Tumors of Extrahepatic Bile Duct

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10.1 Benign Tumors of Extrahepatic Bile Duct

The rate of extrahepatic biliary benign tumors is very low, accounting for less than one tenth the rate of malignant biliary tumors, and the diameter of the tumor varies from several milimeters to centimeters; thus, intrabiliary growth often leads to stenosis of the bile ducts resulting in obstructive jaundice, of which adenoma is the most common type which accounts for about 75% of all benign tumors of extrahepatic bile duct.

10.1.1 Adenoma

The discovery rate of extrahepatic biliary adenoma (bile duct adenoma, BDA) in biliary surgeries is 0.1%, much lower than that of adenoma of the gallbladder. And two thirds of the extrahepatic BDA are solitary, and the most common site is the distal one third of the bile duct near the ampulla. BDA grows into the lumen of the bile duct which is often less than 1 cm in diameter, causing varying degrees of biliary stenosis and clinical symptoms due to biliary obstruction. Pathologically, it can be divided into three types:

① Tubular BDA is composed of small tubular glands which are densely arranged, and the gland epithelium is cubic or columnar, often with mucus secreting.
② Papillary BDA is the most common type with multigrade slender papillary branches on the surface [1], and the papilla consists of cubic or columnar epithelial cells containing mucus. The tumor size can reach 3 cm in diameter. It is also known as villous adenoma for the long and slender papilla-like villi (Fig. 10.1).

③ Tubular-papillary BDA consists of tubular glands and papillary structures, with each component accounting for more than 20%. Surgical resection is effective for the treatment of BDA. Dowdy et al. reviewed foreign literature and found 27 cases of BDA with complete pathological data from 1929 to 1960 [2], while Ming-yin Lan et al. (2012) analyzed the 17 cases of BDA reported at home and abroad from 1961 to 2011, including eight cases in upper part, one case in the middle part, and eight cases in the lower extrahepatic biliary system, showing that the male to female ratio was 5:12, the average age was 58.4 (21–73) years, and the clinical manifestations are nonspecific digestive and biliary symptoms.

Oshikiri et al. (2002) reported that glandular epithelium of papillary adenoma may contain atypical hyperplasia or focal carceration [3], and p53and Ki-67 staining can be carried out to evaluate the lesions. Tretiakova et al. (2012) reported that almost all of the extrahepatic biliary benign tumors, including BDA and low-grade dysplasia, were positive for CD10, with the number of positive stained cells ranging from 20 to 80%, and malignant tumors, including adenocarcinoma and high-grade dysplasia, were all CD10 negative, which can be considered as a key point in the differential diagnosis [4].

10.1.2 Granular Cell Tumor

10.1.2.1 Pathogenesis and Mechanism

Abrikossoff first reported granular cell tumor (GCT) in 1926, and in 1952, Coggins reported the first case of biliary GCT [5], also known as granular cell myoblastoma, which is a type of neurogenic tumor derived from Schwann cells based on the evidence in histology, immunohistochemistry, and electron microscopic observations. GCT is often found in the skin, subcutaneous tissues, tongue, breast, and gastrointestinal tract, while cases in the hepatobiliary system are rare with an incidence rate of less than 1% in all GCT. More than

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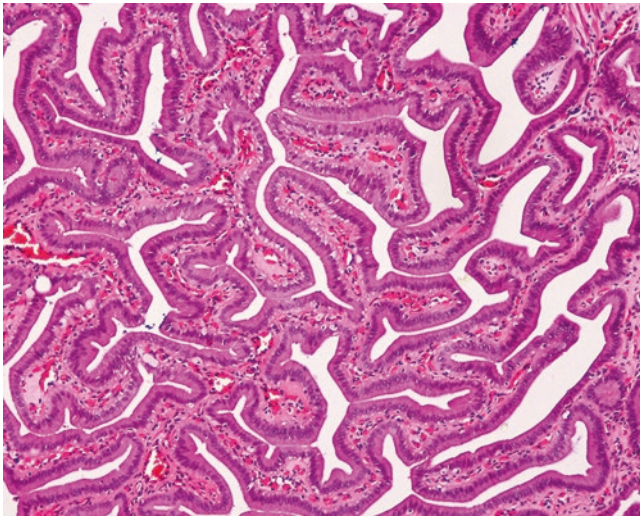e-mail: wmcong@smmu.edu.cn

Fig. 10.1 Extrahepatic biliary adenoma: the adenoma cosists of multigrade slender papillary branches on the surface, with fibrovascular cores, and the papilla consists of cubic or columnar epithelial cells containing mucus

70 cases of GCT in the extrahepatic biliary tree had been reported in the literature by 2012, accounting for less than 10% of biliary benign tumors [6, 7]. The tumor can show multicentric growth pattern, accompanied by GCT lesions in the gallbladder or skin.

10.1.2.2 Clinical Features

Foreign reports of granular cell tumor involve mainly the Negro population (60.5%) and young females (81%), with an average age of 33.9 (11–63) years. The clinical manifestations are similar to those of sclerosing cholangitis and cholangiocarcinoma, including abdominal pain (88%) and jaundice (53%). The lesions are often found in the junction of the cystic duct, common hepatic duct, and common bile duct [8], including common bile duct (58.1%), common hepatic duct (23.3%), cystic duct (14%), gallbladder, and duodenal ampulla (2.3%) [7]. Portal granular cell tumor can be similar to portal cholangiocarcinoma.

10.1.2.3 Gross Features

The lesions are often solitary without capsule, brownish yellow or yellowish white, and the average diameter is 1.6 (0.5–4) cm.

10.1.2.4 Microscopic Features

Tumor cells are arranged in sheets, acini, or clusters, with connective tissue separation. The tumor cells are polygonal or round in a larger size, rich in eosinophilic granular cytoplasm, with indistinct cell borders, and small and darkly stained nuclei (Fig. 10.2). These tumor cells can invade the whole layers of the bile duct wall, as well as nerve and small blood vessels in the biliary wall [7].
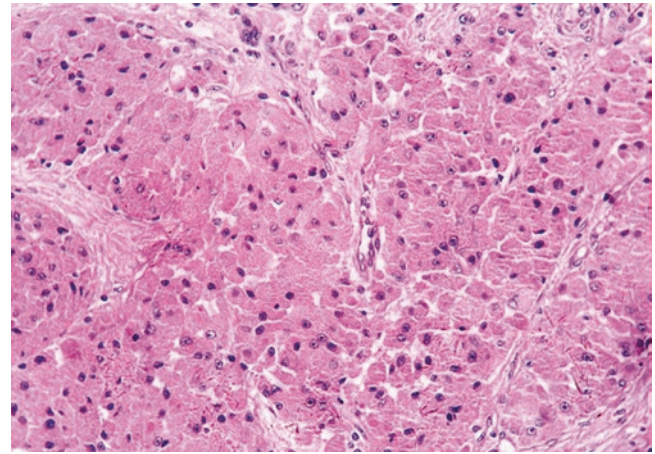

Fig. 10.2 Granular cell tumor of extrahepatic biliary: the tumor cells are arranged in acini, with abundant eosinophilic granular cytoplasm

10.1.2.5 Immunohistochemistry

The tumor is positive for S-100, GFAP, and NSE staining.

10.1.2.6 Electron Microscopic Observation

Large quantities of lysozyme granules in the cytoplasm can be observed.

10.1.2.7 Differential Diagnosis

Although there is no report of malignant GCT of the bile duct, we should also pay attention to this kind of tumor. Generally, malignant GCT should show corresponding pathological biological behaviors, including invasion of surrounding tissues and cellular atypia, mitotic figures, rapid growth, tumor diameter >4 cm, metastasis and recurrence, etc.

10.1.2.8 Treatment and Prognosis

GCT of the gallbladder or cystic duct can be treated with simple cholecystectomy, and GCT of pancreatic segment of extrahepatic bile ducts often needs to be treated with Whipple surgery, while postsurgical radiotherapy and chemotherapy are not necessary for benign GCT lesions.

10.1.3 Cystadenoma

Ninety percent of cystadenoma are found in intrahepatic biliary system, and extrahepatic biliary adenoma is rare with about 100 cases in the current literature. Ninety-five percent of cystadenoma are mucinous, and the rest are serous. The average onset age of the patients is 48–58 years, and 80% of the patients manifest as obstructive jaundice. The serum CA19-9 can be elevated. Thickened cystic wall displayed on imaging, with calcification and papilla in the septa of the cystic cavity, suggests malignancy of the tumor [9]. Grossly,

the tumor is often a solitary, spherical, or round mass, cyst-solid in texture, and the section shows multilocular structures, containing mucus or serous fluid. The tumor grows and extends along the biliary lumen of 2.5–28 cm in size. Histologically, 80% of cystadenomas are characterized by a monolayer of cubic or columnar epithelium and underlying ovary stroma (Fig. 10.3). The patients are predominantly females. Ovary stroma can be positive for ER and PR. However, cystadenoma without ovary stroma is often found in the elderly with no significant gender difference. The stromal component is hyalinized collagen connective tissue [10]. The postsurgical recurrence rate of biliary cyatadenoma is 10%, which may develop into cystadenocarcinoma. Studies have shown that the prognosis of hepatobiliary cystadenoma with ovary-like stroma is better than that of cases without ovary-like stroma [11]. This kind of tumor should be differentiated from simple cyst, cystic hamartoma, intraductal papillary tumor of bile duct, etc.

