Pathology

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A.S.-Y. Leong and C. Pairojkul

3.1 Introduction

In 1965, Gerald Klatskin, a pathologist at Yale University, drew attention to an adenocarcinoma in the porta hepatis that had distinctive clinical and pathological features. He concluded that the tumor was frequently overlooked because of failure to clinically probe and explore the biliary confluence and tributaries. In the 13 patients studied, death occurred from obstruction causing hepatocellular failure and hepatobiliary infection, rather than massive infiltration of the liver or extrahepatic metastasis [1]. Adenocarcinoma of the bile duct epithelium or cholangiocarcinoma (CC) at the confluence of the right and left hepatic ducts has come to be known as "Klatskin tumor".

Cholangiocarcinoma (CC) is conventionally divided into three groups, intrahepatic or peripheral CC arising in the liver, hilar CC that arise at the confluence of the right and left hepatic ducts (in this chapter, CC arising in the right and left hepatic bile ducts and the common hepatic bile duct are considered as hilar CC), and distal CC that arise between the hepatic hilum and the ampulla of Vater. While this anatomical division is useful and convenient from a clinical standpoint because of differences in epidemiology, presentation, management and prognosis, the histological appearances are very similar among tumors arising at any of these anatomical sites and bear a strong resemblance to adenocarcinoma of the pancreatic ducts. By convention, adenocarcinomas of the gallbladder are grouped separately but they are also closely related to epithelial tumors of the extrahepatic bile ducts, although those in the gallbladder show prominent geographic, gender, and racial differences not observed with extrahepatic bile duct carcinomas.

CC accounts for about 3 % of all gastrointestinal cancers worldwide and intrahepatic CC comprises 10–20 % of all primary liver cancers [2]. It is interesting that the incidence of intrahepatic CC is said to be rising in several parts of the world including Europe, Australia and Japan, whereas, extrahepatic CC has declined slightly [3–5]. The same has been observed in North America where a three-fold increase for intrahepatic CC has been reported between 1975 and 1999 [3, 5]. There are suggestions however, that this apparent increase has been the result of a change in classification. CC are topographically categorized as intrahepatic or extrahepatic by the International Classification of Diseases for Oncology (ICD-O). Hilar CC (Klatskin tumors) are extrahepatic CC but the second edition of the ICD-O assigned them a histology code 8162/3 which cross-referenced to intrahepatic CC. In the United States, studies that included this code (8162/3, Klatskin) grouped what is an extrahepatic or hilar CC with intrahepatic CC, perhaps accounting for an overestimation of intrahepatic CC incidence by 13 % and a corresponding decrease in incidence of extrahepatic CC by 15 %. Similar results have been published from Europe [6] where the same ICD-O codes are employed [7]. However, in one study which examined the incorrect coding of Klatskin tumors as intrahepatic CC, the age-adjusted annual intrahepatic CC incidence remained increased by about 4 % [8]. It has been advocated that terms such as "Klatskin tumor", or "perihilar" CC not be used as they lead to confusion, furthermore, biliary tract cancers should not be "lumped" together in clinical trials, but rather examined and treated as individual, distinct subsets of biliary tract cancers such as intrahepatic and ductal CC [9].

The epidemiology and risk factors for hilar CC are discussed in detail in Chap. 2 and it is suffice to state briefly

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that carcinomas of the extrahepatic ducts are associated with sclerosing cholangitis, ulcerative colitis, abnormal choledochopancreatic junction, choledochal cysts [10, 11] and infestations with the liver flukes *Clonorchis sinensis* and *Opisthorchis viverri* [4, 5]. *C. sinensis* may have been a frequent association of cancer of the bile ducts in China and Korea with an accompanying high prevalence in the local population, but this association is much lower in recent times. Infection with *O. viverrini* in Northeast Thailand, in contrast, remains high and evidence supporting its role in the induction of CC is compelling. Chronic infection and other variables including the host's immune response and the ingestion of dietary carcinogens such as nitrosamines may have a further contributory role [12, 13].

3.2 Clinical Presentation

Hilar CC usually present relatively early with obstructive jaundice that progresses rapidly or fluctuates. Because of their location within the duct confluence, obstruction and accompanying jaundice occurs when the tumor is relatively small and before widespread dissemination or spread into the intrahepatic tributaries occurs. Malaise, weight loss, anorexia, nausea, vomiting, pruritus and right upper quadrant pain are other symptoms. In patients with hilar CC, the intrahepatic bile ducts are dilated, the gallbladder is not palpable and the common duct is often collapsed. In contrast, those patients with carcinoma in the common bile duct or cystic duct have a distended gallbladder and marked dilatation of the proximal bile duct system.

3.2.1 Gross Appearance

Macroscopically, carcinomas of the extrahepatic bile ducts can be grouped into three types, viz, sclerosing/scirrhous, nodular, or papillary. Sclerosing/scirrhous tumors, the most common, are very firm and cause an annular thickening of the bile duct, often with diffuse infiltration and fibrosis of the periductal tissues. Nodular tumors are characterized by firm, irregular nodules that project into the lumen of the duct. Features of both types are often combined, hence the frequently used descriptor "nodular-sclerosing". The nodular-sclerosing variant is often firm or hard because of the desmoplastic response and varies from white to tan (Figs. 3.1 and 3.2), with a propensity to show radial infiltration into surrounding tissues and is difficult to resect (Fig. 3.3). They may also show diffuse spread linearly along the ducts distally and proximally into intrahepatic

Fig. 3.1 Nodular-sclerosing carcinoma arising in the common bile duct and right hepatic duct with linear extension along the two main intrahepatic tributaries draining the anterior and posterior segments. The periductal tissue is thickened by tumor infiltration and a desmoplastic response, and the proximal intrahepatic bile ducts are dilated. The liver shows marked cholestasis. The gall bladder was collapsed (not shown)

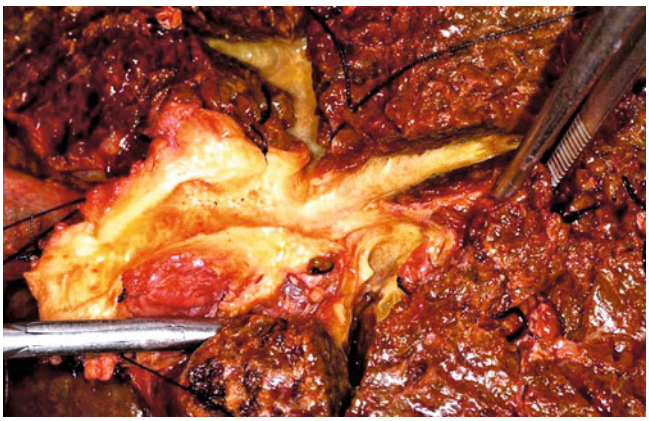

Fig. 3.2 Nodular-sclerosing carcinoma in the common bile duct and right hepatic duct. There is infiltration of the periductal tissues to produce an annular thickening. The segmental bile ducts are dilated and the liver shows marked cholestasis

tributaries (Figs. 3.1 and 3.2). Necrosis is very uncommon. The papillary variant accounts for approximately 10 % of all CC, and while occasionally seen at the hilus, is more common in the distal bile duct. These tumors are soft and friable, and may show only early transmural invasion. While convenient and useful to guide the operative procedure, extent of resection, and prognosis, macroscopic separation of the variants is often not possible because of overlapping gross features, the exception being the papillary carcinoma which, being largely exophytic is more readily identifiable (Fig. 3.4).

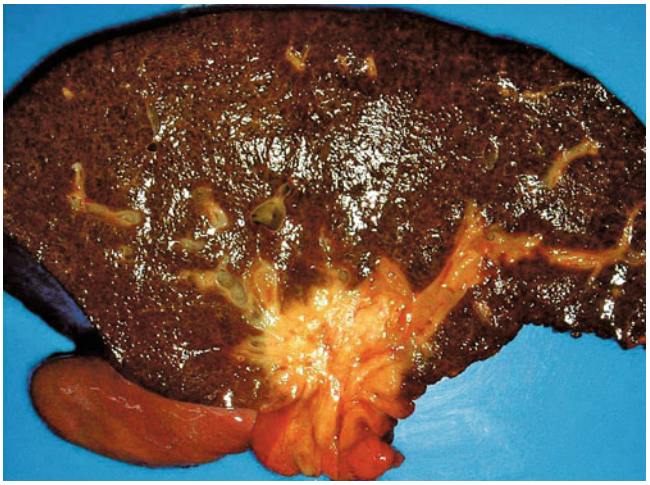

Fig. 3.3 Hilar cholangiocarcinoma arising in the right hepatic duct and showing radial infiltration into the immediate surrounding tissues. While the intrahepatic ducts are edematous, there is no macroscopic involvement. Cholestasis is less pronounced than in the previously illustrated examples of nodular sclerosing cholangiocarcinoma

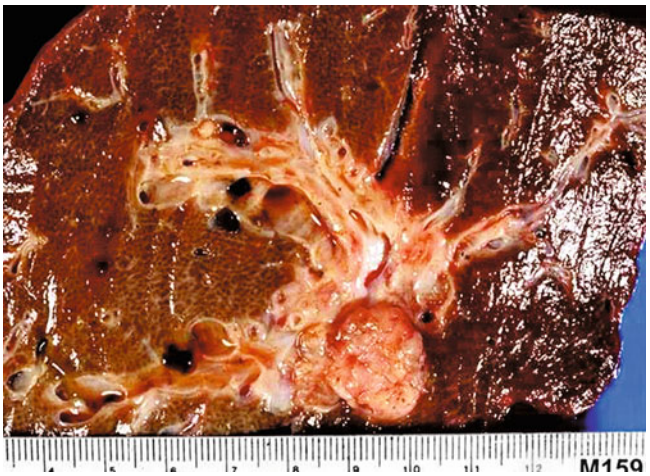

Fig. 3.4 Papillary cholangiocarcinoma at the hilum arising in the left hepatic duct. The polypoid tumor shows no apparent infiltration and appears limited to the wall of the duct. There is dilation of the intrahepatic bile ducts, some of which contain small pigmented calculi

3.2.2 Staging

Several systems have been described for staging of extrahepatic CC. They include the Bismuth-Corlette system [14] employed at Memorial Sloan–Kettering Cancer Center (MSKCC) [15], American Joint Committee on Cancer (AJCC) [16], and Japanese Society of Biliary Surgery (JSBS) [17]. The College of American Pathologists staging system, based on the AJCC/UICC TNM staging (7th edition) is as follows [18]:

Primary tumor (pT)	
pTX	Cannot be assessed
pT0	No evidence of primary tumor
pTis	Carcinoma in situ
pT1	Tumor confined to bile duct, with extension up to muscle layer or fibrous tissue
pT2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
pT2b	Tumor invades adjacent hepatic parenchyma
pT3	Tumor invades unilateral branches of the portal vein or hepatic artery
pT4	Tumor invades main portal vein or its branches bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Regional lymph nodes (pN)	
pNX	Cannot be assessed
pN0	No regional lymph node metastasis
pN1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
pN2	Metastasis to periaortic, pericaval, superior mesentery artery, and/or celiac artery lymph nodes
Specify	Number examined……..
	Number involved…….
Distant metastasis (pM)	
pM0	Cannot be assessed
pM1	Distant metastasis, specify site(s), if known……

It has been argued that existing staging systems are largely applicable only after surgical tumor resection as with the AJCC system [19], or provide little prognostic indication or help in the selection of patients for surgical treatment as in the case of the Bismuth-Corlette system [19–23]. On the other hand, the modified system proposed by Burke et al. [24] not only provided anatomical localization of the tumor but also defined the local extent, allowing better stratification of patients for surgical exploration [22] and can be employed preoperatively with imaging studies [23]. Essentially, the modified staging system classifies hilar CC according the local extent of tumor based on the location and extent of bile duct involvement, the presence or absence of portal venous invasion, and presence or absence of hepatic lobar atrophy [23].

