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Mucin-producing bile duct tumors: radiological–pathological correlation and diagnostic strategy

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Abstract Mucin-producing bile duct tumors are characterized by intraductal papillary tumors producing large amounts of mucin. The tumor comprises macroscopically prominent intraductal papillary neoplastic epithelia and produces a large amount of viscid mucin, resulting in dilatation of the bile ducts. The surface of the tumor is frond-like, velvety, or serrated. The tumor exhibits five intraductal growth patterns; polypoid intraductal growth, mucosal spreading growth, cast-like intraductal growth, cystic tumor, and intraductal floating tumors. Imaging features reflect the interplay between the morphology of the tumor, the amount of mucin production, and biliary dilatation. This review article describes the radiological manifestations of the tumor, based on pathological-radiological correlation and biological behavior.

Keywords Mucin-producing bile duct tumor · Biliary papillary tumor · Superficially spreading bile duct tumor · Biliary intraductal floating tumor · Biliary cystic tumor

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Introduction

Mucin-producing bile duct tumor has been the subject of recent attention due to its peculiar histopathology, biological and clinical behavior, varied radiological manifestations, the good prognosis of the patients [1–10], and the histopathological similarity of the tumors to intraductal papillary mucinous neoplasm of the pancreas [11–16]. The tumor exhibits prominent papillary proliferation of neoplastic epithelia (Fig. 1) and shows various features of intraductal tumor growth. These tumors are often encountered in patients with inflammatory biliary lesions such as hepatolithiasis [1, 3, 6, 17] and clonorchiasis [1, 3, 6, 18].

A tumor that has arisen from the mucosa may stay and attach to only a limited area of the bile ducts, or more often, it spreads superficially along the mucosa and inner surface of the bile duct and is lined by a myriad of tiny frond-like papillary projections. Even when a tumor spreads diffusely along a considerable length of the bile duct mucosa, the tumor does not show an invasive nature [1]. Many tumors are dormant in the bile duct for a considerable, asymptomatic, period of time. Only in the late stage in some cases, an invasive carcinoma develops and shows a clinical course similar to that of usual cholangiocarcinoma [1, 12].

The tumors produce abundant mucin, sometimes in profuse amounts, and the mucin is excreted into the bile ducts. The viscid mucin, in addition to the soft fragile tumor itself, fills the bile duct lumen and this causes partial obstruction and results in tubular dilatation of the affected segmental or lobar bile ducts [7, 9, 10]. The bile ducts are rarely completely obstructed because the patency of the lumen is maintained between the bile duct wall and the papillary surfaces of intraductal tumors. Often, the bile ducts distal to the tumor are dilated as well because of the large amount of sticky mucin.

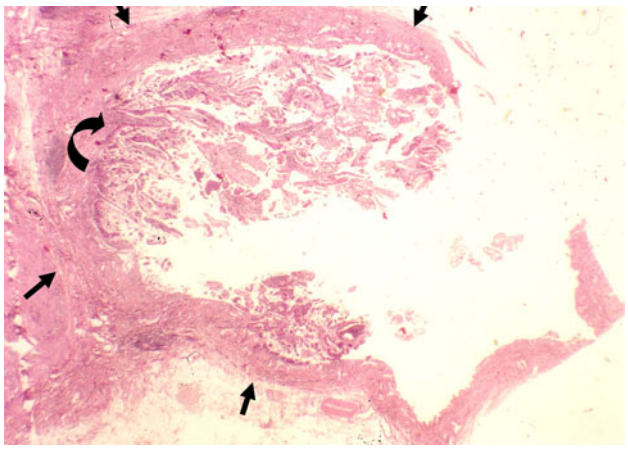

Fig. 1 Microphotograph of mucin-producing papillary adenocarcinoma, showing a myriad of frond-like papillary infoldings comprising slender fibrovascular stalks (*curved arrow*) covered by columnar epithelial cells. *Arrows* point to the wall of the bile duct. H&E ×40 (reproduced from reference [9] with permission)