10.1.4 Papillomatosis

Caroli first described multiple papillomatosis of bile duct in 1958, and there have been nearly 140 biliary cases up to now, the pathogenesis of which may be related to bile stimulation and chronic inflammation of the bile duct, including bile duct stones, *Clonorchis sinensis*, Caroli's disease, ectopic pancreas, abnormal biliary tree, and primary sclerosing cholangitis [12]. Male patients are slightly more common with a male to female ratio of 2:1, and the common age range is 60–70 years. One case of the disease was found in the Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, concerning a
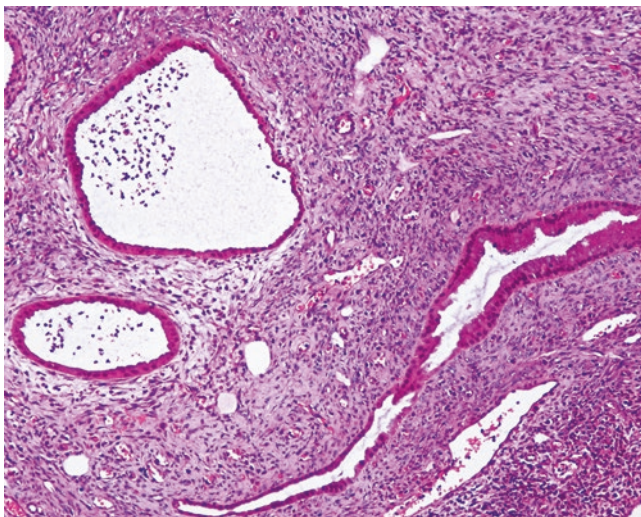
54-year-old female, with multiple submucosal papillary lesions on the upper segment of common bile duct via choledochoscope, which was diagnosed as papillomatosis of the common bile duct based on the microscopic features (Fig. 10.4). Extrahepatic biliary papillomatosis may involve both the intrahepatic and extrahepatic biliary systems, and clinical manifestations are characterized as recurrent obstructive jaundice and cholangitis. ERCP examination is useful in establishing the diagnosis. Histologically, the tumor grows inward the biliary cavities with papillary structures and should be differentiated from canceration of papillomatosis or papillary adenocarcinoma based on the careful identification of the atypia of the tumor cells and the existence of biliary wall invasion. It has also been considered as a low malignant tumor according to its clinical and biological behaviors. Lee et al. (2004) suggested in a study that the canceration rate of biliary papillomatosis was as high as 83% [13]. Surgical resection is the preferred therapy; however, recurrence rate is high due to unresectable margin of the lesions or multi-lesion. Thus, for cases involving multigrade branches of bile ducts with high malignant potential, liver transplantation may be the best choice to improve the prognosis [14].

10.1.5 Adenofibromyomatous Hyperplasia

Adenofibromyomatous hyperplasia has a low incidence in extrahepatic bile duct, and most of the cases are found in the Vater ampulla at the end of the common bile duct. Imaging shows irregularly thickened wall of the common bile duct, and the formation of tumor-like nodules can be diagnosed as adenomyoma. Histologically, it presents hyperplasia of
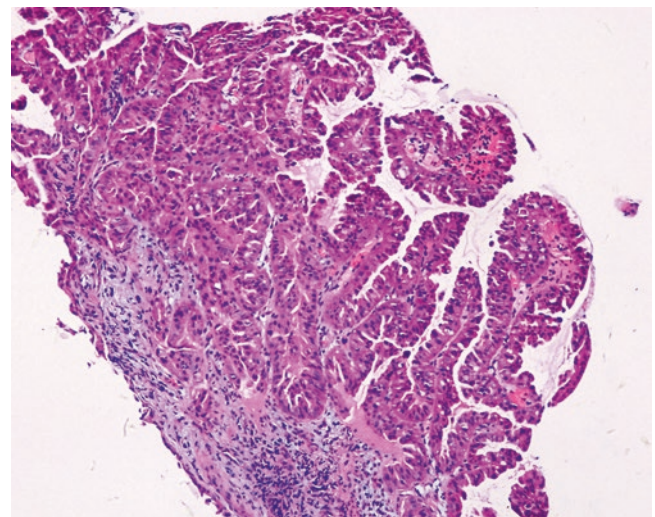

Fig. 10.3 Cystadenoma of extrahepatic biliary: the cystadenoma is characterized by a monolayer of cubic or columnar epithelium and underlying ovary stroma

Fig. 10.4 Papillomatosis of extrahepatic biliary: the tumor grows inward the biliary cavities with papillary structures

submucosal glands and smooth muscles (Fig. 10.5). Muriel et al. (2009) reported one case of diffuse adenomyomatosis in the lower part of the common bile duct, extending a length of 4 cm, with microcysts of 1–3 mm in diameter on the cystic wall. The microscopic observation shows benign hyperplasia of glands with focal low-grade intraepithelial neoplasia [15]. Cases with atypia in the hyperplastic mucosal glands and obstructive jaundice should be differentiated from cholangiocarcinoma.

10.1.6 Angioleiomyoma

Pönkä et al. (1983) reported one case of an 80-year-old female with a space-occupying lesion in the common bile duct via ERCP, which was pathologically confirmed as angioleiomyoma [16].

10.1.7 Leiomyoma

So far, five cases of leiomyoma have been reported in the literature [17], including three cases of common bile duct leiomyoma which were all located in the pancreatic segment of the common bile duct, possibly related to the existence of the circular smooth muscle or sphincter. The tumor is only a few millimeters in diameter, and no other special symptoms or signs are found apart from obstruction jaundice. Serum CA19-9, CEA, and AFP were negative.
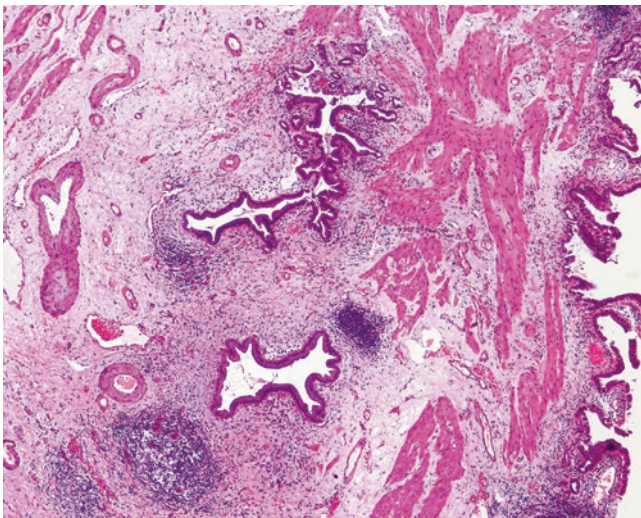

Fig. 10.5 Adenofibromyomatous hyperplasia of extrahepatic biliary: the lesion presents hyperplasia of submucosal glands and smooth muscles

10.1.8 Traumatic Neuroma

Traumatic neuroma is caused by tumor-like hyperplasia of the nerve and fibrous tissues in the injured bile duct wall, with varying components of the nervous tissues. It is often found in the residues of cystic duct after cholecystectomy. Herrera et al. (2009) reported 15 cases of traumatic neuroma in postsurgical extrahepatic biliary system after liver transplantation. The incidence rate of traumatic neuroma is 3.5% (15/428), and the lesions may originate in the common bile duct wall (type I) or the peripheral nerve tissue (type II) [18]. In addition, a few cases of neurofibromatous hyperplasia are found secondary to chronic cholecystitis.

10.1.9 Paraganglioma

Less than five cases of biliary paraganglioma have been reported in the literature, with the first case reported by Sarma et al. in 1980 [19]. Hitanant et al. (1984) reported a case of a 5 cm × 2 cm × 1.8 cm paraganglioma in the common hepatic duct which was surgically excised [20]. Caceres et al. (2001) reported one case of a 28-year-old female with surgically excised paraganglioma in the common bile duct, who manifested as right upper abdominal pain for more than 3 months, with normal serum catecholamine and no symptoms caused by biliary obstruction, and she showed good condition during the 6-year follow-up after the resection. Its microscopic features are similar to common paraganglioma, and the tumor consists of chief cells and supporting cells, forming cellular nests (cellular sphere), containing rich granular cytoplasm. Fibrous septa with abundant capillaries are found between these nests. Immunohistochemistry staining shows that the nest margin contains S-100-positive supporting cells containing neuroendocrine particles which can be found in electron microscopic images [21]. Malignant biliary paraganglioma has been reported in rare cases and should be carefully distinguished.