The T staging system for hilar CC [20, 21] is as follows:

T1 Tumor involving biliary confluence ± unilateral extension to secondary biliary radicles. No liver atrophy or portal vein involvement.

T2 Tumor involving biliary confluence ± unilateral extension to secondary biliary radicles with ipsilateral portal vein involvement ± ipsilateral lobar atrophy. No main portal vein involvement.

T3 Tumor involving biliary confluence + bilateral extension to secondary biliary radicles; OR unilateral

extension to secondary biliary radicles with contralateral portal vein involvement; OR unilateral extension to secondary biliary radicles with contralateral hepatic lobar atrophy; contralateral hepatic lobar atrophy; OR main or bilateral portal venous involvement.

3.2.3 Microscopic Appearances

A number of histological subtypes is recognized in the World Health Organization [25] and Armed Forces Institute of Pathology [26] classifications. Histological subtypes are most commonly described in the gallbladder with less frequent descriptions of the tumors in the extrahepatic bile ducts. Many of the histological subtypes described below in the gallbladder can be seen in the extrahepatic bile ducts but the spectrum of histological types in the latter is much less.

3.2.3.1 Adenocarcinoma

Adenocarcinomas are the most common, accounting for about 90 % malignant epithelial tumors of the extrahepatic bile ducts. They superficially resemble bile duct epithelium with mucin expression frequently present in the cells and glands and may show three primary forms of differentiation, namely, pancreaticobiliary (Fig. 3.5a, b), intestinal (Fig. 3.6), and gastric (Fig. 3.7). A clear distinction of these forms of adenocarcinoma is often difficult to make as the features overlap. Furthermore, about one third of all such tumors show focal intestinal differentiation with goblet and neuroendocrine cells, the latter may show expression of peptide hormones and serotonin but their presence does not warrant a diagnosis of neuroendocrine carcinoma. An extremely well-differentiated variant may simulate adenoma and Paneth cells may rarely be present. Other histological variants of intestinal type adenocarcinoma can occur, viz, a papillary adenocarcinoma composed predominantly of papillary fronds lined by cuboidal or columnar cells with varying amounts of mucin and intestinal metaplasia with collections of Paneth cells (Fig. 3.8) and occasional neuroendocrine and goblet cells [25, 26]. Such papillary carcinomas may fill the duct lumen before invading the wall (Fig. 3.4) and in a small percentage of cases may show skip lesions. Mucinous adenocarcinoma, another variant, shows abundant mucin secretion and is similar in appearance to those occurring at other sites (Fig. 3.9). Perineural and neural invasion is common, especially with radial spread of these tumors (Fig. 3.10).

Other variants of adenocarcinoma described in the gallbladder such as clear cell and signet ring adenocarcinomas (Fig. 3.6) are very uncommon in the extrahepatic bile ducts. These are generally aggressive tumors.

3.2.3.2 Adenosquamous Carcinoma

Such tumors are composed of two components; a glandular and a squamous component, each varying in quantity and extent of differentiation. Mucin secretion is often evident in the former and intercellular bridges in the latter (Fig. 3.11). Keratin pearls are less common.

3.2.3.3 Squamous Cell Carcinoma

This variant is uncommon and comprises sheets of squamous cells that vary considerably in extent of differentiation (Fig. 3.12). Keratinizing and non-keratinizing types exist and spindle cells may predominate. In the latter, immunohistological stains for cytokeratin are useful to identify their nature.

3.2.3.4 Small Cell Carcinoma

These are endocrine tumors and show varying degrees of differentiation. As such, immunohistological stains for synaptophysin and chromogranin are often necessary to confirm their endocrine nature and serotonin and peptide hormones may be expressed. The tumor is composed of small cells with round or fusiform nuclei with finely stippled chromatin and is arranged in cords, ribbons, trabeculae, nests and sheets with very occasional rosette-like structures (Fig. 3.13). Mixed endocrine-exocrine tumors also exist. These are composite tumors with areas of endocrine carcinoma and adenocarcinoma. Such tumors behave as adenocarcinomas and are clinically more aggressive tumors.

3.2.3.5 Rare Variants of Carcinoma

Other rare variants of carcinoma described in the bile ducts include clear cell carcinoma, hepatoid carcinoma (Fig. 3.14), and signet ring carcinoma.

3.2.3.6 Carcinosarcoma

This tumor needs to be distinguished from squamous cell carcinoma with spindled areas. A true carcinosarcoma, besides displaying the presence of malignant epithelial elements commonly in the form of glands with squamous cell areas, also contains sarcomatous elements in the form of heterologous mesenchymal tissue such as chondrosarcoma, osteosarcoma, and rhabdosarcoma. The mesenchymal component should be devoid of cytokeratin.

3.2.4 Grading

Adenocarcinoma is conventionally divided into three grades. Well differentiated adenocarcinoma requires the presence of glands in 95 % of the tumor, in moderately differentiated adenocarcinoma 40–95 % of the tumor should contain glands and in poorly differentiated adenocarcinoma 5–39 % of the tumor should contain glands [25].

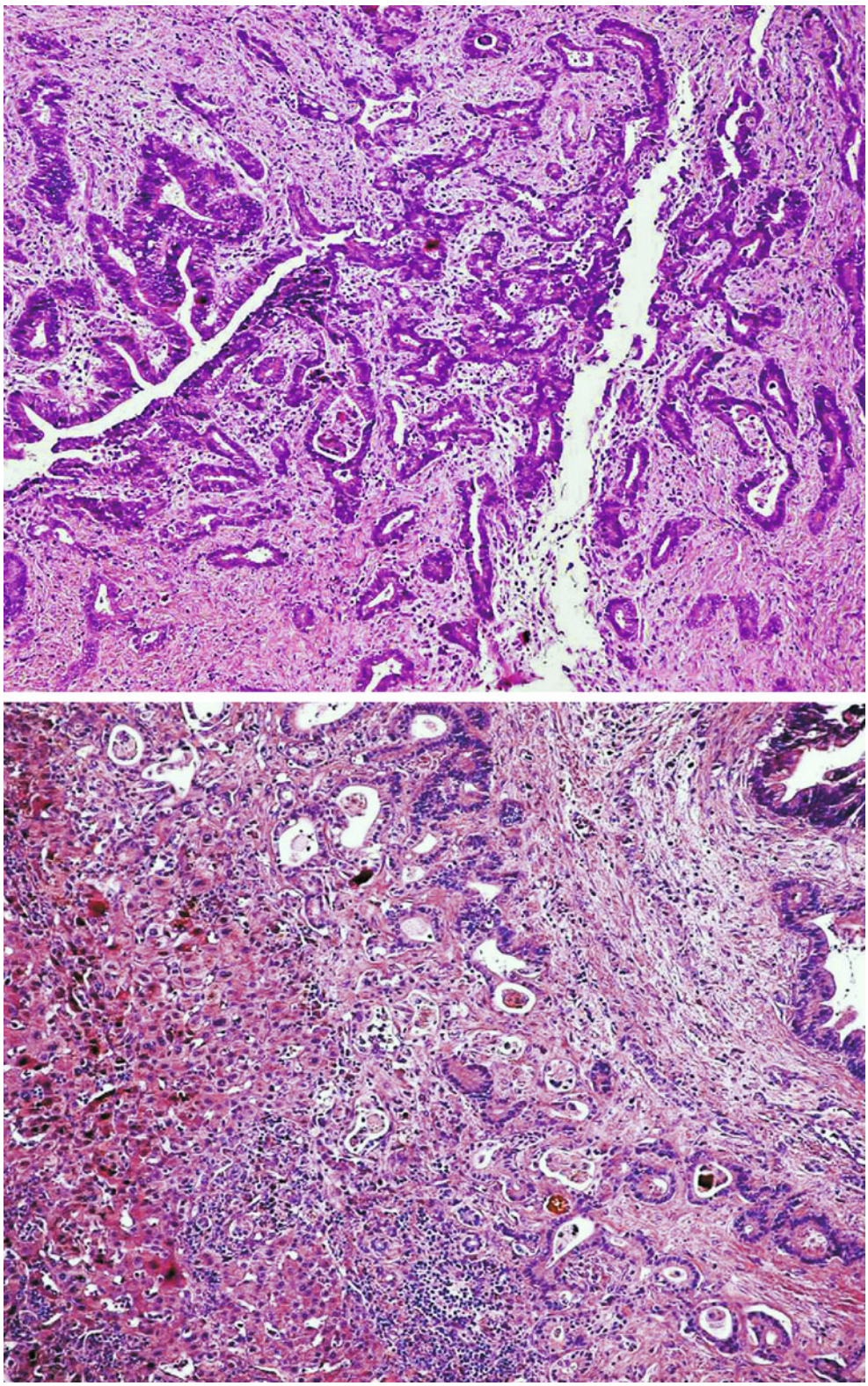

Fig 3.5 (**a**) Cholangiocarcinoma with pancreaticobiliary type differentiation. Atypical glands infiltrate the periductal tissue associated with a densely desmoplastic stroma. (**b**) There is tumor extension along the intrahepatic ducts with infiltration into surrounding hepatic parenchyma by similar-appearing atypical glands which evoke a fibrous response