Because of the long protracted course and the mucin production, clinical and radiological manifestations of mucin-producing bile duct tumor vary, different from the usual cholangiocarcinoma, which presents simply with a mass and bile duct obstruction. Patients may present with cholangitis rather than obstructive jaundice [7, 9, 10]. Sometimes, a physician may encounter the patients during a screening procedure using ultrasound or computed tomography (CT) scanning, the patients presenting with tubular or cystic bile duct dilatation. A widely patulous opening of the duodenal papilla and extrusion of mucin from the ampulla of Vater may be observed during an endoscopic examination [3].

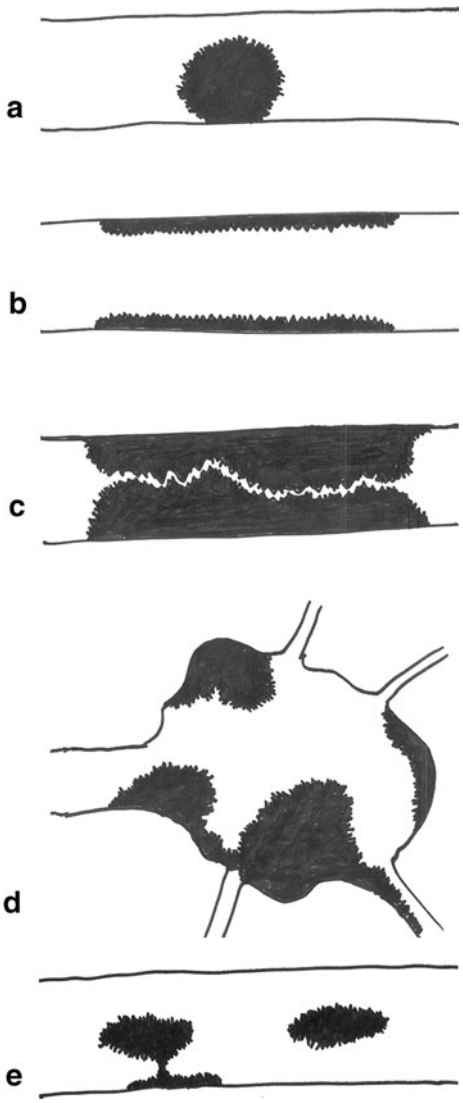

Fig. 2 Schematic drawing of mucin-producing tumors of the bile duct. **a** Polypoid intraductal tumor. **b** Mucosal spreading growth. **c** Cast-like intraductal tumor. **d** Cystic tumor. **e** Floating tumors

Mode of tumor growth

A mucin-producing bile duct tumor comprises macroscopically prominent intraductal papillary growth of neoplastic epithelia and microscopic papillary proliferation with delicate fibrovascular cores (Fig. 1) [16]. Therefore, the surface of the tumor is frond-like, velvety, or serrated. The tumor may present in five intraductal growth patterns: polypoid intraductal tumor, mucosal spreading growth, cast-like intraductal tumor, cystic and aneurysmal dilatation, and an intraductal floating tumor (Fig. 2).

A mucin-producing tumor arises from the mucosal surface of the bile ducts, forming a polypoid mass (Fig. 3). Frequently, a tumor may spread along the mucosa of the bile duct, and this superficial spread is the most striking feature of the tumor (Figs. 4, 5). The mucosal layer becomes thickened due to the superficial spreading of tumor cells. Frequently, an intraductal tumor may present with intraductal cast-like features [9] due to its intraluminal growth (Fig. 6). The height of the intraluminal growth depends upon the histological malignancy, with an invasive tumor having a greater height than that of a tumor with noninvasive histology [19]. There may be multiple intraductal tumors with intervening normal mucosa along the bile ducts, involving a wide area of both the intra- and extrahepatic bile ducts. These tumors have been classified as papillomatosis in the current WHO tumor classification. However, these tumors show a wide spectrum of histopathological features with variable malignant potential [3]. Occasionally, a tumor produces a large cystic dilatation of the bile duct with or without the presence of intraluminal masses [2, 7, 8, 20] (Fig. 7).