10.1.10 Neurofibroma

Neurofibroma is rare, and less than 20 of cases have been found in foreign literature so far [22]. Most of the tumors are associated with neurofibromatosis type 1 gene (NF1), but there are also reports of primary neurofibroma in the common bile duct [23]. Sukanta (2011) et al. reported one case of a 47-year-old female with neurofibroma in the common bile duct which was surgically excised. A lesion of 2 cm×2.5 cm

of the common bile duct was found, causing stenosis and resulting in progressive obstructive jaundice. Two cases of extrahepatic biliary neurofibroma have been diagnosed in the Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, concerning a 57-year-old male with a 2 cm × 1.8 cm lesion and a 68-year-old female with a 0.4 cm × 0.5 cm lesion, respectively. The tumors are grossly solid, grayish white, and nodular, while the microscopic observation shows that they are similar to common neurofibroma, with spindle tumor cells in wavy, spiral, or fence-like arrangement, and no atypia is observed. Immunohistochemistry shows that the tumors are positive for neural markers such as S-100 (Fig. 10.6).

10.1.11 Inflammatory Myofibroblastic Tumor

Extrahepatic biliary inflammatory myofibroblastic tumor (IMT) is a special type of inflammatory pseudotumor, which is more prone to present invasive behaviors, or is an independent type of lesions containing myofibroblasts. Its histological features are the same with those of intrahepatic IMT [24], and cases with positive expression of anaplastic lymphoma kinase (ALK) concern more young patients with a good prognosis. On the contrary, ALK negative cases are more common in elder patients with higher rate of metastasis. Biliary IMT lesions are often benign in nature; however, Kim et al. (2011) reported one case of portal IMT with high invasiveness, consisting of atypic tumor spindle cells, with common mitotic figures, and the myofibroblasts were positive for SMA and vimentin. Metastasis in the right chest wall was found 4 months after surgery, and malignant spindle cells were found in biopsy [25]. Thus, invasive IMT should be identified in the diagnosis of IMT.

10.1.12 Inflammatory Pseudotumor

Extrahepatic biliary inflammatory pseudotumor (IPT) has been reported in more than ten cases, and its histological features are the same with intrahepatic IPT. It consists of chronic inflammatory cells and hyperplastic fibrous connective tissues, causing biliary obstruction which leads to jaundice clinically, similar to the manifestation of portal cholangiocarcinoma or extrahepatic cholangiocarcinoma (ECC). Blanton et al. (2011) reported one case of a 20-year-old female with persistent jaundice. Abdominal CT showed dilatation of intrahepatic bile ducts, with obscure soft tissue densities in the portal area. ERCP demonstrated that an irregular stenosis was shown in the middle of the common hepatic duct, and choledochoscopic observation showed ulcerative changes. Cytological and choledochoscopic biopsy showed no definite malignant lesions. Postsurgical pathological examination confirmed the composition of spindle myofibroblasts, plasma cells, lymphocytes, eosinophilic granulocytes, and neutrophils, leading to obstruction and thickened wall of the common bile duct (incorrect, reference resource was not found), suggesting the possible existence of IPT in suspected cases of extrahepatic biliary malignant tumor. Some patients have IgG4-related sclerosing cholangitis in the background of autoimmune pancreatitis, with marked elevation of serum IgG4, and immunohistochemistry shows the presence of large quantities of IgG4-positive plasma cells. And these patients are sensitive for hormone therapy.
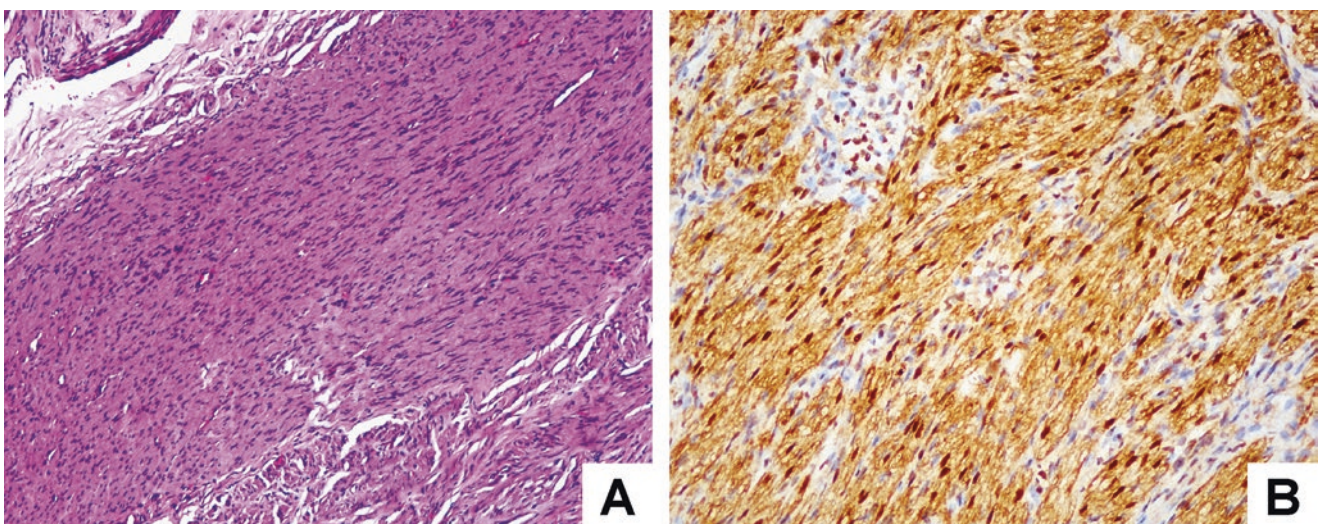

Fig. 10.6 Neurofibroma of extrahepatic biliary: (**a**) spindle tumor cells are in wavy, spiral, or fence-like arrangement and no atypia is observed; (**b**) immunohistochemistry shows that the tumor is positive for neural marker S-100

10.1.13 Gastrinoma

Gastrinoma is common in the pancreas and duodenum, while cases involving the extrahepatic biliary (including the common bile duct and common hepatic duct) are rare with only about ten cases reported in the literature, suggesting the possible origination in the stem cells of the ventral pancreatic bud. It manifests clinically as typical Zollinger-Ellison syndrome, but biliary obstruction or jaundice is rare. The tumor can form a mass larger than 1 cm in diameter on the biliary wall. Immunohistochemistry shows that it is positive for CgA and Syn and positive or negative for gastrin. Hepatic MRI and CT or single photon emission computed tomography of somatostatin receptor are helpful to exclude metastatic tumors originating from the liver or the "gastrinoma triangle." Early detection and surgical resection receive a good prognosis, with disappearance of clinical symptoms and return to normal serum gastrin [26].

10.1.14 Eosinophilic Cholangitis

According to statistics, about 10% of tumors causing portal stenosis are confirmed as benign tumors after surgical resection, which are also known as malignant masquerade. For instance, eosinophilic cholangitis in the common bile duct shows similar clinical and imaging features to cholangiocarcinoma. Dubay et al. (2010) reported one case of a 29-year-old female with upper abdominal pain and other digestive symptoms, and magnetic resonance cholangiopancreatography showed a 2 cm long stenosis in the middle of the common bile duct. Endoscopic ultrasound images showed an 8 mm focal wall thickening of the common bile duct, which was reactive bile duct epithelium shown in puncture examination, without tumor cells. The pathological examination showed that the thickened common bile duct wall contains infiltration of a large number of mature eosinophilic inflammatory cells and formation of eosinophilic abscess, with proliferated fibroblasts, and the pathological diagnosis was eosinophilic cholangitis. The disease often can be accompanied by increased eosinophilic granulocytes in the blood, and the differential diagnosis needs to be made to exclude the use of steroid hormone, parasite infection, and allergic reaction [27].