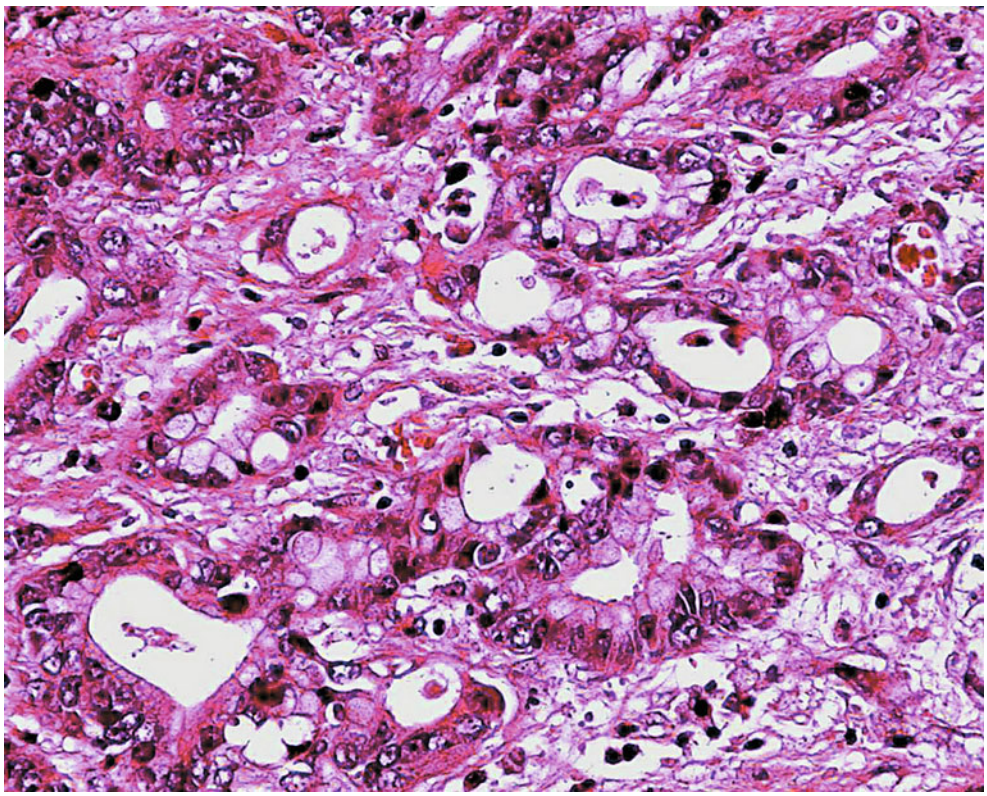

Fig. 3.6 Hilar cholangiocarcinoma with intestinal type differentiation. The atypical infiltrating glands contain cytoplasmic vacuoles of mucin which was also present in the glandular lumen. Scattered cells lining the glands have prominent cytoplasmic vacuoles that displace the crescentic nuclei peripherally to produce a signet cell appearance. When such cells predominate and infiltrate the stroma as single cells, the tumor is designated signet cell carcinoma

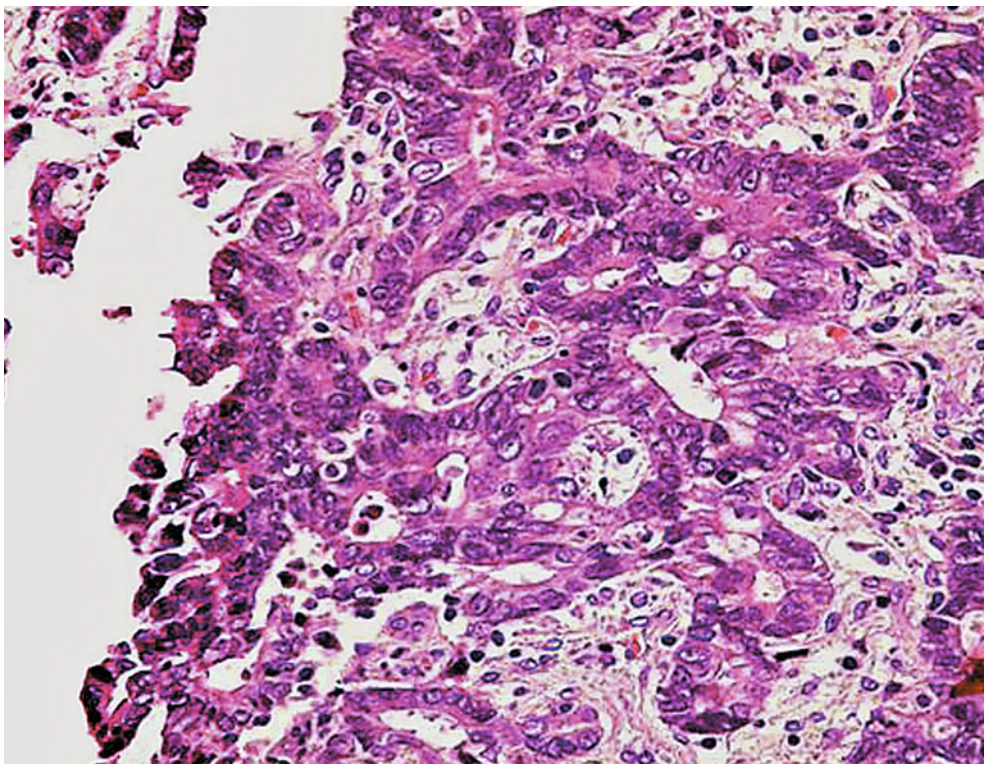

Fig. 3.7 The distinction of intestinal from gastric type differentiation is often difficult as in this example where the tumor is composed of infiltrating atypical glands that also secrete variable amounts of mucin. Unless areas of differentiation into distinct gastric type mucosa such as oxyntic cells are found, the separation cannot be made. The histological distinction has not been shown to be of prognostic relevance

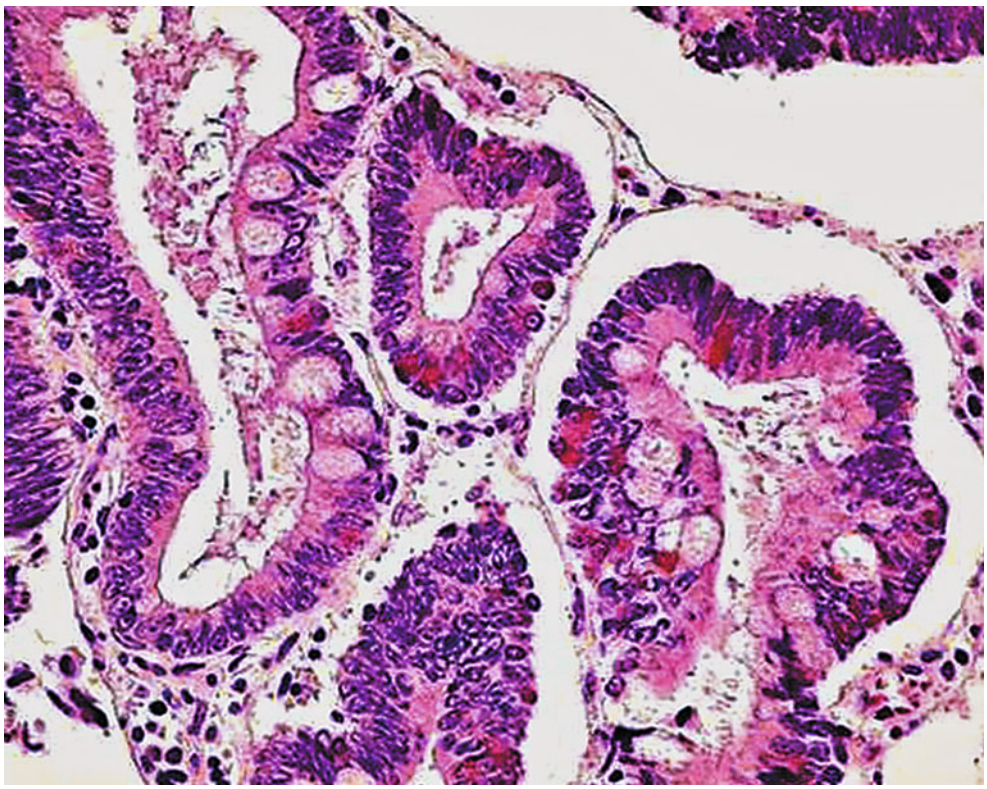

Fig. 3.8 Foci of Paneth cell metaplasia are present in this well-differentiated variant of papillary adenocarcinoma. Occasional neuroendocrine and goblet cells may also be found

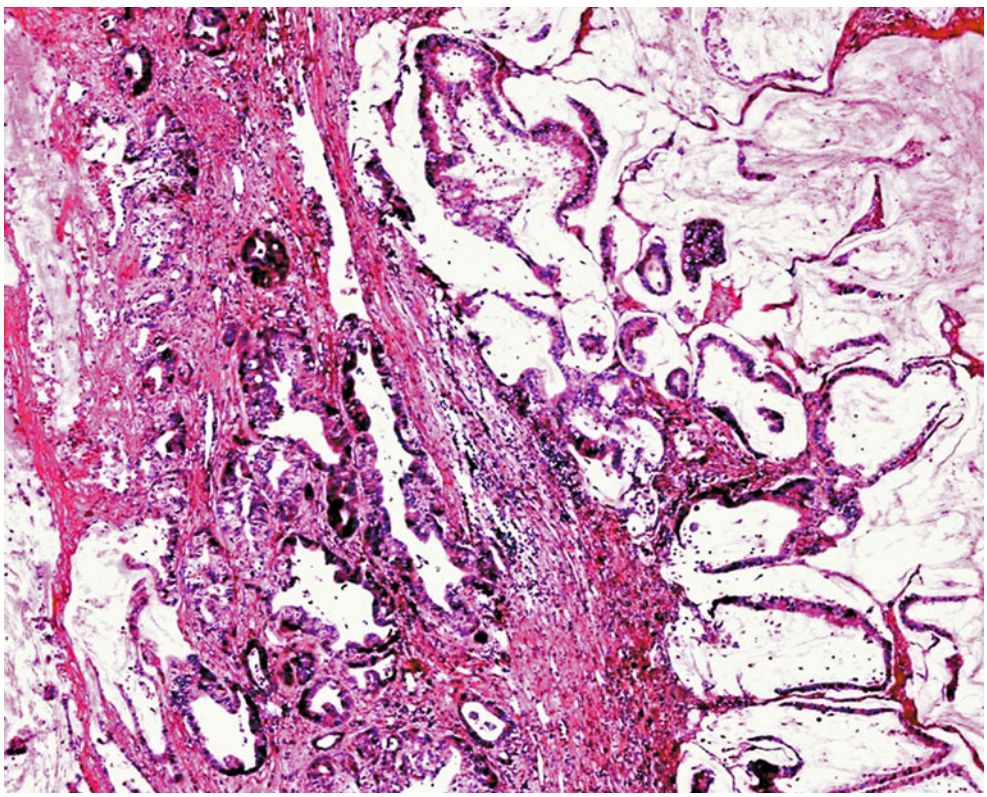

Fig. 3.9 Mucinous adenocarcinoma is not an uncommon form of cholangiocarcinoma. Abundant mucin distends the glands and a mild to moderate inflammatory response is present