Not infrequently, the tumor cells slough off. This is because the papillary tumors have a weak and friable stalk

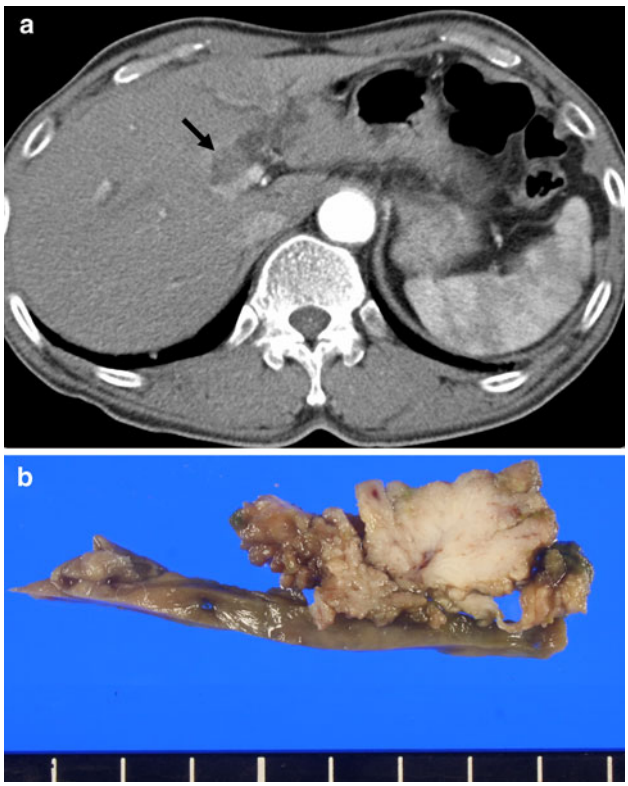

Fig. 3 Polypoid intraductal tumor. **a** Contrast-enhanced computed tomography (CT) image shows a round tumor (*arrow*) filling the proximal part of the common hepatic duct. **b** Photograph of cut surface of the intraductal polypoid tumor. *Scale increment* 5 mm

