lymph nodes that led to obstructive jaundice evident in this young male patient. Thus, although negative preoperative tissue diagnosis will not avert surgery, it is of value as it might identify infectious causes of strictures, like tuberculosis, which can dramatically alter treatment.

Recent studies have attempted to improve preoperative diagnosis of biliary strictures, by exploring novel imaging or histologic techniques that may enhance sensitivity and specificity of less invasive measures. A study assessing the sensitivity of endoscopic ultrasound-guided fine needle aspiration cytology (EUS-FNA) in diagnosing malignant biliary strictures found that, out of 22 patients, EUS-FNA identified 16 cases to be malignant and 6 to be benign [47]. Following final histological examination, EUS-FNA was accurate on all accounts, correctly identifying the 16 histologically proven malignant cases and the 6 benign cases. Ohshima and colleagues concluded that EUS-FNA is a sensitive and safe diagnostic modality in patients with suspected malignant biliary strictures and may prove to be useful in the preoperative workup of these patients when imaging studies are unclear or biopsy results are negative. In a recent retrospective study, Yu and coworkers set to assess criteria for differentiating infiltrative cholangiocarcinoma from benign CBD strictures using three-dimensional dynamic contrast-enhanced (3D-DCE) magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) imaging [48]. The ultimate goal was to establish certain imaging predictors that are specific to cholangiocarcinoma versus benign strictures. 3D-DCE MRI and MRCP images were retrospectively reviewed from 28 patients with infiltrating cholangiocarcinoma and 23 patients with benign CBD stricture etiologies [48]. The results established two statistically significant predictors on 3D-DCE MRI and MRCP that suggest infiltrating cholangiocarcinoma when present. These two malignancy predictors were increased ductal thickness and hyperenhancement of the involved CBD during the equilibrium phase of the study [48]. Utilization of both predictors concomitantly led to the correct identification of 92.9 % ($n = 26$) of malignant strictures and 91.3 % ($n = 21$) of benign strictures [48]. They concluded that the use of 3D-DCE MRI and MRCP should be implemented in the diagnostic

workup of strictures suspicious for malignancy, although the number of patients is small in this series and the findings should be validated in other series prior to broad application.

Garcea et al. evaluated whether initial bilirubin values could assist in early discrimination between malignant versus benign causes of obstructive jaundice. Over 1000 patients with documented obstructive jaundice were analyzed during the time period of 2008–2010. The authors concluded that the greatest sensitivity and specificity for malignancy was a bilirubin >100 μmol/L [49]. While bilirubin level alone is not sufficient to rule out malignancy, it may aid clinicians as an adjunct test in the initial work up of biliary strictures and subsequently influence later treatment options. Similarly, Hashim and associates reported that the phosphatidylcholine concentration in the bile of cholangiocarcinoma patients was significantly less than those with benign biliary disease. Furthermore, it was discovered that taurine-conjugated (H-26) and glycine-conjugated (H-25) bile acids were significantly elevated in cholangiocarcinoma bile versus that from benign etiologies [50]. Adapting the routine use of these biomarkers, in conjunction with new imaging modalities, may enable physicians to significantly improve the sensitivity and specificity of a preoperative diagnosis. Improvements in less-invasive, diagnostic measures may ultimately help avoid radical surgical procedures in patients with benign etiologies.

Heterotopic Tissue

Symptomatic heterotopic tissue arising in the biliary tree is exceedingly rare. In 1967, Whittaker and colleagues initially observed heterotopic gastric mucosa in a cystic duct that had obstructed the gallbladder [2]. Later, Kalman and associates (1981) reported a 1-cm papillary tumor in the common hepatic duct. On histological examination, the tumor expressed gastric fundal mucosa that replaced the full thickness of the bile duct wall [51]. More recently, Fukuda and associates reported the occurrence of heterotopic gastric mucosa in the hilar bile duct in an asymptomatic 58-year-old male. Workup included an abdominal CT, which exhibited wall thickening from the upper common hepatic duct to the left hepatic bile duct, and subsequent ERCP, which revealed stenosis at the junction of left hepatic bile duct [52]. Again, unable to rule out malignancy, the patient underwent a left hepatectomy, caudate lobe and extrahepatic bile duct resection. Microscopic analysis of the surgical specimen revealed a polypoid lesion composed of mucous glands resembling gastric fundic glands, with parietal and chief cells [52]. The authors concluded that the lesion was heterotopic gastric mucosa in the hilar bile duct. Kim et al. reported a biliary duplication cyst with heterotopic gastric mucosa obstructing the biliary system in an 8-year-old girl who initially presented with several months of abdominal pain. Preoperative workup revealed a mass in the portal triad. Intraoperative exploration revealed a cystic mass, with significant inflammation, which ultimately created a “Mirizzi-like” picture [52]. Consequently, this led to complete obstruction of the right and left hepatic duct confluence. Postoperative histological examination

revealed the specimen to be a duplication cyst that was lined with heterotopic gastric mucosa [52]. The diagnosis could only be ascertained with surgical resection in this case, further underlining the difficulties of making a firm diagnosis in the preoperative setting for these complex biliary processes.

Summary

Although biliary lesions resulting in obstruction are commonly due to malignancy, benign tumors or pseudotumors are differential diagnoses that warrant significant consideration when the clinician is faced with a patient suffering from obstructive jaundice. As highlighted throughout this chapter, definitive preoperative diagnosis of these benign etiologies remains a considerable challenge. While recent advances have been noted in regard to new imaging or tissue sampling techniques, surgery continues to remain the gold standard for diagnosis and treatment of these benign processes "masquerading" as malignant entities.

Conflicts or Disclosures None

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