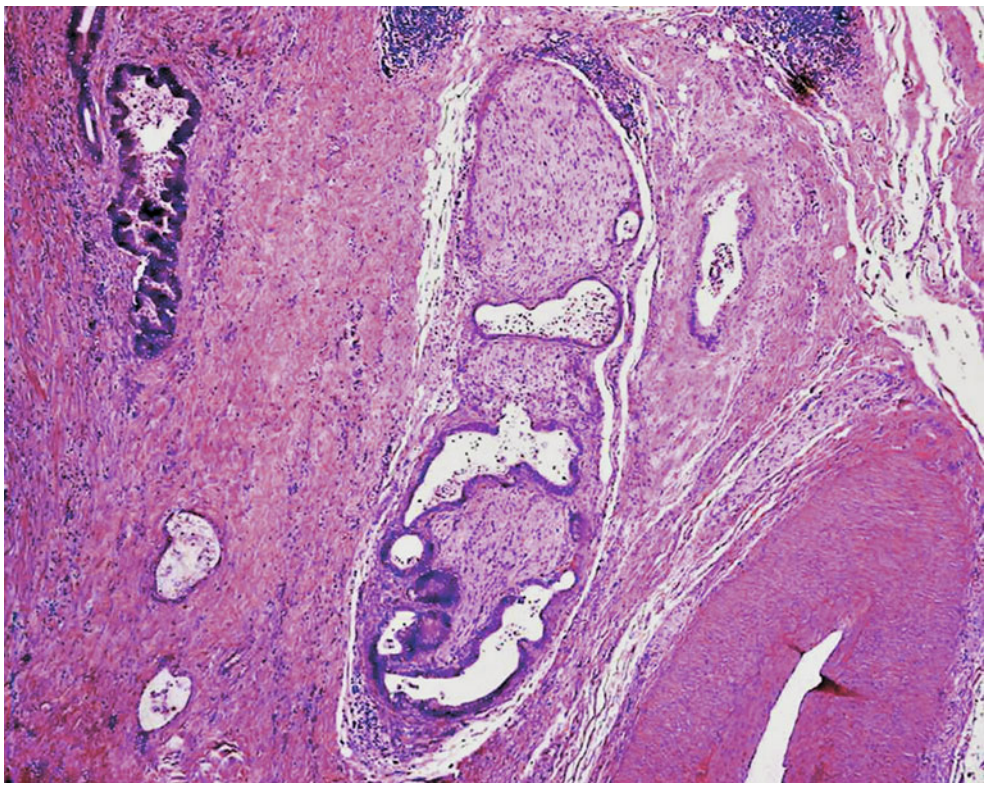

Fig. 3.10 There is prominent neural infiltration in the periductal tissue in this hilar cholangiocarcinoma

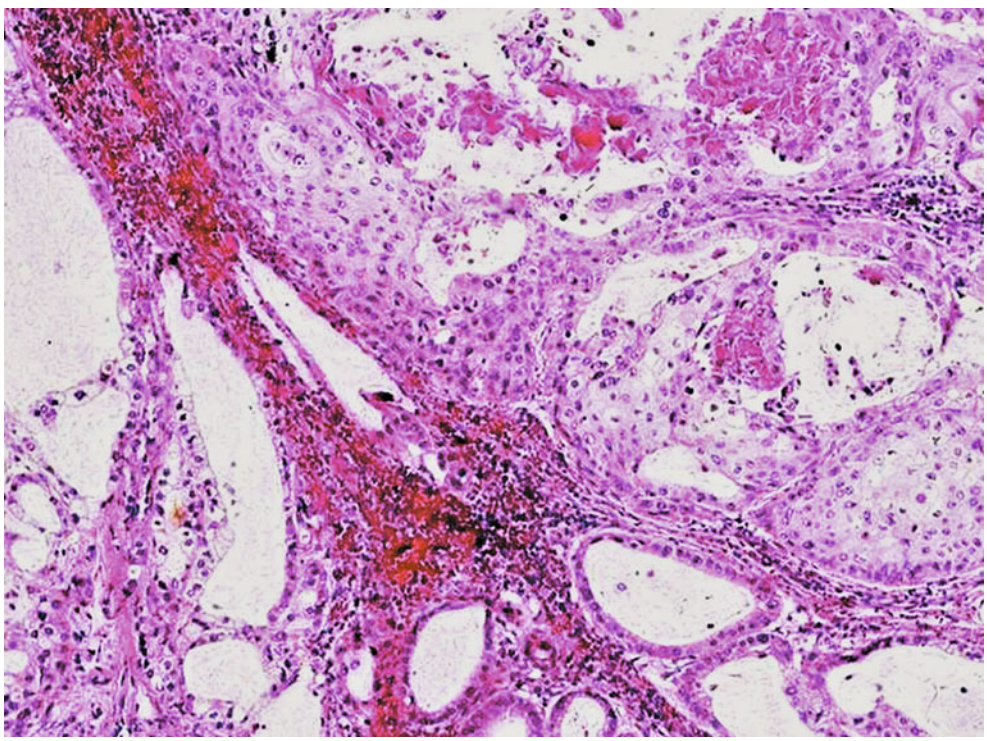

Fig. 3.11 Adenosquamous carcinoma composed of sheets of squamous cells with intercellular bridges. There are distinct glands in the adjacent stroma

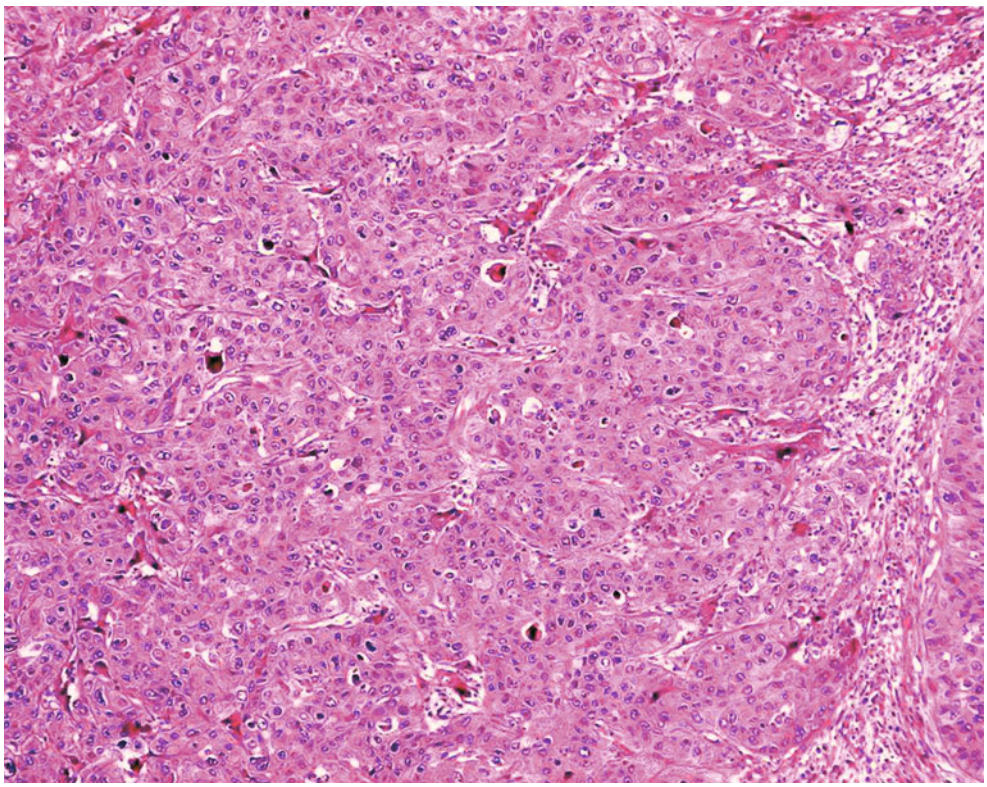

Fig. 3.12 Squamous cells carcinoma composed of sheets of well differentiated squamous cells with distinct intercellular bridges and eosinophilic keratinized cytoplasm. Keratin pearls are not present

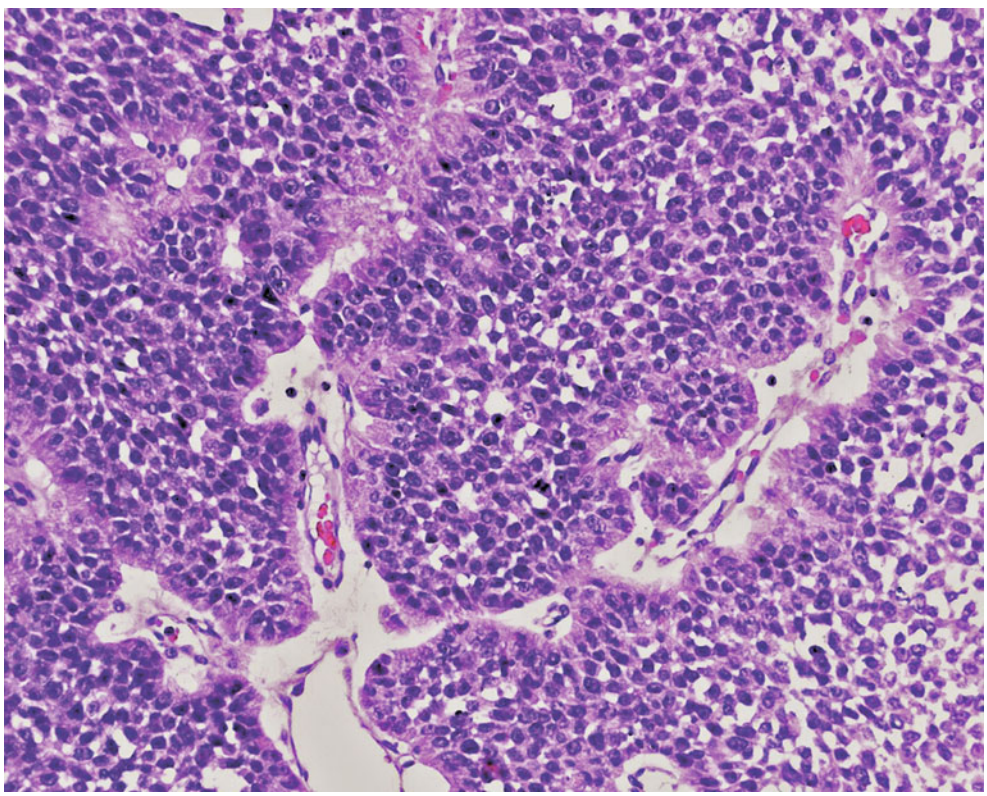

Fig. 3.13 Small cell carcinoma showing small cells with high nuclear cytoplasmic ratio and hyperchromatic nuclei arranged in sheets and nests