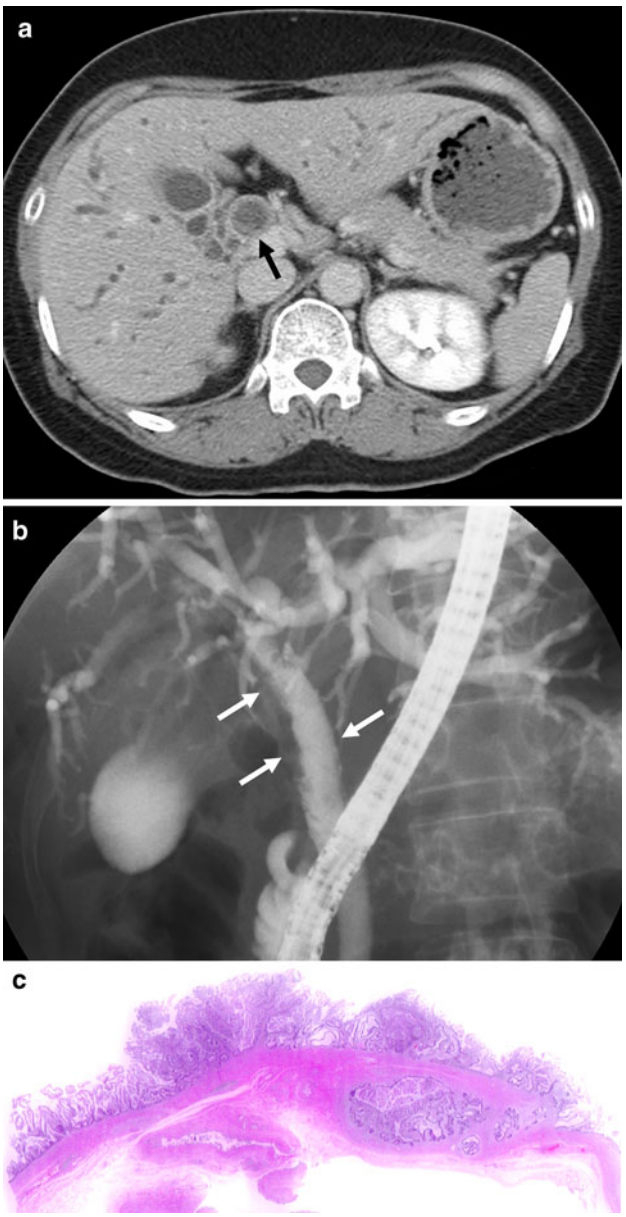

Fig. 4 Mucosal spreading growth. **a** Contrast-enhanced CT image shows extrahepatic bile duct dilatation and wall thickening (*arrow*), reflecting intraductal mucosal spread. **b** Endoscopic retrograde cholangiogram shows fine irregularity and filling defects (*arrows*) along the common hepatic duct. **c** Photograph of the resected specimen shows fine papillary tumors lining the common hepatic duct (*arrows*). **c** H&E ×1

and the tumor cells are easily detached, owing to sticky mucin stagnation and repeated infection of the bile ducts. Bile duct infection may precipitate tumor sloughing. Histopathologically, a papillary tumor consists of dysplastic papillary epithelial cells with slender, frond-like fibrovascular cores, with the very thin and narrow connective tissue core being supported by the lamina propria [1]. As the papillary projections are slender and long (Fig. 1), the tumor may be friable and the tumor may detach easily and spontaneously, and may float in the bile ducts [21] (Fig. 8).

Radiological–pathological correlations

The imaging findings of mucin-producing bile duct tumors depend on the formation of an intraductal tumor, mucin secretion, and partial bile duct obstruction, and the interplay of these three factors. When tumor formation predominates, the result is intraductal papillary mass formation, while when the mucin production predominates, the result is gross dilatation of the bile ducts. The degree of bile duct dilatation depends on the amount and speed of mucin production combined with the presence of a mass. Occasionally, when a tumor grows along the bile ducts without the tumor being visible, or when a friable tumor sloughs off, there may be only bile duct dilatation [22]. When the neoplastic part of the intrahepatic bile duct undergoes saccular dilatation associated with the production of a massive amount of mucin, the involved bile ducts look like balloons [2, 8, 20].