10.1.15 Neurilemmoma

Neurilemmoma derives from Schwann cells, also known as Schwannoma, and the predilection site is the digestive tract including the stomach, colon, and esophagus, while cases involving extrahepatic biliary system are rare with 15 cases reported in the foreign literature by 2012 [28]. Domestic cases of extrahepatic biliary neurilemmoma including those reported by our hospital can also be found [29]. The patients present a male to female ratio of 1:4, and an age range of 15–64 years (44 years old on average), and most of them (11/15) have symptoms of obstructive jaundice. The tumor originates in the Schwann cells of peripheral nerve of the biliary wall, with a capsule, and intratumorous hemorrhage, hyaline degeneration, and cystic degeneration can be found in some cases. The tumor consists of two main structures. Antoni A type contains densely distributed spindle or oval cells in the palisade and plexiform form. Antoni B type consists of loose and disordered tumor tissues in the myxoid matrix with edema. It is currently believed that neurilemmoma deriving in the digestive tract is mainly Antoni A type without mutations of neurofibromatosis type 2 gene (NF2) [30]. And it should be differentiated from neurofibroma, gastrointestinal stromal tumor, and leiomyoma. Immunohistochemistry shows that it is positive for S-100 and vimentin and negative for CD117 and CD34. Surgical resection prompts a good prognosis.

10.1.16 Heterotopias

Heterotopias of gastric mucosa into the extrahepatic biliary system are the most common type, and nine cases have been reported in the foreign literature with a male to female ratio of 2:1 and an average age of 37 (3–83) years. Of which six cases are found in the location near the junction of common bile duct and cystic duct, while the rest are located in the left hepatic duct, portal bile duct, and ampulla. The lesions are 3–25 mm in size, and the patients may present jaundice, abdominal pain, etc [31]. In addition, other ectopic tissues include pancrea, duodenum, accessory liver, adrenal gland, and thyroid gland, and imaging shows biliary occupying lesions. In histology, these ectopic tissues consist of normal parenchymal cells of the primary organs. However, malignancy has also been discovered in them and should be carefully observed when necessary.

Moreover, other benign non-epithelial tumors of the extrahepatic bile duct include lipomyoma, lymphangioma, angioma, melanoma, etc. The histomorphology is similar to those in soft tissues, which need not be repeated here.

10.2 Malignant Tumors of Extrahepatic Bile Duct

10.2.1 Extrahepatic Cholangiocarcinoma

10.2.1.1 Pathogenesis and Mechanism
Cholangiocarcinoma is usually abbreviated for extrahepatic cholangiocarcinoma (ECC). Extrahepatic bile ducts include

the left and right hepatic duct, common hepatic duct, cystic duct, and common bile duct, and according to the orientation of the common bile duct and the relationship with the surrounding organs, it can be divided into superior-duodenum, posterior-duodenum, and pancreatic and duodenal wall segments. The incidence of ECC is low and knowledge on ECC is far more less than that on intrahepatic cholangiocarcinoma. And 50–75% of the tumors are found in the upper one third of extrahepatic bile ducts including the portal area, and the lesions are more common in the confluence of thecommon bile duct, hepatic duct, and cystic duct. Cases in the middle one third (segment of the common bile duct between the cystic duct and the inferior margin of duodenum) account for 10–25%, while cases involving the lower one third segment (segment of the common bile duct between the inferior of duodenum and Vater ampulla) account for 10–20%. The predilection age is 60–70 years, and no gender difference is found related to the incidence. According to the domestic joint analysis on the 1979 autopsy cases of malignant tumors conducted by 38 departments of pathology of medical university, ECC accounted for only 0.07%. And according to the statistics provided by Shanghai Cancer Research Institute, male and female standardized incidences of gallbladder carcinoma and cholangiocarcinoma from 1978 to 2000 had been raised from 1.6/100000 and 2.3/100000 to 3.8/100000 and 5.4/100000, which were 2.46/100000 and 3.77/100000 in 2005, respectively, suggesting a drop in the incidence. Furthermore, it has been reported that new cases of gallbladder carcinoma and extrahepatic cholangiocarcinoma reached about 9810 in the USA in 2012, with 3200 death cases. And statistics of related data from 1985 to 2005 showed that the incidence of ECC in males and females were 1.1/100000 and 0.7/100000, respectively [32, 33].

The pathogenesis of ECC remains unclear, and the etiology may include ulcerative colitis (the incidence of which may be 9–21 times higher than that in normal population), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and several congenital biliary malformations such as congenital choledochocyst, congenital cyst of common bile duct (CCC), congenital malformation of the biliary tract, Carroli's disease, congenital hepatic fibrosis, polycystic liver and anomalous pancreatico-choledocho-ductal junction, biliary stones, parasitic infections (such as *Clonorchis sinensis*), exposure to chemical carcinogens, etc. (such as thorium anhydride), and patients with these lesions should be followed up closely. Other risk-increasing factors include diabetes, smoking, drinking, and infection of HBV/HCV [34–36]. Wang et al. (2011) made a meta-analysis on ECC, showing that 28–50% of the patients were (40% on average) p53 positive, the higher expression levels of which were associated with poorer staging of the tumor and histological type, vascular invasion, and lymphatic metastasis [37]. Chung et al. (2009) examined the tissue microarray of 221

cases of ECC and found elevation of phosphorylation AKT and mTOR levels [38], as well as reduction of PTEN expression in ECC, suggesting the possible application of PTEN, PTEN/p-AKT, and PTEN/p-mTOR as indicators for evaluation of the prognosis of ECC. Kawamoto et al. (2007) discovered that ECCs contain amplification of HER-2 gene (21.4%) and positive expression of the protein (31.3%); the practical significance needs further confirmation [39].

Nitta et al. (2014) found that the high expression rate of Ambra1, an autophagy protein, in cholangiocarcinoma was 71%, and the remaining 29% showed low expression. Ambra1 expression and lymphatic metastasis ($P = 0.0391$) or poor postsurgical 2-year overall survival rate ($P = 0.0209$) were significantly correlated, suggesting that autophagy played an important role in the invasive growth process of cholangiocarcinoma [40]. Nitta et al. (2014) found that epithelial-mesenchymal transition (EMT) is an important phenotype feature for cholangiocarcinoma and EMT associated markers showed significant correlation with the poor prognosis of cholangiocarcinoma, including E-cadherin ($P = 0.0208$), N-cadherin ($P = 0.0038$), and S-100A4 ($P = 0.0157$) [41].

10.2.1.2 Clinical Features

Wen-bing Wang et al. (2008) published a group of data showing that ECC patients were predominantly male, accounting for about 69% in all cases, while females accounted for only 31%, and the age range was 30–82 years with an average age of 58.6 years. Jaundice was the most common clinical symptom, which appeared earlier than that in gallbladder carcinoma with progression or volatility, found in 81.4% of all the cases. Other clinical manifestations included upper abdominal pain (29.2%), upper abdominal distension and discomfort (13.7%), itch (9.3%), fever (8.1%), and lack of appetite (5%) [42]. Laboratory tests showed elevation of tatal bilirubin and marked elevation of serum CEA and CA19-9. A total of 563 cases of surgically excised ECC were diagnosed in the Department of Pathology, Eastern Hepatobiliary Surgery Hospital, the Second Military Medical University from 2007 to 2014, and the average age of the patients was 59.1 (13–82) years, including 359 males and 204 females, with a male to female ratio of 1.76:1.

There are two basic points of the imaging features of ECC: ① biliarty obstruction caused by tumor lesions and ② direct signs of the tumor and the biliary invasion in imaging. The X-ray examination shows soft Rattan-like expansion of the bile ducts proximal to the obstruction, with irregular concentric or eccentric stenosis in the obstructive bile duct. And endoscopic retrograde cholangiopancreatography (ERCP) is very useful for the location of the ECC lesions, while endoscopic ultrasound has a diagnostic accuracy of 86% for detection of the infiltration depth of the ECC. Combined application of ERCP and percutaneous transhepatic

cholangiography (PTC) can show the complete superior and inferior margins of the tumor, which is of crucial significance in determining the size, region, and treatment regime of the tumor; however, it may cause hemorrhage, bile leakage, biliary tract infection, pneumothorax, and other complications, due to its invasiveness. Magnetic resonance cholangiopancreatography (MRCP) is noninvasive, nonradioactive with arbitrary tomography and high resolution for soft tissues, etc., and the tumor is mainly the signal of soft tissue masses or thickened biliary wall, with irregular biliary stenosis. It is of important value in detection of the infiltration into the surrounding tissues and lymphatic metastasis, due to its good capacity in angiography, especially the advantage in the simultaneous imaging of both the superior and inferior segments of the obstructive bile duct after 3D reconstruction with high sensitivity and specificity. With the application of new technology of high-resolution ultrasound, detection rate of extrahepatic biliary cholangiocarcinoma can be up to 90.16% via color Doppler ultrasound [43].

10.2.1.3 Gross Features

In China, the incidence of ECC is higher than that of ICC, especially in portal ECC, accounting for 40–60% of malignant tumors of bile duct [44]. And the incidence for cholangiocarcinoma in foreign countries is 50% in portal area and 40% in extra-portal areas, while less than 10% of intrahepatic cholangiocarcinoma are found [45]. Since Klatskin first described the clinical and pathologcial features of hilar cholangiocarcinoma in 1965, it was also named as Klatskin tumor in former literatures and was preciously divided into four types: type I, tumor confined in the common hepatic duct; type II, tumor located in the confluence of the left and right hepatic ducts; type IIIa, tumor with invasion of the confluence of common hepatic duct and common bile duct and the right hepatic duct; type IIIb, tumor with invasion of the confluence of common hepatic duct and common bile duct and the left hepatic duct; and type IV, tumor with invasion of both the left and right hepatic duct.