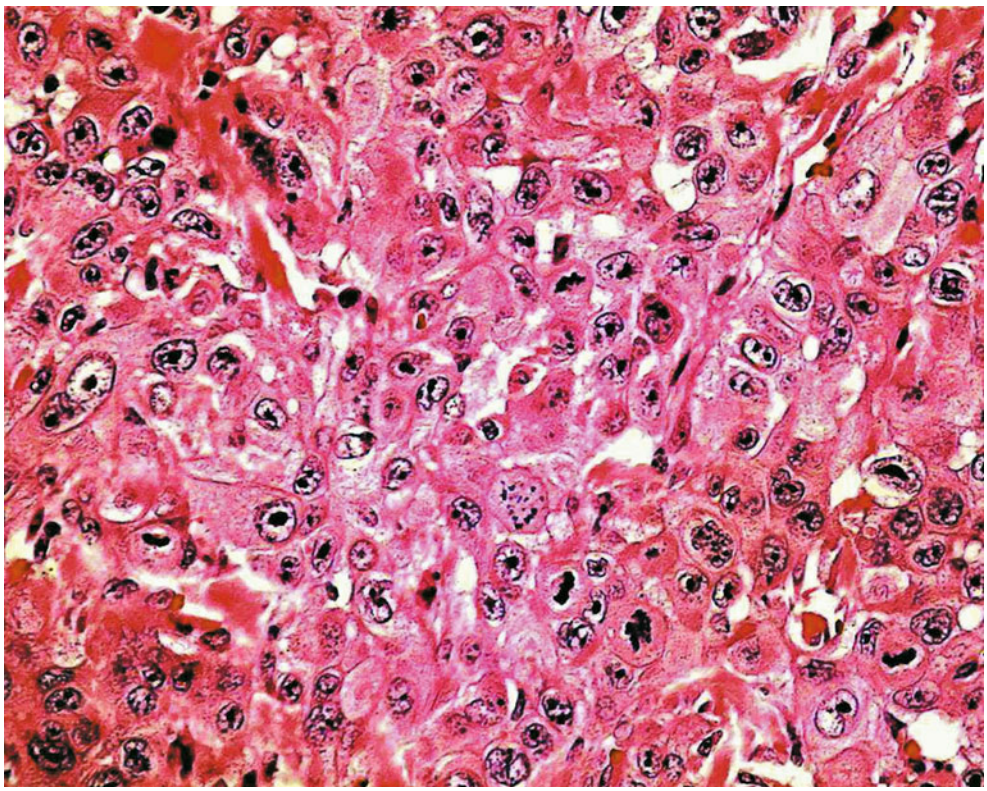

Fig. 3.14 Cholangiocarcinoma with hepatoid features. The large cells with vesicular nuclei and central nucleoli have abundant granular eosinophilic cytoplasm and resemble hepatocytes. This variant is very uncommon

3.2.5 Precursor Lesions

A number of precursor lesions arise in the extrahepatic bile ducts and include adenomas, biliary cystadenoma, papillomatosis (adenomatosis) and various grades of intraepithelial neoplasia (dysplasia) up to carcinoma in situ.

3.2.5.1 Adenoma

Adenomas are benign neoplasms of the biliary epithelium. They are commonly polypoid, single and well-demarcated and are more common in the gallbladder than extrahepatic bile ducts being seen in less than 0.5 % of gallbladders removed for cholelithiasis and chronic cholecystitis. A small proportion is known to progress to carcinoma. Biliary adenomas may be tubular, papillary or tubulopapillary as in the colon, and can show gastric pyloric, intestinal, or biliary type mucosa, the gastric pyloric type adenoma being more common in the gallbladder.

3.2.5.2 Biliary Cystadenoma

These are benign cystic tumors lined by columnar epithelium that resembles bile duct or foveolar gastric epithelium and occur almost exclusively in females. Often they are multiloculated and contain mucinous or serous fluid (Figs. 3.15 and 3.16) and are more common in extrahepatic ducts than in the gallbladder [27, 28]. Occasional endocrine cells may be present

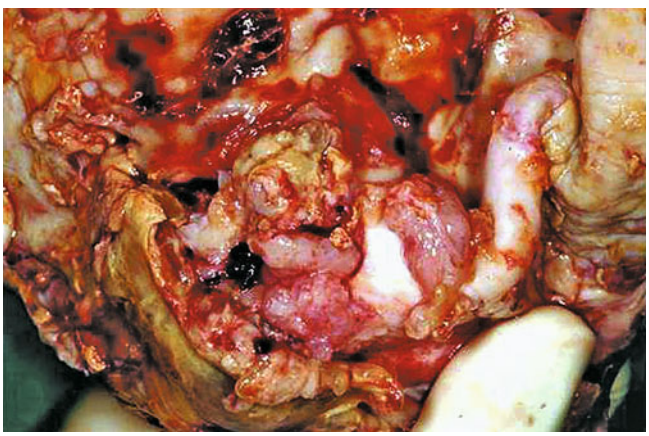

Fig. 3.15 Biliary cystadenoma. The mutilocular cyst contains soft polypoid excrescences and mucinous fluid

and the subepithelial stroma is of varying cellularity and resembles ovarian stroma. This stroma shows immunoreactivity for estrogen and progesterone receptors [29, 30]. Malignant transformation can occur with cystadenocarcinomas occurring equally in both females and males. In these tumors a large papillary mass may be present with areas of grey-white tumor in a thickened bile duct. Adequate sampling is necessary to distinguish benign cystadenomas from cystadenocarcinomas and prognosis is good if curative removal is possible [27, 28].

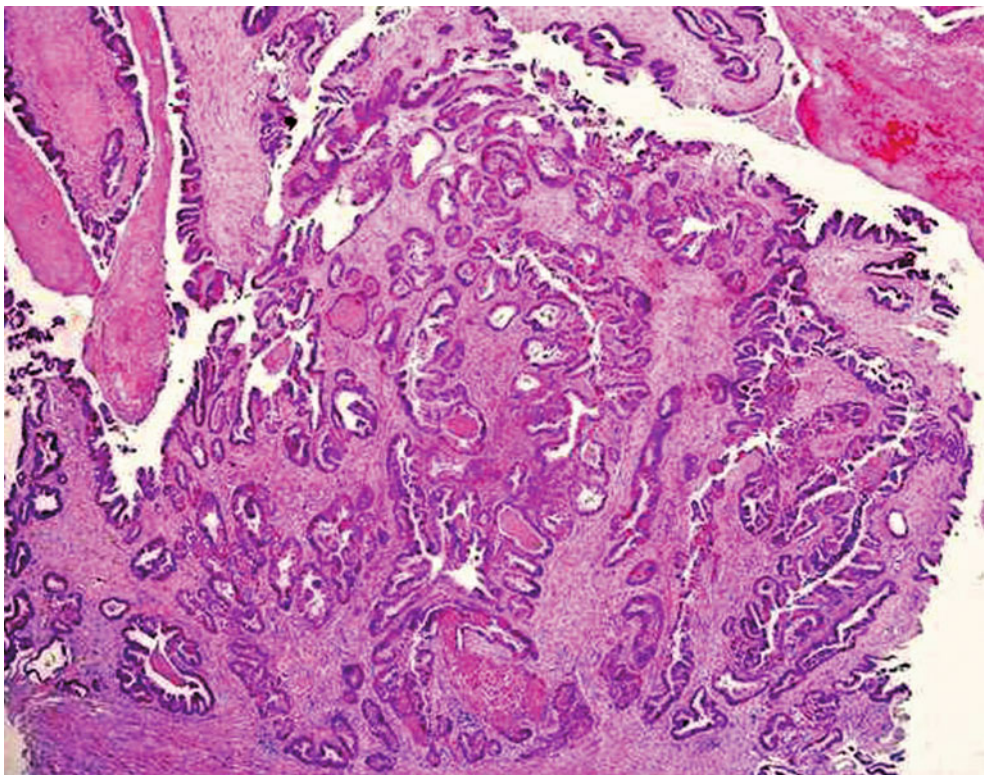

Fig. 3.16 The polypoid masses in biliary cystadenomas are composed of fibrovascular fronds lined by a single layer of cuboidal to columnar cells. Variable nuclear atypia may be seen and focal areas of pseudostrafication may be present. Adequate sampling ensures exclusion of a low-grade carcinoma

3.2.5.3 Papillomatosis

Multiple recurring papillary adenomas may involve large areas of the extrahepatic bile ducts (Figs. 3.17, 3.18 and 3.19) and extend into the gallbladder and intrahepatic bile ducts. Because of their multicentricity complete excision is difficult. The presence of severe dysplastic change in the epithelium lining the papillary adenomas makes distinction from carcinoma difficult hence this lesion is sometimes regarded as a form of low grade carcinoma and is considered a precursor lesion of adenocarcinoma. The potential for malignant transformation is greater compared to solitary adenomas [25, 26].

Fig. 3.17 Multiple papillary tumors are seen extending along the hilum into the intrahepatic bile ducts. Focal skip lesions are present

3.2.5.4 Intraepithelial Neoplasia (Dysplasia)

Intraepithelial neoplasia or dysplastic changes are not recognizable grossly as they are often associated with chronic inflammation and are difficult to distinguish from such changes which include fibrosis, thickening and induration of the mucosa. Careful examination may reveal small cauliflower-like excrescences in the mucosa or granularity and trabeculation.