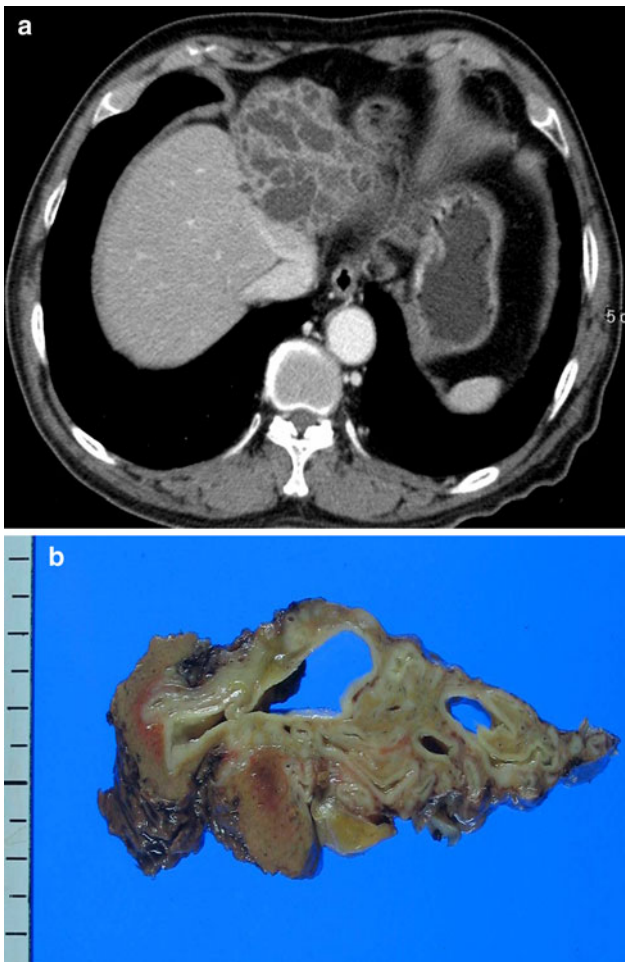

Fig. 5 Mucin-producing papillary tumor presenting only as dilatation of the hepatic lobar bile ducts. **a** Contrast-enhanced CT image shows severe dilatation of the left hepatic lobar bile ducts and very severe atrophy of the hepatic parenchyma. **b** Photograph of the resected specimen shows severe dilatation the left hepatic bile ducts, which were filled with mucin. Hepatic parenchyma is virtually absent. There is no visible tumor present in the bile ducts. *Scale increment* 5 mm

Polypoid/papillary intraductal tumors

An intraductal tumor may present as a small polypoid tumor that measures about 0.5–2 cm in size (Fig. 3). The bile duct may be partially obstructed, depending on the tumor size and location. When a papillary tumor has a narrow pedicle, there may be sufficient free intraluminal surface between the tumor and the bile duct wall, and bile can flow between the tumor and the bile duct wall. On cholangiography, contrast media can easily opacify the proximal bile ducts adjacent to a tumor. The tumor can be demonstrated on ultrasonography, CT, magnetic resonance imaging (MRI), and cholangiography as a polypoid mass in the bile ducts. On cholangiography or MR cholangiography, the tumor surface appears villous or velvety. Sometimes, a cauliflower-like mass can be demonstrated.

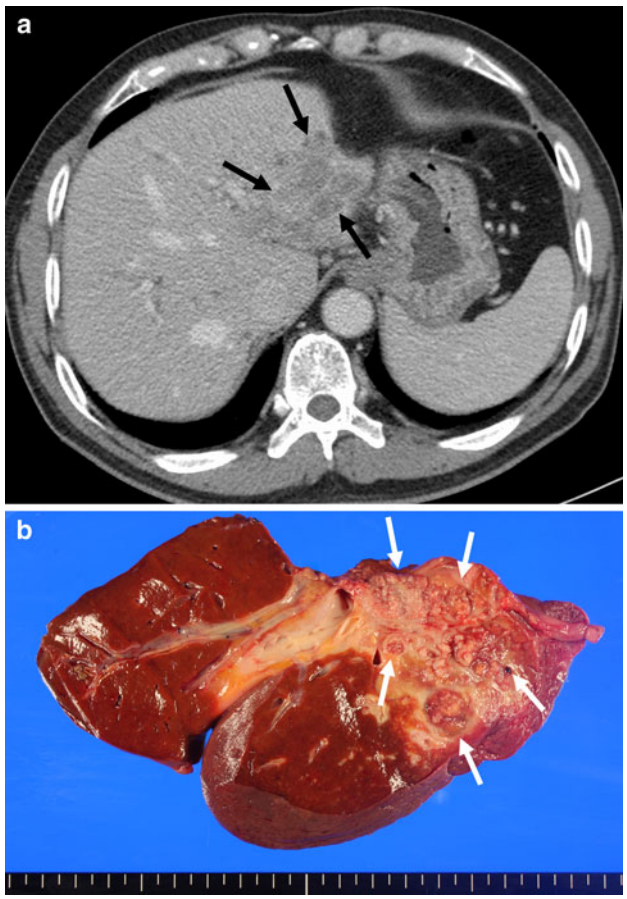

Fig. 6 Cast-like intraductal tumor. **a** Contrast-enhanced CT image shows cast-like tumor filling the lateral segmental bile ducts of the left hepatic lobe (*arrows*). **b** Photograph of the resected specimen shows papillary tumors filling the intrahepatic bile ducts (*arrows*). *Scale increment* 5 mm