On gross appearance, ECC can be divided into four types. ① Polypoid-papillary type: tumor is papillary, cauliflower, or polypoid, growing inward the biliary lumen, also known as intraductal type (Fig. 10.7). This type rarely invades the surrounding tissues and can be developed from multiple adenomas or papillomatosis, and papillary adenocarcinoma can grow in polypoid pattern occluding the lumen. Necrosis and detachment of the tumor may cause fluctuant jaundice. ② Nodular type: the tumor is nodular, with a diameter of 1–5 cm, surrounded by fibrous tissues. ③ Sclerosing type: the tumor grows invasively in the biliary wall, resulting in thickness and stiffness of the biliary wall and circular stenosis of the lumen, while the definite tumorous margin cannot be determined grossly, also known as interductal type. ④

Fig. 10.7 Extrahepatic cholangiocarcinoma: polypoid-papillary type, the tumor is papillary, cauliflower, or polypoid, growing inward the biliary lumen

Diffusely infiltrating type: this type often grows and disseminates along the biliary lumen.

10.2.1.4 Microscopic Features

The vast majority of tumors are adenocarcinomas of varying degrees of differentiation, and well-differentiated cases are similar to biliary adenoma. The diagnosis of malignant cases is difficult to make, in which increased atypia, karyoplasmic ratio, and obvious nucleoli of the same glands, or stromal and perinervous infiltration, concentric interstitial reaction around the same glands, are the key features of malignancy in the diagnosis. According to the cellular morphology, the tumors can be divided into biliary type, intestinal type, and foveolar type, similar to the classification of adenocarcinoma of the gallbladder. However, biliary type of the tumor shows more mature appearance of extrahepatic biliary differentiation and contains more fibrous connective stroma. In addition, cholangiocarcinoma cells often produce mucus and express CEA, with metaplasia and dysplasia in the surrounding epithelium, such as squamous metaplasia and clear cell degeneration or neuroendocrine differentiation, or even with changes of small cell neuroendocrine carcinoma. Well-differentiated adenocarcinoma is rare, which is similar to adenoma consisting of gastric foveolar epithelium. On the basis of cellular arrangement, it can be divided into the following four categories.

10.2.2 Papillary Adenocarcinoma

The carcinoma cells are tall – columnar or cubic – forming papillary structures (Fig. 10.8a–c). About 72% of the papillary adenocarcinomas are located in bile ducts outside the portal area [35].
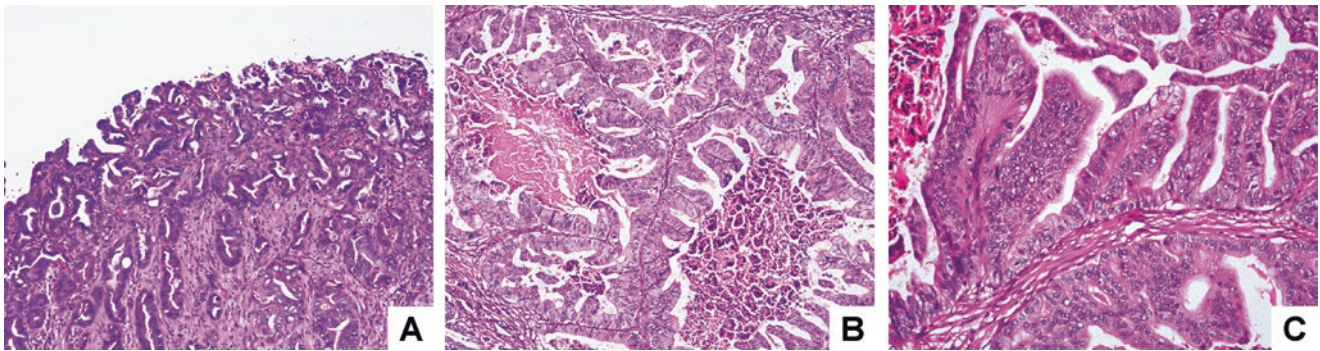
Fig. 10.8 Extrahepatic cholangiocarcinoma: (**a**) the carcinoma cells are tall, columnar or cubic, forming papillary structures, infiltrating from mucosal surface to submucosa; (**b**) tumor necrosis; (**c**) obvious mitotic figures
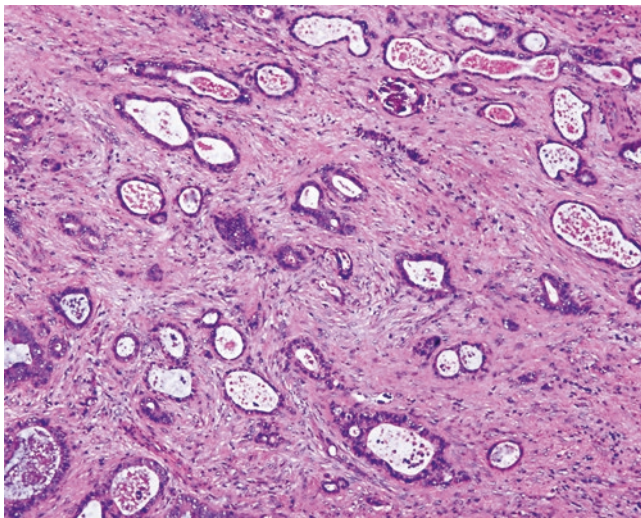

Fig. 10.9 Tubular adenocarcinoma of extrahepatic biliary: the carcinoma cells are arranged in irregular tubular structures and show an infiltrative growth pattern

10.2.3 Tubular Adenocarcinoma

The carcinoma cells are cubic and arranged in irregular tubular structures (Fig. 10.9).

10.2.4 Poorly Differentiated Adenocarcinoma

The tumor is solid in cord or sheet structures (Fig. 10.10a–b).

10.2.5 Undifferentiated Adenocarcinoma

The carcinoma cells are polymorphic, giant cell-like, or sarcomatoid and grow in diffuse distribution.

10.2.6 Other Types

Similar to the gallbladder, squamous cell carcinoma (Fig. 10.11), adenosquamous carcinoma (mucoepidermoid carcinoma), mucinous adenocarcinoma (Fig. 10.12a–b), signet ring cell carcinoma, clear cell adenocarcinoma, spindle cell carcinoma, etc. can also be found in extrahepatic biliary system.

10.2.6.1 Immunohistochemistry

The positive rate for CK7, EMA, and CEA can be higher than 85%, and the positive rate for CK19 and CA19-9 can also be high. And foveolar pattern is positive for MUC5AC. Specific staining shows normal bile duct epithelium and contains acid mucin, while sulfuric acid mucin is found in cells of ECC.

10.2.6.2 Pathological Staging

In 2010, WHO proposed the TNM staging system for distal cholangiocarcinoma (Table 10.1).