Intraepithelial neoplasia can be papillary or more commonly flat. Papillary intraepithelial neoplasia is characterized by short stumpy fibrovascular fronds covered by dysplastic epithelium which may be columnar, cuboidal, or elongated with varying degrees of nuclear atypia, loss of polarity and occasional mitosis. Pseudostratification may occur in later stages and papillae may form. The cytoplasm is usually eosinophilic and contains non-sulphated acid and neutral mucin. Goblet cells may be seen and an abrupt transition of dysplastic from normal-appearing epithelium is often seen. Distinction of intraepithelial neoplasia from the epithelial atypia of repair is based on the homogeneous population seen in the former which is also often widespread in the mucosa [25, 26]. In addition, the heterogeneous cell population in repair which comprises columnar mucus-secreting

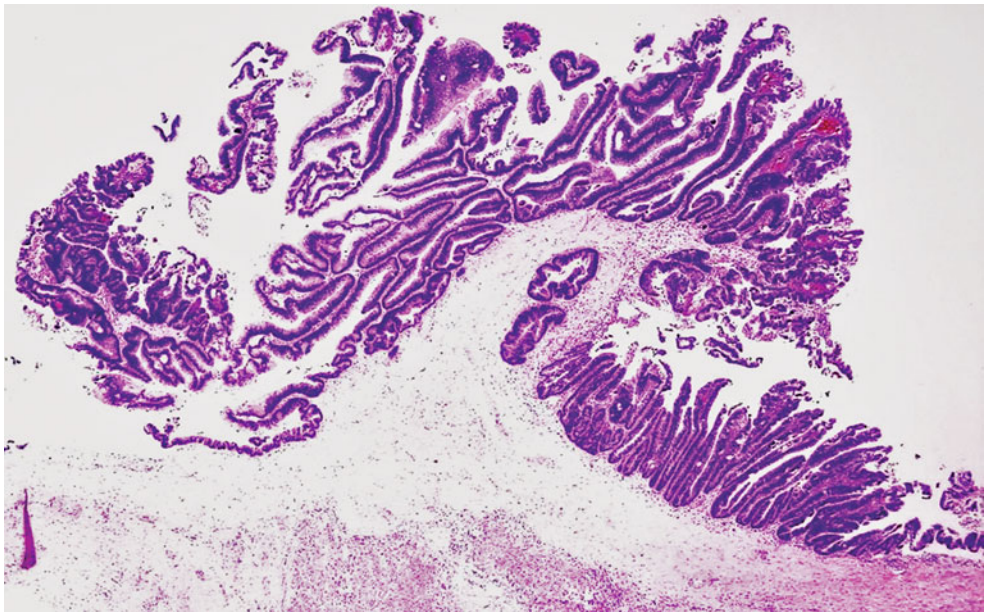

Fig. 3.18 Low power view of a papillary adenoma

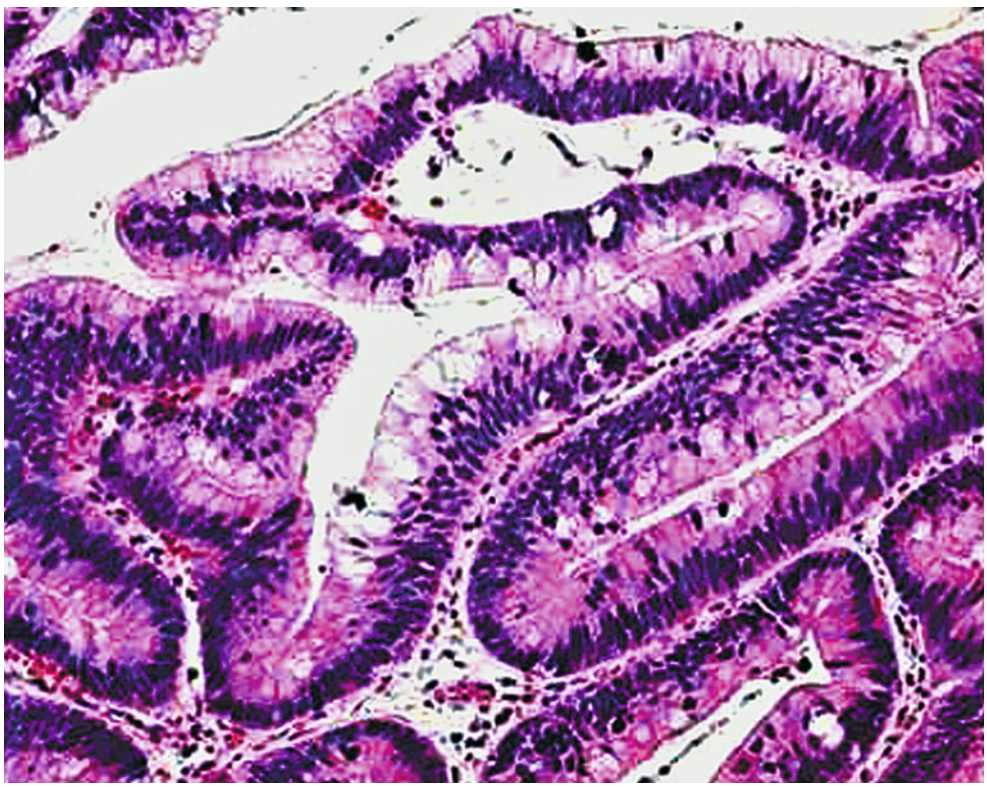

Fig. 3.19 High magnification of papillary adenoma shows papillary fronds lined by a single layer of tall columnar mucin-secreting cells. Nuclear atypia is mild to moderate and pseudostratification is not seen

cells, low cuboidal cells, atropic-appearing epithelium, and pencil-like cells display a gradual transition of the cellular abnormalities unlike the abrupt transition seen in intraepithelial neoplasia (Fig. 3.20). Immunoreactivity for p53 also helps in the identification of true dysplastic changes.

The two morphological forms of intraepithelial neoplasia in the bile ducts have been named biliary intraepithelial neoplasia (BilIN) for the non-papillary type and biliary intraductal papillary neoplasia (biliary IPN) for the papillary type. BilINs are a group of flat, pseudopapillary, or micropapillary

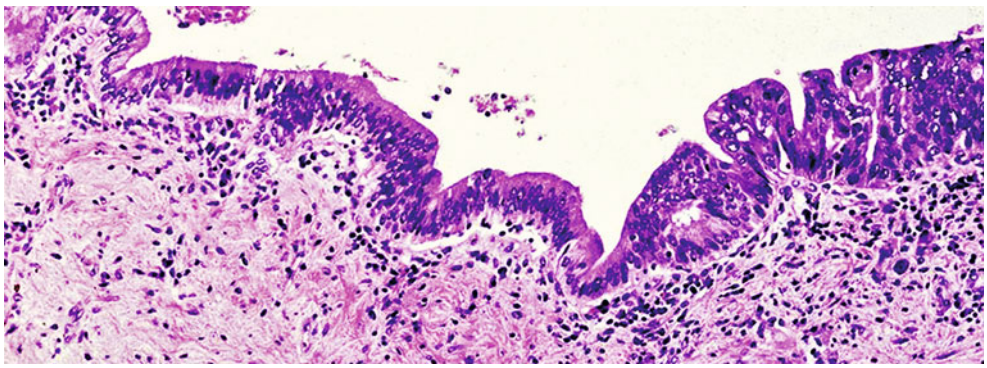

Fig. 3.20 Biliary dysplasia. A sharp transition is seen from the normal biliary epithelium on the left and dysplastic epithelium on the right. This transition can be enhanced by staining for p53 expressed in the dysplastic cells

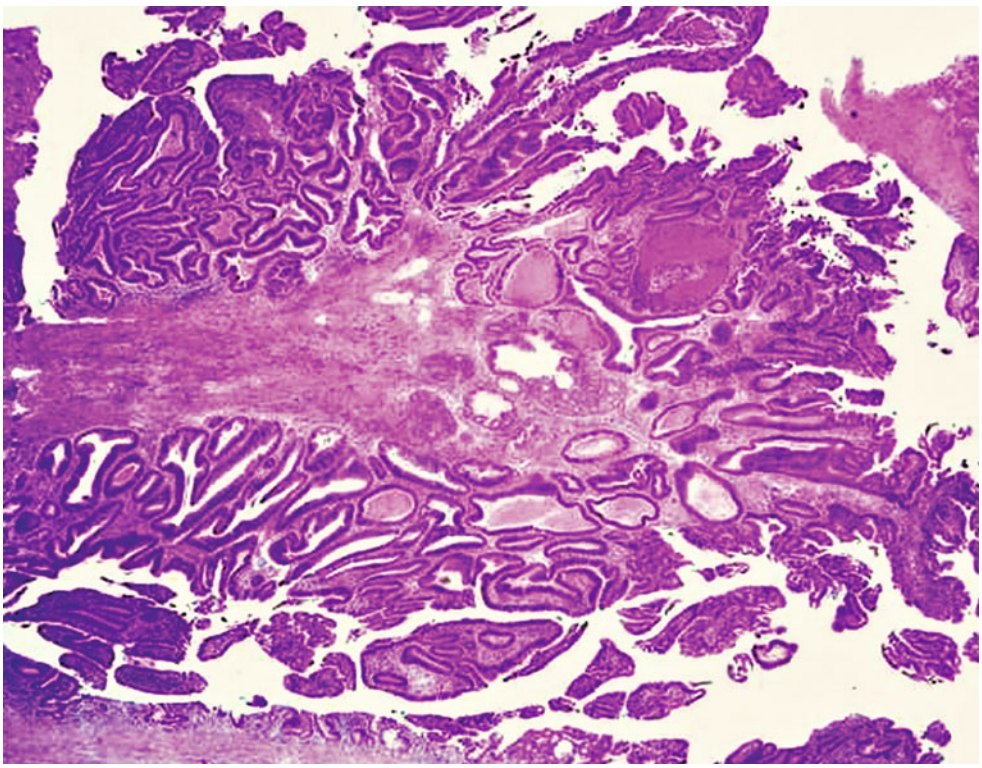

Fig. 3.21 Biliary adenoma. Fibrovascular fronds are lined by columnar cells with minimal atypia. There is no invasion of the fibrous stalk

lesions classified by a recent international consensus into three categories (grades) based on the degree of atypia: BilIN-1, BilIN-2, and BilIN-3, the last-mentioned also include carcinoma in situ (Figs. 3.20, 3.21 and 3.22) [31, 32]. Since BilINs share morphology and expression patterns of mucin core proteins (MUC1 and MUC2) with pancreatic intraepithelial neoplasia (PanIN) [32], it has been suggested that they represent the counterpart of PanIN [33, 34]. Biliary IPNs are grossly visible, non-invasive, intraductal papillary proliferations and resemble pancreatic intraductal papillary mucinous neoplasms (IPMN) [34]. Biliary IPNs, including biliary papillomatosis, show macroscopic mucinous hypersecretion in about 30 % of cases and may display three different forms of differentiation, namely, pancreaticobiliary, intestinal, and gastric. It is currently recognized that these two forms of intraepithelial neoplasia represent at least two pathways of carcinogenesis in bile duct adenocarcinoma, viz, a dysplasia-carcinoma sequence via BilIN and an adenoma-carcinoma sequence via biliary IPN [31].