Mucosal spreading growth

A mucin-producing bile duct tumor may present with a mucosal spreading growth pattern without the formation of a mass (Fig. 4). In this type of tumor, it may be difficult or impossible to recognize a tumor in the bile ducts as seen on imaging; only thickening of the bile ducts can be seen. The bile ducts are dilated due to the presence of excessive mucin. The bile ducts may be further dilated by partial obstruction caused by stagnation of the viscid mucin.

In some cases in which papillary tumors spread along the mucosa without mass formation, in association with the massive production of mucus, the bile ducts are much dilated and there may be profound atrophy of the hepatic parenchyma of the affected hepatic lobe or segments [22] (Fig. 5). This occurrence can be explained by longstanding increased ductal pressure to the adjacent hepatic parenchyma due to the partial obstruction and the presence of excessive stagnant mucin. In a severe case, the affected hepatic parenchyma is virtually absent, resulting

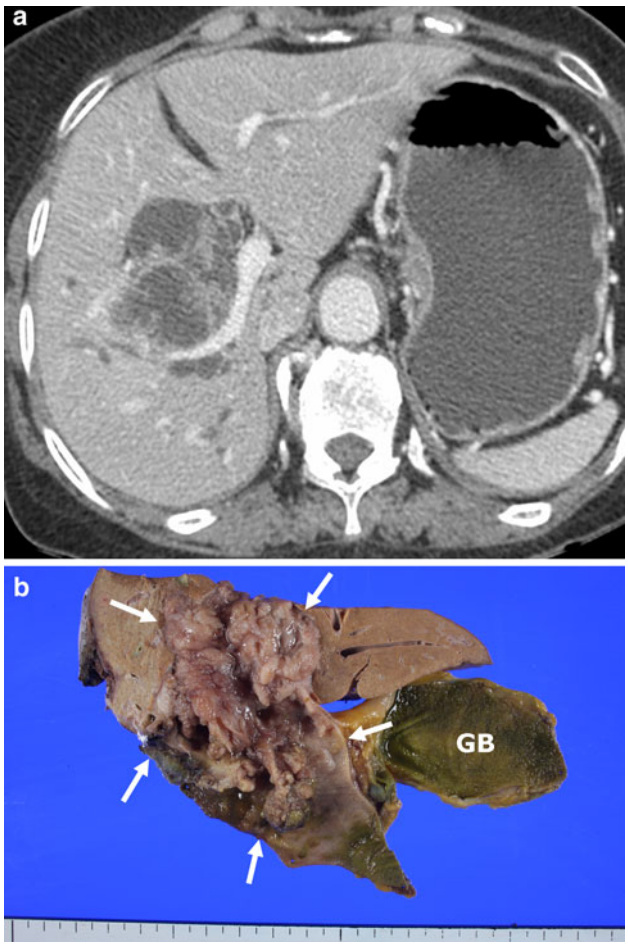

Fig. 7 Cystic tumor. **a** Contrast-enhanced CT image shows cystic dilatation of the intrahepatic ducts harboring multiple papillary tumors. **b** Photograph of the resected specimen shows innumerable papillary tumors in the aneurysmally dilated bile ducts (*arrows*). The cyst has collapsed but it was filled with mucin. *GB,* Gallbladder. *Scale increment* 5 mm