10.2.6.3 Treatment and Prognosis

The prognosis of ECC is significantly better than that of gallbladder carcinoma, possibly due to the early discovery and treatment of ECC because of jaundice, and the 5-year survival rate is 18–54% [46], while 5-year survival rates in cases with focal infiltration and metastasis are 24 and 2%, respectively. ECC shows focal invasiveness in growth pattern, and the resection rate is 10–90%, with focal postsurgical recurrence, which is a common and poor prognosis. The pathways for its metastasis include the following: from the cystic duct to gallbladder, direct invasion throughout the biliary wall to the liver, along the biliary nerve or nerve sheath (Fig. 10.13a–b), and vascular and lymphatic metastasis. Murakami et al. (2011) proposed the independent factors influencing the long-term prognosis for cholangiocarcinoma, including UICC TNM staging ($P = 0.007$), adjuvant chemotherapy
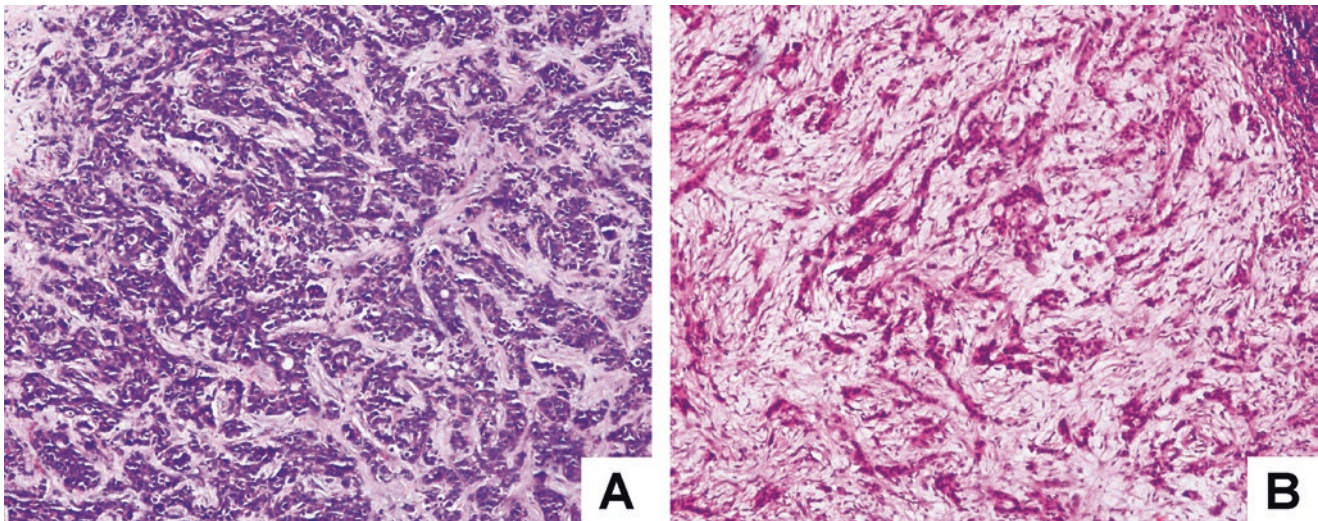
Fig. 10.10 Poorly differentiated adenocarcinoma of extrahepatic biliary: (**a**) sheet and nest structures; (**b**) cord structure
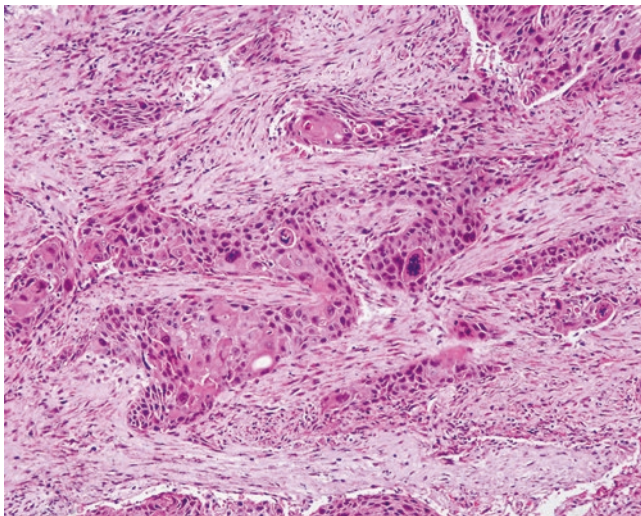

Fig. 10.11 Squamous cell carcinoma of extrahepatic biliary: squamous carcinoma is irregular cord-like, with keratin pearls, intercellular bridges and visible mitotic figures

($P = 0.009$), surgical margin ($P = 0.012$), and lymphatic metastasis ($P = 0.014$). Yoshiaki et al. (2013) reported a group of 133 cases of ECC, with a neural invasion rate of 74% (98/133), and 5-year survival rates for cases with or without neural invasion of 28 and 74%, respectively, suggesting neural invasion is a crucial factor affecting the prognosis. The Chinese Chapter of the International Hepato-Pancreato-Biliary Association and Hepatosurgical group, Surgery Branch of Chinese Medical Association (2014), developed Diagnosis and Treatment for Cholangiocarcinoma (consensus of surgery experts), proposing that TNM staging should be the basis for the determination of indication and basic principles for surgeries of distal cholangiocarcinoma.

Stage 0–I: for tumors located in the upper and middle segments of the common bile duct, simple resection of related bile ducts is suitable. And for tumors in the distal end of the common bile duct, pancreaticoduodenectomy should be implemented.

StageIIA: combined resection of cholangiocarcinoma and adjacent involving tissues or pancreaticoduodenectomy.

StageIIB: tumors in the upper and middle segment of the common bile duct should be treated by resection of cholangiocarcinoma plus lymphadenectomy, and tumors of distal common bile duct should be treated with pancreaticoduodenectomy plus lymphadenectomy.

Stage III–IV: nonsurgical treatments.

For cases with clinical staging as 0, I, or IIA and suspected lymphatic metastasis, lymphadenectomy should also be implemented [47].

10.2.7 Hilar Cholangiocarcinoma

Hilar cholangiocarcinoma, also known as Klatskin tumor in the past, is a special subtype of cholangiocarcinoma, which originates in the confluence of the hepatic ducts and may extend a long segment of bile duct. Based on a domestic meta-analysis on 2280 cases of Klatskin tumor, Feng Li et al. (2013) found that the male to female ratio of Chinese patients with hilar cholangiocarcinoma was about 1.87:1 and the average age was 56.2(17–84) years. The clinical manifestations include jaundice (35%), abdominal distention and abdominal pain (26%), emaciation (13%), clay-colored stools (8%), itch (8%), hepatomegly (6%), fever (3%), and ascites (1%). The pathological classification on the 1380 lesions in the 2280 patients showed that well-differentiated
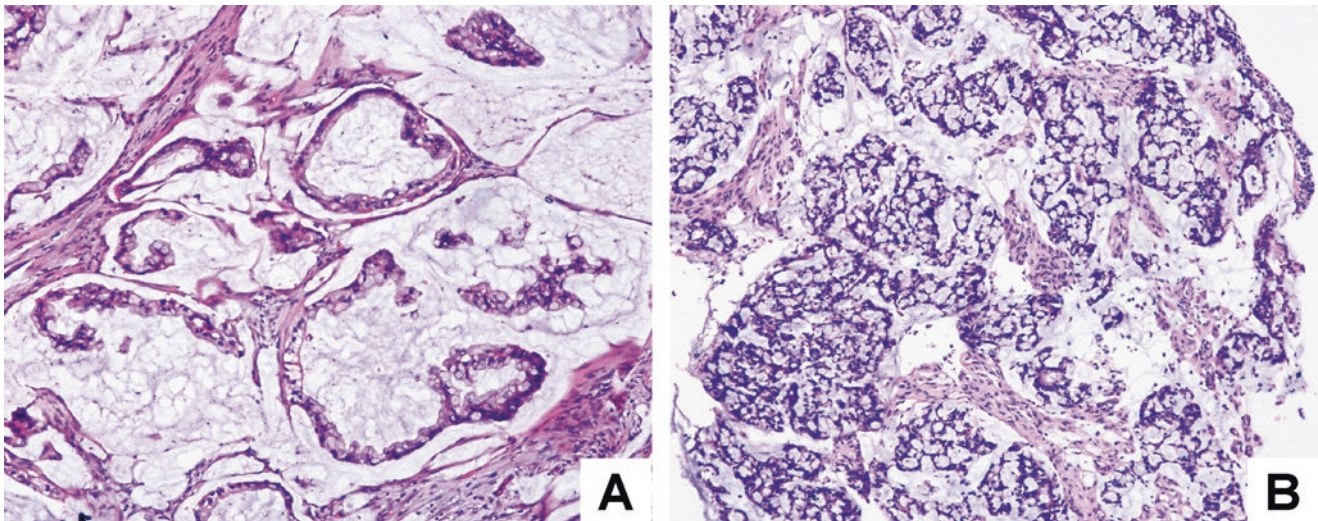
Fig. 10.12 Mucinous adenocarcinoma of extrahepatic biliary: (**a**) abundant mucus in the tumorous glands; (**b**) abundant mucus in the cytoplasm

Table 10.1 TNM staging for distal cholangiocarcinoma (AJCC 2010)

Primary tumor (T)			
T_x Primary tumor cannot be assessed			
T_0 No evidence of primary tumor			
Tis Carcinoma in situ			
T_1 Tumor confined to the bile duct histologically			
T_2 Tumor invades beyond the wall of the bile duct			
T_3 Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without the involvement of the celiac axis or the superior mesenteric artery			
T_4 Tumor involves the celiac axis or the superior mesenteric artery			
Regional lymph nodes (N)			
N_x regional lymph nodes cannot be assessed			
N_0 No regional lymph node metastasis			
N_1 Regional lymph node metastasis			
Distant metastasis(M)			
M_0 No distant metastasis(no pathologic M_0; use clinical M to complete stage group)			
M_1 Distant metastasis			

Stage	T	N	M
0	Tis	N_0	M_0
IA	T_1	N_0	M_0
IB	T_2	N_0	M_0
IIA	T_3	N_0	M_0
IIB	T_1	N_1	M_0
	T_2	N_1	M_0
	T_3	N_1	M_0
III	T_4	Any N	M_0
IV	Any T	Any N	M_1

