Biliary Papillomatosis: Correlation of Radiologic Findings with Percutaneous Transhepatic Cholangioscopy

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ABSTRACT

Aim: To correlate the radiologic findings with percutaneous transhepatic cholangioscopy (PTCS) in patients with pathologically confirmed biliary papillomatosis.

Methods: Thirteen patients diagnosed with pathologic papillomatosis or intraductal papillary neoplasms of the bile ducts were retrospectively reviewed. The imaging results from ultrasonography, multi-detector computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP) and percutaneous cholangiography (PTC) were correlated with the findings of PTCS.

Results: Papillary neoplasms of the bile ducts usually appeared on ultrasound as a non-shadowing echogenic mass (60%) within dilated bile ducts. Localised dilatation of the bile duct with mild enhancing nodularities was the most common multi-detector CT finding (61.5%), followed by localised biliary dilatation with mild wall thickening (15.4 %). MRCP showed that the bile duct was locally dilated and filled with material of intermediate signal intensity (60%). An abnormal filling defect (71.4%) was the most common finding when PTC was used. In six patients who underwent PTCS, underlying fish egg-like intraluminal nodularities were noted with or without multifocal cauliflower-like papillary masses. In nine cases, the pathologic finding was intraductal papillary cholangiocarcinoma in the underlying biliary papillomatosis. Three patients were diagnosed as papillomatosis with high grade dysplasia and one as villous adenoma with underlying papillomatosis.

Conclusions: Imaging is useful for detecting bile duct tumours that cause obstruction, but its ability to detect fine features of intraductal papillary tumours is limited. Percutaneous transhepatic cholangioscopy is an effective approach that allows the direct visualisation and tissue confirmation of growing papillary tumours.

Key words: intraductal biliary neoplasm – intraductal papillary neoplasm of the bile duct – intraductal tubular neoplasm of the bile duct – intraductal tubulopapillary neoplasm of the bile duct – biliary tract neoplasms/diagnosis – papilloma/diagnosis.

Abbreviations: IPNB: intraductal papillary neoplasm of the bile duct; CT: computed tomography; PTCS: percutaneous transhepatic cholangioscopy; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; PTC: percutaneous cholangiography; PTBD: percutaneous transhepatic biliary drainage

INTRODUCTION

Biliary papillomatosis or intraductal papillary neoplasm of the bile duct (IPNB) are rare diseases of the biliary tract characterised by the distinctive papillary proliferation of the bile duct epithelial cells around the slender fibrovascular stalks [1]. These diseases are histologically classified as papilloma, papillomatosis, and papillary adenocarcinoma. Biliary papillomatosis usually manifests as a multicentric papilloma involving the intrahepatic or extrahepatic biliary tree [2]. It can also be classified as either mucin-hypersecreting type or nonmucin-producing type. The two types appear similar macroscopically and microscopically. In addition, these tumours grow slowly and are less aggressive than classic adenocarcinomas [1].

Radiographic diagnosis of papillomatosis is difficult, and only a few cases have been reported in the English literature [2-5].

Recently, the development of multi-detector computed tomography (CT) has made it possible to visualise disease features in small structures. Percutaneous transhepatic cholangioscopy (PTCS) allows the direct visualisation of
tissues for biopsy and appears to be a promising technique for
detecting bile duct disease at an early stage.

The purpose of this study was to correlate the radiologic
findings of patients with pathologically confirmed biliary
papillomatosis or IPNB with the PTCS findings. We also
present the differential diagnosis and diagnostic problems
associated with these diseases.

METHODS

Patients

Between March 2000 and December 2012, 13 patients (10
male and 3 female, with an age range of 52-74 years and a
mean age of 62.8 years) with confirmed biliary papillomatosis
or IPNB were pathologically analyzed at Inje University
Busanpaik Hospital and Haeundaepaik Hospital were evaluated
retrospectively. The study protocol was approved by Inje
University's Institutional Review Board, and written informed
consent was waived.

Radiologic study

The diagnostic imaging modalities included in the
study were ultrasonography, multi-detector CT, endoscopic
retrograde cholangiopancreatography (ERCP), magnetic
resonance cholangiopancreatography (MRCP) and
percutaneous cholangiography (PTC).

Four-phase multi-detector CT was performed using a CT
scanner that acquired unenhanced and contrast-enhanced
CT images using nonionic contrast medium at a volume of
100 ml and a rate of 3 mL/sec along the antecubital vein.
Following the intravenous administration of contrast media,
arterial-phase, portal venous-phase and equilibrium-phase
scans were initiated using a fixed delay method, 30 sec, 70 sec,
and 180 sec, respectively. The portal venous phase CT images
were reconstructed into multiplanar reformatted coronal and
sagittal images. MRCP was obtained using either a 1.5-T MR
scanner (Signa Excite, GE Healthcare, Milwaukee, WI, USA)
using an 8-channel, phased-array torso coil (USA Instruments,
Aurora, OH, USA) and a single shot fast spin echo technique
or a 3-T MR unit (Achieva TX, Philips Medical Systems, Best,
The Netherlands) with a torso array coil and a half-Fourier
acquisition single shot turbo spin echo technique. Radiologic
findings were analysed by two experienced radiologists with
5 and 10 years of experience. Interpretations of the results of
abdominal ultrasonography, multi-detector CT, MRCP, PTC,
and ERCP were made by the consensus of the two radiologists.