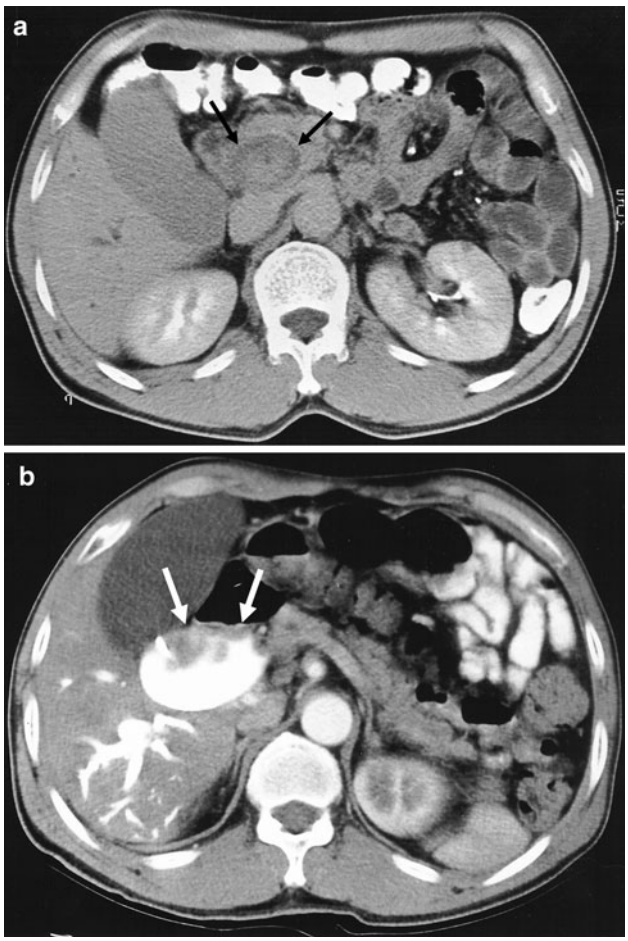

Fig. 8 Floating tumors. **a** Contrast-enhanced CT scan 10 days before patient's admission to hospital shows an enhancing tumor in the common bile duct. Note the tumor is in the center of the lumen (*arrows*). **b** CT image after cholangiography shows several floating filling defects in the nondependent part of the common bile duct, representing floating tumors (*arrows*). The tumor fragments float, probably because the specific gravity of the iodine-containing contrast media is heavier than the tumor fragments. (reproduced from reference [21] with permission)

in compensatory hypertrophy of the unaffected hepatic lobe. Biliary epithelial hyperplasia with or without dysplastic change falls into this category [22].

Cast-like intraductal tumor

When a tumor shows predominant intraductal growth along a considerable length in the lumen, the tumor may present with a cast-like feature as seen on radiological evaluation (Fig. 6). The lumen of the bile duct may be lined with a myriad of tiny papillary frond-like projections that appear similar to coral-reef projections or stalactites in a cave. Even when the tumor involvement is of considerable length, the lumen is not obliterated. In biliary papillomatosis, there may be multiple tumor sites with intervening normal mucosa between the papillary lesions [3]. The height of the papillary projections varies: when the papillary projections are long, the entire lumen may be filled with a myriad of minute stalactite-like tumors. The proximal and distal bile ducts are usually dilated due to the disturbance of flow of the sticky mucin.

On cholangioscopy, a myriad of tiny projections are seen along the involved segments [3]. Depending upon the height of the papillary projections, the lumen shows frond-like, villi-like, coral-reef-like or fish egg-like appearances [3]. On sonography, a cast-like intraductal mass is depicted in a segment of intrahepatic or extrahepatic bile ducts. Usually the bile duct walls are well preserved as uniform, echogenic lines, reflecting the intactness of the wall. On CT and MRI, the tumor presents as an enhancing intraluminal mass. The bile duct wall is intact and the periductal fat tissue is clear. On cholangiography and MR cholangiography, the cast-like tumor surface is irregular, reflecting the papillary surface of the tumor. The bile duct lumen is irregular and ragged and

innumerable tiny ovoid or round filling defects may be demonstrated [9, 21]. Mostly, the lumen is not obliterated and the contrast media flows into the proximal bile ducts.