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adenocarcinoma or tubular papillary adenocarcinoma accounted only for 39.9% (550/1380), while moderately and poorly differentiated adenocarcinoma accounted for 38.6% (533/1380) [48]. The results were consistent with the recent reports in foreign literature [49], and it is also one of the main causes of the poor prognosis of hilar holangiocarcinoma. The pathological features are not identical to the previously described poorly differentiated adenocarcinoma by Klatskin, and current studies show that hilar holangiocarcinoma is mainly well-differentiated adenocarcinoma with focal infiltration, slow growth, and obvious fibrosis, while the rate of lymphatic and distal metastasis is low. The clinical course is long; however, the recurrence rate in cases with R0 (negative resectional margin) is as high as 50–70% [50]. Wen-long Yu et al. (2009) conducted a multifactorial analysis on a group of 205 cases of hilar cholangiocarcinoma, showing that lymphatic metastasis and depth of biliary infiltration are two independent risk factors impacting on the postsurgical long-term survival, and they advocated that intraoperative frozen sections should be inspected to evaluate the condition of lymph node regions with high incidence of metastasis such as portal area and base of common hepatic artery and the depth of the tumorous invasion into the biliary wall and the surrounding tissues, which can be relied on as a histological evidence for determing the region of surgical resection to improve the rate of R0 surgical resection and long-term therapeutic effects for the patients [51]. It should be differentiated from sclerosing cholangitis (TP53 negative) in diagnosis. In 2010, WHO proposed the TNM staging for hilar cholangiocarcinoma (Table 10.2).
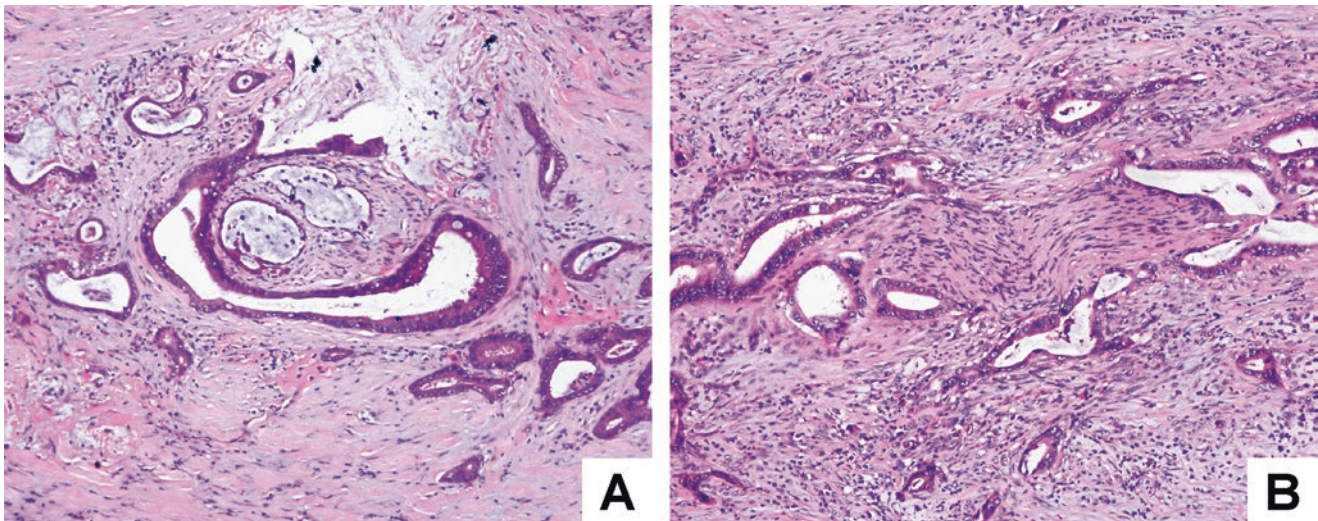
Fig. 10.13 Extrahepatic cholangiocarcinoma: tumorous glands are along or inside the biliary nerve or nerve sheath (**a** & **b**)

Table 10.2 TNM staging for hilar cholangiocarcinoma (AJCC 2010)

Primary tumor (T)	
T_x primary tumor cannot be assessed	
T_0 No evidence of primary tumor	
Tis Carcinoma in situ	
T_1 Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue	
T_{2a} Tumor invades beyond the wall of the bile duct to surrounding adipose tissue	
T_{2b} Tumor invades adjacent hepatic parenchyma	
T_3 Tumor invades unilateral branches of the portal vein or hepatic artery	
T_4 Tumor invades main portal vein or its branches bilaterally, the common hepatic artery, the second-order biliary radicals bilaterally, and unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement	
Regional lymph nodes (N)	
N_x Regional lymph nodes cannot be assessed	
N_0 No regional lymph node metastasis	
N_1 Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)	
N_2 Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes	
Distal metastasis(M)	
M_0 No distant metastasis	
M_1 Distant metastasis	

Stage	T	N	M
0	Tis	N_0	M_0
I	T_1	N_0	M_0
II	T_{2a-b}	N_0	M_0
III A	T_3	N_0	M_0
III B	T_{1-3}	N_1	M_0
IV A	T_4	N_{0-1}	M_0
IV B	Any T	N_2	M_0
	Any T	Any N	M_1

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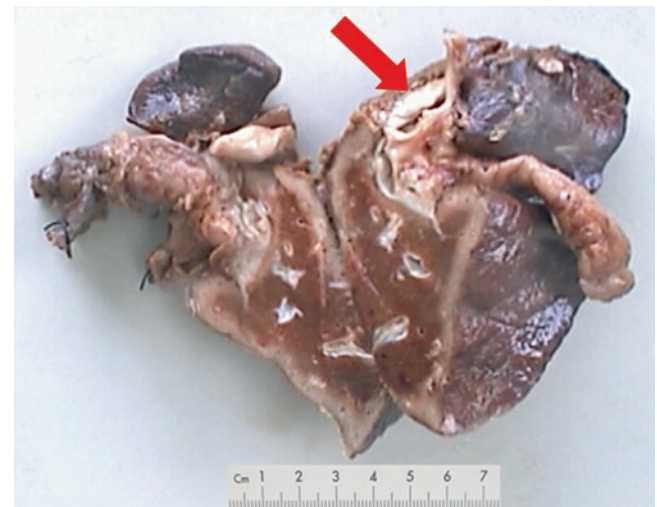

Fig. 10.14 Cystadenocarcinoma of extrahepatic biliary: the tumor is grossly cystic and solid and located in the portal area (*arrow* shows the tumor)

10.2.8 Cystadenocarcinoma

The extrahepatic biliary cystadenocarcinoma often manifests as jaundice in the corresponding patients. And when weight loss and ascites occur, exacerbation of the disease is indicated. Portal cystadenocarcinoma is often misdiagnosed as Klatskin tumor, and the tumor can be found in the bifurcation between the left and right hepatic ducts in the portal area. The tumor is grossly cystic and solid, with hemorrhage and necrosis, and grows invasively along the hepatic ducts (Fig. 10.14). Microscopic images show the tumor is tubular adenocarcinoma containing mucus in the lumen, and the cells are arranged in multilayers with focal dysplasia and moderate mitotic figures (Fig. 10.15). Radical resection of
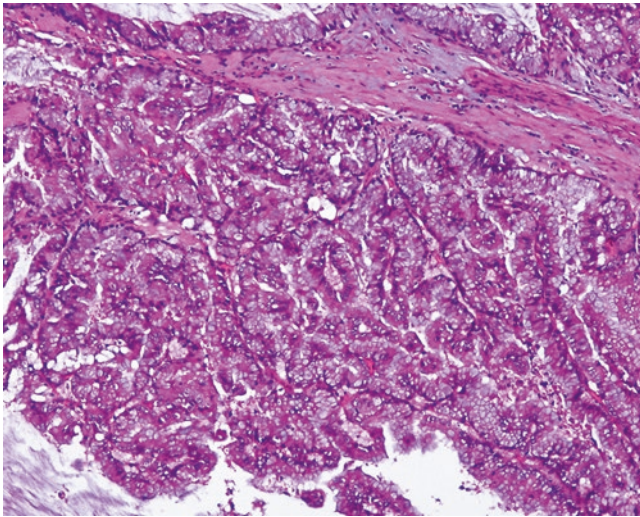
Fig. 10.15 Cystadenocarcinoma of extrahepatic biliary: the tumor is tubular adenocarcinoma, and the cells are tall-columnar and arranged in multilayers with focal invasion into the duct wall

the tumor plus partial resection of the liver tissue can lead to a good prognosis [52].