3.3 Immunohistochemistry

Immunohistology is not particularly helpful in the identification of biliary carcinoma. In the case of distinguishing reactive atypia from intraepithelial neoplasia, as mentioned above, p53 immunoexpression may be useful in identifying the latter.

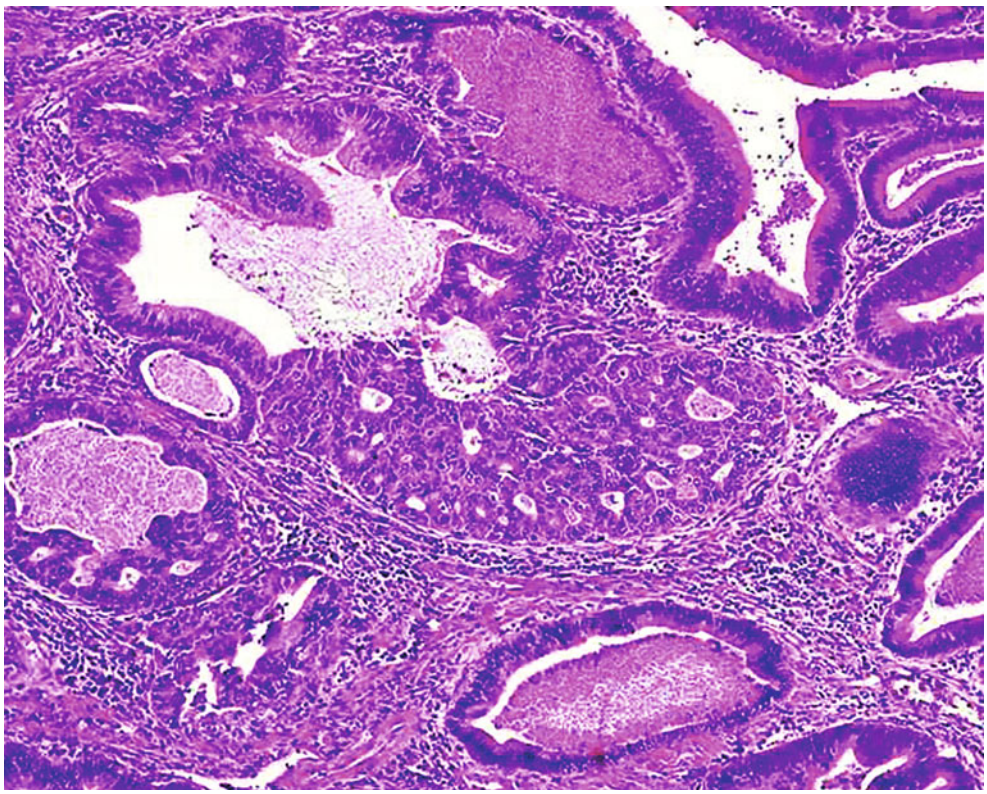

Fig. 3.22 High magnification of another adenoma which shows focal microinvasion of the inflamed fibrovascular stroma by small atypical glands that form a cribriform pattern in the center of the field

Immunohistological studies of hilar CC are uncommon although several studies of intrahepatic CC are available. CC express CK7, CK19, BerEP4 and show cytoplasmic staining for CEA, unlike hepatocellular carcinoma which express HepPar1 and show membranous staining for polyclonal CEA [35]. However, the role of immunohistochemistry to identify possible surrogate prognostic markers suffer from the drawback that correlation is weak as long-term survival in such tumors is poor. HER2/neu overexpression has been shown to correlate with nodal metastasis and with nuclear translocation of β-catenin, both markers showing significant correlation with high histological grade and high Ki-67 proliferation index, as well as with reduced immunoexpression of E-cadherin and FAT, the latter a newly described member of the cadherin superfamily [36]. K-*ras* and *p53* correlate with the microscopic types of CC, with k-*ras* mutations being more common in the periductal infiltrating than in mass-forming CC, whereas *p53* mutations had the reverse association. CDX2 and MUC2 have been employed to identify tumors of the intraductal papillary type of CC and over-expression of c-Met is said to be a feature of longer survival. Other markers studied include B-cell lymphoma-2 (Bcl-2), transforming growth factor β, telomerase, MUC4, p27, cyclin D1 but none has proven reliable [37, 38].

3.4 Molecular Genetics

Much of the published molecular genetics of CC relates to intrahepatic CC and carcinoma of the gallbladder and has been previously described [15, 39]. Mutations of the *RAS* and *TP53* genes are the most common abnormalities identified in both these conditions [39]. The molecular events associated with the development of CC have been investigated but are incompletely understood. Likewise, the changes that distinguish papillary from nodular-sclerosing lesions that are prognostically different (see below) are unclear [15, 40–42]. Abraham et al. [42], in an analysis of 14 cases of papillary bile duct carcinomas, failed to identify any unifying molecular derangements, although the study population was heterogeneous and there was no direct comparison to nodular-sclerosing tumors. Despite gaps in our understanding of these tumors, it is reasonable to postulate differences in the genetic changes between invasive papillary tumors and purely nodular-sclerosing lesions. The finding of highly invasive tumors with some residual papillary carcinoma components would suggest the possibility of overlap between two distinct pathogenetic mechanisms. Alternatively, this finding may represent the slow evolution of noninvasive papillary carcinomas to more invasive and aggressive tumors, an explanation that is possible but would require a long symptom-free period [43, 44].

3.5 Prognostic and Predictive Factors

The extent of the tumor largely determines prognosis with histological type influencing prognosis to a lesser extent. Polypoid tumors are most often papillary carcinomas and have the best prognosis, and non-invasive papillary carcinomas have a better prognosis than other types of invasive carcinomas [44, 45]. In one study of 13 patients with extrahepatic bile duct papillary carcinomas and 174 invasive papillary carcinomas complied by the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute from 1981 to 1990, papillary carcinomas confined to the ductal wall had better 10-year relative survival rates than adenocarcinoma limited to the wall (21 % versus 12 %). Furthermore, when there was lymph node metastasis, papillary carcinoma had better prognosis than adenocarcinoma (10-year survival rate of 12 % versus 5 %) [45]. When invasive, papillary carcinomas may show a tubular or mucinous pattern and the former is said to show a worse prognosis [39]. The difference in outcome between papillary and nodular-sclerosing CC appears to be related, at least in part, to differences in disease biology. However, the data show that the favorable impact of papillary histology on survival is most pronounced in patients with less invasive cancers, suggesting that once a certain critical degree of invasiveness is reached, the clinical behavior of papillary CC approaches that of nodular-sclerosing tumors [15, 36]. This contrasts somewhat with a recent report from that summarized results from the SEER database that showed a survival advantage of papillary CC even in patients with more invasive tumors and tumors associated with regional lymph node metastases [40]. Whether more invasive CC of papillary origin are distinct from nodular-sclerosing cancers is thus less clear and may be clarified through a better understanding of the pathogenesis of CC.

Perineural and lymphatic permeation are significant prognostic factors. Perineural spread has been reported in 75 % of hilar CC, lymph node metastasis in 50 % and venous invasion in 38 % [46]. In one study of 564 cases of CC, locoregional lymph node metastasis occurred more frequently in distal CC (60 %) compared to hilar CC (28 %) and intrahepatic CC (29 %) [47].

Clearance of the surgical margin is an important prognostic indicator for all forms of CC [48, 49]. The lowest rate of negative margins was found in hilar CC. However, there is no clear-cut definition of margin clearance. Japanese authors require a 5 mm clearance [50, 51] whereas this is not the case in Western countries [18]. Furthermore, the examination of surgical margins with frozen sections will reduce the accuracy of detection of involvement especially of dysplasia and carcinoma-in-situ.

3.6 Differential Diagnoses

A variety of structures and tissues occur at the porta hepatis and both benign and malignant tumors arising in any of these tissues can produce compression of the common bile duct resulting in a clinical presentation similar to that of bile duct epithelial proliferation [52]. The list of such tumors that have been considered in the clinical differential diagnoses include granular cell tumor [53], inflammatory myofibroblastic tumor [54], embryonal carcinoma [55], neurilemmoma [56], malignant lymphoma [57], and heterotopic pancreatic tissue [58] as well as reactive conditions like tuberculosis [59], sclerosing mesenteritis [60], sarcoidosis [61], and IgG4 sclerosing disease [62]. Metastatic tumors can produce similar symptoms and presentation.

References

1. Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis: an unusual tumor with distinctive clinical and pathological features. Am J Med. 1965;38:241–56.
2. Shahip Y, El-Sharag HB. The epidemiology of cholangiocarcinoma. Semin Liver Dis. 2004;24:115–24.
3. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology. 2001; 33:1353–7.
4. Khan SA, Taylor-Robinson SD, Toledano MD, et al. Changing international trends in mortality rates for liver, biliary and pancreatic tumors. J Hepatol. 2002;37:806–13.
5. West J, Wood H, Logan RFA, et al. Trends in the incidence of primary liver and biliary tracts cancers in England and Wales 1971–2001. Br J Cancer. 2006;94:1751–8.
6. Khan SA, Thomas HC, Davidson BR, et al. Cholangiocarcinoma. Lancet. 2005;366:1303–14.
7. Shaib YB, Davila JA, McGlynn K, et al. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? J Hepatol. 2004;40:472–7.
8. Welzel TM, McGlynn KA, Hsing AW, et al. Impact of classification of hilar cholangiocarcinomas (Klatskin tumor) on the incidence of intra- and extrahepatic cholangiocarcinoma in the United States. J Natl Cancer Inst. 2006;98:873–5.
9. Blechacz BRA, Sanchez W, Gores GJ. A conceptual proposal for staging ductal cholangiocarcinoma. Curr Opin Gastroenterol. 2009;25:238–9.
10. Kagawa Y, Kashihara S, Kuramoto S, et al. Carcinoma arising in a congenitally dilated biliary tree. Report of a case and review of the literature. Gastroenterology. 1978;74:1286–94.
11. Boberg KM, Bergquist A, Mitchell S, et al. Cholangiocarcinoma in primary sclerosing cholangitis: risk factors and clinical presentation. Scand J Gastroenterol. 2002;37:1205–11.
12. Vatanasapt V, Sripa B, Sithithaworn P, et al. Liver flukes and liver cancer. Cancer Surv. 1999;33:313–43.
13. Migasena P, Reaunsuwan W, Changbumrung S. Nitrates and nitrites in local Thai preserved protein foods. J Med Assoc Thai. 1980; 63:500–55.
14. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. Surg Gynecol Obstet. 1975;140:170–8.

15. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg. 2001;234:507–17.
16. American Joint Committee on Cancer. Extrahepatic bile ducts. In: Greene FL, Page DL, Fleming ID, editors. AJCC cancer staging manual. 6th ed. New York: Springer; 2002. p. 145–50.
17. Japanese Society of Biliary Surgery. Extrahepatic bile ducts. In: Nagakawa T, Kayahara M, Tashiro S, editors. Classification of biliary tract carcinoma. 2nd ed. Tokyo: Kanchara; 2004. p. 11–32.
18. Washington K, Berlin J, Brannton P, et al. Protocol for the examination of specimens from patients with carcinoma of the perihilar bile ducts. 2009. http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2009/PerihilarBileDucts_09protocol.pdf. Accessed on 30 Nov 2010.
19. Kim HJ. TNM staging of hilar cholangiocarcinoma. Korean J Gastroenterol. 2005;46:20–7.
20. Zervos EE, Osborne D, Goldin SB, et al. Stage does not predict survival after resection of hilar cholangiocarcinomas promoting an aggressive operative approach. Am J Surg. 2005;190:810–5.
21. Weber A, Landrock S, Schneider J, et al. Long-term outcome and prognostic factors of patients with hilar cholangiocarcinoma. World J Gastroenterol. 2007;13:1422–6.
22. Chen R-F, Li Z-H, Zhou J-J, et al. Preoperative evaluation with T-staging system for hilar cholangiocarcinoma. World J Gastroenterol. 2007;21:5754–9.
23. Jarnagin W, Winston C. Hilar cholangiocarcinoma: diagnosis and staging. HPB. 2005;7:244–51.
24. Burke EC, Jarnagin W, Hochwald SN, et al. Cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. Ann Surg. 1998;228:385–94.
25. Albores-Saavedra J, Scoazec JC, Wittekind C, et al. Carcinoma of the gallbladder and extrahepatic bile ducts. In: Hamilton SR, Aaltonen LA, editors. World Health Organization classification of tumours. Tumors of the digestive system. Lyon: International Agency for Research on Cancer Press; 2000. p. 206–14.
26. Albores-Saavedra J, Henson DE, Klimstra D. Tumors of the gallbladder and extrahepatic ducts, Atlas of tumor pathology, vol. 3. Washington D.C.: Armed Forces Institute of Pathology; 1999.
27. Devaney K, Goodman ZD, Ishak KG. Hepatobiliary cystadenoma and cystadenocarcinoma. A light microscopic and immunohistochemical study of 70 patients. Am J Surg Pathol. 1994;18:1078–91.
28. Ishak KG, Willis GW, Cummins SD, et al. Biliary cystadenoma and cystadenocarcinoma: report of 14 cases and review of the literature. Cancer. 1977;39:322–38.
29. Abdul-Al HM, Makhlouf HR, Goodman ZD. Expression of estrogen and progesterone receptors and inhibin-alpha in hepatobiliary cystadenoma: an immunohistochemical study. Virchows Arch. 2007;450:691–7.
30. Wheeler DA, Edmondson HA. Cystadenoma with mesenchymal stroma (CMS) in the liver and bile ducts. A clinicopathologic study of 17 cases, 4 with malignant change. Cancer. 1985;56:1434–45.
31. Zen Y, Adsay NV, Bardadin K, et al. Biliary intraepithelial neoplasia: an international interobserver agreement study and proposal for diagnostic criteria. Mod Pathol. 2007;20:701–9.
32. Zen Y, Sasaki M, Fujii T, et al. Different expression patterns of mucin core proteins and cytokeratins during intrahepatic cholangiocarcinogenesis from biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct—an immunohistochemical study of 110 cases of hepatolithiasis. J Hepatol. 2006;44:350–8.
33. Kloppel G, Kosmahl M. Is the intraductal papillary mucinous neoplasia of the biliary tract a counterpart of pancreatic papillary mucinous neoplasm? J Hepatol. 2006;44:249–50.
34. Zen Y, Fujii T, Itatsu K, et al. Biliary papillary tumors share pathological features with intraductal papillary mucinous neoplasm of the pancreas. Hepatology. 2006;44:1333–43.
35. Leong AS-Y, Sormunen RT, Tsui WM-S, et al. Immunostaining for liver cancers. With special reference to Hep Par 1 antibody. Histopathology. 1998;33:318–24.
36. Settakorn J, Kaewpila N, Burns G, et al. Fat, E-cadherin, β-catenin, HER 2/neu, Ki67 immunoexpression and histologic grade in intrahepatic cholangiocarcinoma. J Clin Pathol. 2005;58:1249–54.
37. Leong TY-M, Leong AS-Y. Prognostication in intrahepatic cholangiocarcinoma. Adv Anat Pathol. 2006;13:99–100.
38. Leong TY-M, Wannakrairot P, Lee ES, et al. Review: pathology of cholangiocarcinoma. Curr Diagn Pathol. 2007;13:54–64.
39. Nakanuma Y, Sripa B, Vatanasapt V, et al. Intrahepatic cholangiocarcinoma. In: Hamilton SR, Aaltonen LA, editors. World Health Organization classification of tumors. Tumors of the digestive system. Lyon: International Agency for Research on Cancer Press; 2000. p. 173.
40. Rashid A. Cellular and molecular biology of biliary tract cancers. Surg Oncol Clin N Am. 2002;11:995–1009.
41. Albores-Saavedra J, Murakata L, Krueger JE, et al. Non-invasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts. Cancer. 2000;89:508–15.
42. Abraham SC, Lee JH, Hruban RH, et al. Molecular and immunohistochemical analysis of intraductal papillary neoplasms of the biliary tract. Hum Pathol. 2003;34:902–10.
43. Albores-Saavedra J, Henson DE, Klimstra D. Dysplasia, carcinoma in situ, and invasive carcinoma of the extrahepatic bile duct. In: Rosai J, Sobin LH, editors. Tumors of the gallbladder, extrahepatic bile ducts and ampulla of Vater. Washington D.C.: AFIP; 2000. p. 191–215.
44. Jarnagin WR, Bowne W, Klimstra DS, et al. Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. Ann Surg. 2005;241:703–14.
45. Hoang MP, Murakata LA, Katabi N, et al. Invasive papillary carcinomas of the extrahepatic bile ducts: a clinicopathologic and immunohistochemical study of 13 cases. Mod Pathol. 2002;15:1251–8.
46. Yamaguchi K, Chijiiwa K, Saiki S, et al. Carcinoma of the extrahepatic bile duct: mode of spread and its prognostic implications. Hepatogastroenterology. 1997;44:1256–61.
47. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg. 2007;245:755–62.
48. Nakeeb A, Pitt HA, Sohn TA, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg. 1996;224:463–73.
49. Sasaki R, Takeda Y, Funato O, et al. Significance of ductal margin status in patients undergoing surgical resection for extrahepatic cholangiocarcinoma. World J Surg. 2007;31:1788–96.
50. Uenishi T, Hirohashi K, Kubo S, et al. Histologic factors affecting prognosis following hepatectomy for intrahepatic cholangiocarcinoma. World J Surg. 2001;25:865–9.
51. Ogura Y, Takahashi K, Tabata M, et al. Clinicopathological study on carcinoma of the extrahepatic bile duct with special focus on cancer invasion on the surgical margins. World J Surg. 1994;18:778–84.
52. Dumitrascu T, Ionescu M, Clurea S, et al. Klatskin-mimicking lesions—a case series and literature review. Hepatogastroenterology. 2010;57:961–7.
53. Bilanovic D, Boricic I, Zdravkovic D, et al. Granular cell tumor of the common hepatic duct presenting as cholangiocarcinoma and acute acalculous cholecystitis. Acta Chir Iugosl. 2008;55:99–101.
54. Gohy S, Hubert C, Deprez P, et al. Benign biliary inflammatory pseudotumor mimicking Klatskin tumor. Hepatogastroenterology. 2007;54:1348–52.

55. Lee JA, Kim TW, Min JH, et al. A case of undifferentiated (embryonal) liver sarcoma mimicking Klatskin tumor in an adult. Korean J Gastroenterol. 2010;55:144–8.
56. Kamani F, Dorudinia A, Goravanchi F, et al. Extrahepatic bile duct neurilemmoma mimicking Klatskin tumor. Arch Iran Med. 2007;10:264–7.
57. Kang HG, Choi JS, Seo JA, et al. A case of primary biliary malignant lymphoma mimicking Klatskin tumor. Korean J Gastroenterol. 2009;54:191–5.
58. Heer C, Pfortner M, Hamberger U, et al. Heterotopic pancreatic tissue in the bifurcation of the bile duct: rare diagnosis mimicking a Klatskin tumor. Chirurg. 2010;81:151–4.
59. Arora R, Sharma A, Bhowate P, et al. Hepatic tuberculosis mimicking Klatskin tumor: a diagnostic dilemma. Indian J Pathol Microbiol. 2008;51:382–5.
60. Medina-Franco H, Listinsky C, Mel Wilcox C, et al. Concomitant sclerosing mesenteritis and bile duct fibrosis simulating Klatskin tumor. J Gastrointest Surg. 2001;5:658–60.
61. Pungpapong S, Steers JL, Wallace MB, et al. Hepatobiliary sarcoidosis mimicking Klatskin's cholangiocarcinoma. Gastrointest Endosc. 2006;64:124–5.
62. Cheung MT, Lo IL. IgG4-related sclerosing lymphoplasmacytic pancreatitis and cholangitis mimicking carcinoma of the pancreas and Klatskin tumour. ANZ J Surg. 2008;78:252–6.