Cystic tumors

A papillary tumor of the bile duct forms a cystic tumor and it resembles a sac or aneurysm (Fig. 7). There may be mural nodules or multiple fungating masses attached to the aneurysmally dilated cyst wall [2, 7, 9, 20]. The cystic tumor communicates with the bile ducts and mucus drains and thus the bile ducts distal to the cystic tumor are dilated, as the dilated ducts are filled with a large amount of mucus (mucobilia) [2, 20].

Cyst formation can be explained as follows. When a tumor arises in an intrahepatic bile duct, the bile duct may become partially obstructed by the tumor itself, with the chance of obstruction being higher in a small peripheral duct. Because of continual mucin production by the tumor, the bile ducts harboring the tumor may form a cystic tumor resembling an aneurysm [20]. Within the cystically dilated bile ducts, intracystic fungating masses with papillary surfaces, mural nodules of variable size, or features of multiple trabeculae may be present (Fig. 7) as seen on imaging [20].

Floating tumors

As intraductal papillary tumors are very friable, they slough off spontaneously due to stagnation of the viscid mucin and recurrent infection. This process occurs because papillary tumors consist of innumerable minute frond-like projections. When a tumor grows to a certain size, it sloughs off and floats in the bile ducts. The floating tumor may then reside within the bile ducts, imbibing nutrients from bile juice and the tumor may grow substantially. Like stones, the detached tumor fragments float within the bile ducts [20] (Fig. 8). These sizable, floating tumors may occlude the duodenal papillary orifice or escape from the bile duct through the papillary orifice and then disappear. These characteristics of a floating tumor can be confused with bile duct stones both radiologically and clinically [21]. When a balloon catheter is inserted into the bile duct and retracted, lumps of tumor masses can be extruded through the papilla of Vater [3, 21]. As seen on imaging, only thickening of the bile ducts is seen. The bile ducts remain dilated because of the presence of mucin and chronic incomplete obstruction.

Relative values of diagnostic modalities and diagnostic strategy

Ultrasonography is sensitive for the detection of bile duct dilatation. However, ultrasonography has limited value for depicting an intraductal mass, especially when the mass is small. Mucin is anechoic, as is bile, and thus the presence of mucin is not detected on ultrasonography.

CT and MRI are sensitive for the detection of bile duct dilatation and for the depiction of an intraductal mass. MR cholangiography is valuable for the evaluation of the extent of bile duct involvement. In one report concerning the detection of a mass of biliary papillomatosis, sonography was shown to be sensitive in 41% of the cases and CT was shown to be sensitive in 50% of the cases [3]. These low detection rates may be related to the diffuse or multiple papillomatosis rather than the presence of a solitary polypoid mass. For the detection of the presence of mucin, neither CT nor MRI is sensitive.

Cholangiography is valuable for the detection of a mass and its extent when the bile ducts are well opacified. However, this modality has limited value when the bile ducts are not well opacified, especially when the opacification is hampered by the presence of a large amount of mucin. When there is a small filling defect in the bile duct, it is difficult or impossible to differentiate a small tumor from a thick mucus ball.

Percutaneous or peroral cholangioscopy has some advantages over the use of radiological imaging [3]. A cholangioscopic evaluation provides detailed information regarding the presence and evaluation of tumor extent, and the technique can be used in obtaining biopsy material for pathological confirmation. Bile duct mucosa is directly observed and a small tumor or subtle mucosal change can be readily detected. When there is a suspicion of an abnormality, a biopsy may prove the diagnosis. Therefore, a percutaneous transhepatic or peroral cholangioscopic examination is an indispensable preoperative diagnostic procedure for diagnosis and determination of extent, especially for diffuse papillomatosis [3]. Additionally, the presence of mucin is readily demonstrated. However, it is not always possible to access the intended intrahepatic bile ducts. Therefore, CT, MRI, and MR cholangiography are utilized as noninvasive techniques for the detection of a mass and for the evaluation of tumor extent and bile duct dilatation, and although invasive, cholangiography and cholangioscopy are necessary for the evaluation of tumor extent and can provide a road map for surgery or biliary intervention.

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