10.2.9 Fibrosarcoma

Fibrosarcoma (FS) found in extrahepatic biliary system is rare, and one related case was diagnosed in the Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University. The patient was a 37-year-old female who complained progressive dark urine with itchy skin. Ultrasound type B showed regular shape of the liver with smooth capsule, and a 3.4 cm × 2.4 cm flocculent echo was found in the median segment of the common bile duct. CT images showed a long and column mass in the right upper abdomen corresponding to the region posterior the duodenum, which was 6.5 cm × 3 cm in size with a clear boundary and homogeneous density. The lesion invaded upward to the portal area, compressing the common hepatic duct and portal vein with relatively smooth walls and marked tumorous surface adjacent to the liver. Significant homogeneous enhancement of the lesion was shown in arterial phase and decreased density in portal vein and delayed phases, which was still hyperdense compared to the liver on the same section. The liver is normal in size and morphology, and no abnormal densities were found in the liver parenchyma. Intrahepatic bile ducts were expanded in a rattern type, while no expansion was found in the inferior to the portal bile duct and the gallbladder underwent atrophy and collapse. MRI demonstrated that the liver had a smooth and even rim with soft and ratten-shaped intrahepatic bile ducts, which was dilated and broken at the middle of the portal bile duct. Density of soft tissue in the portal areas which was about

4 cm × 3 cm in size was enhanced significantly, and compression, narrowing, and translocation of the upper common bile duct were found. Serology showed AFP, 8.8 µg/L; CA19-9, 334.4 U/ml; and HBsAg negative. The preoperative diagnosis was portal cholangiocarcinoma. During the operation, it was observed that the liver was enlarged with cholestasis, reaching subcostal 2 cm, tawny, median textured, and no tumor nodules. A 5 cm × 6 cm sized and hard mass was palpated in extrahepatic biliary system. Complete resection of portal tumor was carried out.

On gross appearance, the extrahepatic biliary (including common bile duct) mass was 5.5 cm × 5.5 cm × 3 cm in size, and the section was grayish white or grayish yellow, without obvious hemorrhage or necrosis (Fig. 10.16). The microscopic observations showed that tumor cells were spindle or oval, arranged in herringbone, and the nuclei vary in size, with obvious atypia and common mitotic figures (Fig. 10.17). Immunohistochemistry investigations showed the tumor cells were vimentin and PCNA positive and SMA, S-100, and Hep Par-1 negative. The pathological diagnosis was fibrosarcoma (of the portal bile duct).

10.2.10 Rhabdomyosarcoma

Biliary rhabdomyosarcoma (RMS) mainly involves infants and children at an age of 0–14 years, with the average age of 3.5 years, and enbryonal and botroyoid RMS account for 60% and 6% of the disease, respectively. By 2014, there have been 90 cases of hepatic and biliary RMS reported in the literature [53]. Tireli et al. (2005) reported one case of a 3-year-old patient with a surgically resected 8 cm × 4 cm × 3 cm enbryonal RMS in the common bile duct [54], who was treated with postsurgical combined chemotherapy and radiotherapy, showing good condition during 1-year follow-up. One case of a 4-year-old patient with
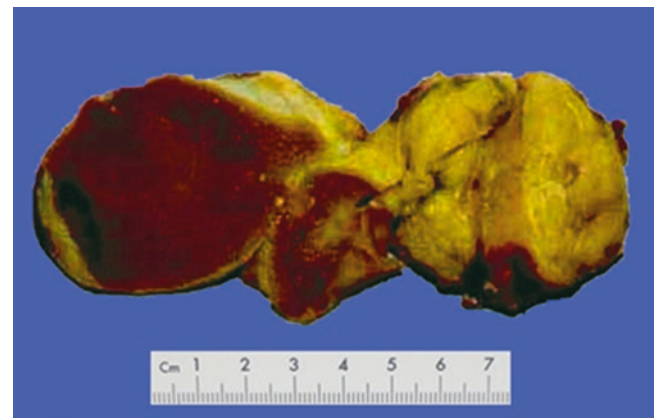

Fig. 10.16 Fibrosarcoma of extrahepatic biliary: the tumor on the *left* is *grayish yellow* and nodular; the gallbladder is on the *right*
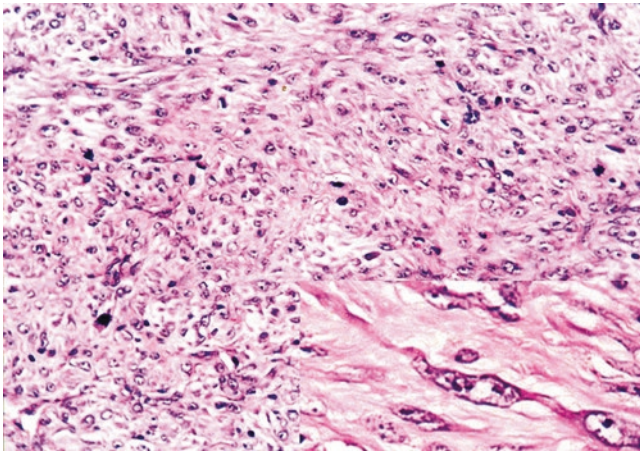
Fig. 10.17 Fibrosarcoma of extrahepatic biliary: the tumor cells were spindle or oval, arranged in herringbone, with collagenous fiber on both sides of the tumor giant cells (*lower right* shows the high magnification)
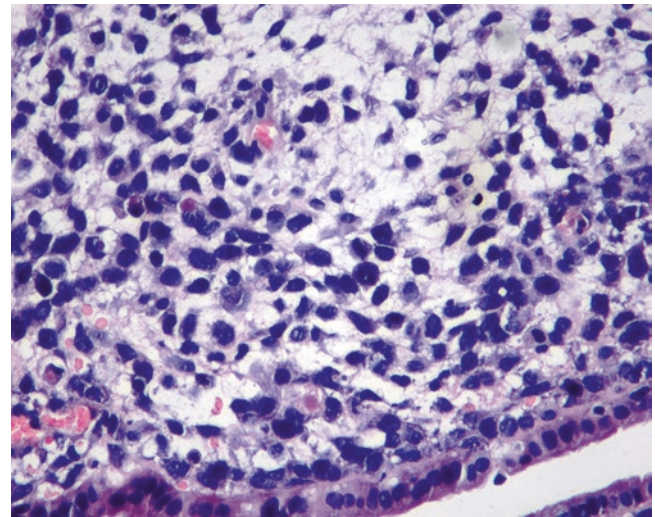

Fig. 10.19 Biliary botroyoid RMS: the nuclei were large and darkly stained, with active mitosis
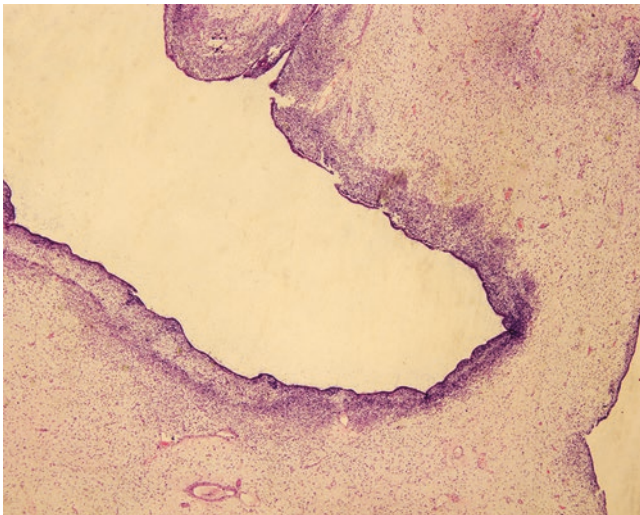

Fig. 10.18 Biliary botroyoid RMS: the tumor cells were densely distributed close to the inferior surface of biliary mucosal epithelium, forming characteristic "forming layer"

RMS was diagnosed in the Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, who received a surgical resection of botroyid RMS lesions involving the common bile duct and the left hepatic duct. The tumor showed a polypoid growth pattern to the luminal surface, and microscopic examination showed interstitial edema with mucus in the submucosal tissue of bile duct, and the tumor cells were densely distributed close to the inferior surface of biliary mucosal epithelium and around the proliferated mucous glands, forming characteristic "forming layer" (Fig. 10.18), while the bile duct walls below it contained much less tumor cells, and invasion could be found in individual neural tissues. The tumor cells were stellate, polygonal, or spindle, with little cytoplasm on

both sides of the nuclei and no marked striations, and the nuclei were large and darkly stained, while bizarre cells and active mitosis (Fig. 10.19) could also be observed. Pathological factors which suggest good prognosis of RMS include no distal metastasis, complete resection of the lesions, botryooid type [55], diameter <5 cm, and onset age <10 years.

Other rare malignant tumors in extrahepatic biliary system include carcinoid, small cell carcinoma, large cell carcinoma [56–58], lymphoma, leiomyosarcoma, Kaposi sarcoma, carcinosarcoma, malignant melanoma, etc., the histomorphology of which is similar to that of correspondent tumors of the liver or soft tissues.

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