PTCS technique

The radiologic findings of papillomatosis and IPNB were
retrospectively reviewed and correlated with PTCS obtained
in six patients. In eight patients, an operation resulting in
pathologic confirmation of the diagnosis was performed. In
five cases, only PTCS or percutaneous transhepatic biliary
drainage (PTBP) biopsy was performed. PTBD was performed
to enable cholangiography. PTBD was performed on the right
side in five patients and on the left side in one patient using a
pigtail catheter (7.5-French; Cook, Bloomington, IN, USA)
under ultrasonographic and fluoroscopic guidance. On the
second or third day after PTBD, the sinus tract was dilated
in one session using 16- or 18-French PTCS catheters or
dilators (Sumitomo, Tokyo, Japan, or Nipro, Tokyo, Japan).
Approximately one week after dilatation, the sinus tract was
mature and allowed the insertion of a cholangioscope into
the biliary tree without the need for sheaths. A fiberoptic
cholangioscope (CHF-P; Olympus Optical Co., Tokyo, Japan,
or FCN-15; Pentax; Asahi Optical Co., Tokyo, Japan) was
inserted through the mature sinus tract. To control pain and
anxiety, 50 mg of Demerol (meperidine hydrochloride) were
administered to most patients; 3 to 5 mg of midazolam were
also administered, depending on the general condition, age,
body habitus, and cardiopulmonary status of the patient.
During the cholangioscopic examination, the mucosal
appearance of bile duct tumours and strictures was studied.
Multiple targeted biopsies were performed with forceps under
direct cholangioscopic visualisation.

Pathologic analysis

For pathologic analysis, biliary papillomatosis and IPNB
were classified into five classes according to the degree of
cytologic and structural atypia. Features such as increased
nuclear-to-cyttoplasm ratio, loss of polarity, hyperchromatism,
pleomorphism, prominent nuclei, abnormal mitosis,
cribiform pattern and multilayering, and presence of invasion
were used to guide the classification [6].

Class 1 was defined as biliary papillomatosis with
low-grade dysplasia showing mild nuclear atypia, focal
multilayering, and no invasion. Class 2 was defined as biliary
papillomatosis with high-grade dysplasia showing moderate
nuclear atypia, a cribiform pattern, and multilayering. Class
3 was defined as biliary papillomatosis with carcinoma in
situ, which is characterised by severe nuclear atypia with
pleomorphism, atypical mitosis, and occasional necrosis
but no stromal invasion. Class 4 was defined as carcinoma
in situ with microscopic foci of stromal invasion. In Class 5,
definite invasion occurred into the hepatic parenchyma or a
fibromuscular layer of the bile duct wall. When a lesion showed
mixed types of biliary papillomatosis or when a patient received
multiple cholangioscopic biopsies at different sites, the most
advanced type was used for the final classification. Classes 1
and 2 were interpreted as benign adenoma, and the remaining
classes were interpreted as adenocarcinoma.

RESULTS

Of the 13 patients with pathologically confirmed biliary
papillomatosis or IPNB, all had the nonmucin-producing
type of the disease. The clinical symptoms of these patients
were abdominal discomfort, repeated episodes of right upper
quadrant pain (61.5%, 8/13), jaundice (38.5%, 5/13), and acute
cholangitis (61.5%, 8/13). Five patients had no symptoms
(38.5%, 5/13). These asymptomatic patients were diagnosed
by abdominal ultrasonography or CT performed during a
routine check-up.

On abdominal ultrasonography, biliary papillomatosis
or IPNB usually appeared as a nonshadowing echogenic
mass (60%, 3/5) with dilatation of the common bile duct and
intrahepatic bile ducts. When the disease was confined within
the bile duct, an intact echogenic bile duct wall was visible.
In one case (20%, 1/5), only localised bile duct dilatation was present. In another case (20%, 1/5), there was diffuse biliary dilatation.

On the multi-detector CT, localised bile duct dilatation with mild enhancing nodularities was the most common finding (61.5%, 8/13, Fig. 1A, B, Fig. 2A, B), followed by localised bile duct dilatation with mild wall thickening (15.4%, 2/13), localised bile duct dilatation without an enhancing portion (7.7%, 1/13), diffuse biliary dilatation with a bulging ampulla of Vater (7.7%, 1/13), and localised bile duct dilatation with liver abscess (7.7%, 1/13).

On MRCP, a localised dilatation of a bile duct containing intermediate signal intensity materials (60%, 3/5) was the most common finding. On PTC or ERCP, multiple round or ovoid-shaped filling defects and an irregular fuzzy bile duct wall (71.4%, 5/7, Fig.1C, Fig.2C) were most common. In the six patients who underwent PTCS examination, characteristic fish egg-like, occasionally coral reef-like intraluminal mucosal projections were noted (Fig.1D). Multifocal cauliflower or frond-like papillary masses were identified in four of the six patients (Fig. 2D) Three of these four patients were confirmed to have pathologic intraductal papillary carcinoma (Class 5), and one had intraepithelial carcinoma in papilloma without stromal invasion (Class 3). Of the two patients with fish egg- or coral reef-like intraluminal projectile mucosal lesions without a definite fungating mass, one was confirmed to have villous adenoma with biliary papillomatosis (Class 1) and the other had papillary adenoma and papilloma with high grade dysplasia (Class 2).

Eight patients underwent surgical interventions (partial hepatic resection) and had no lymph node metastasis or vascular invasion. The other five patients underwent only PTBD or PTCS biopsy.

Pathology reports indicated that nine patients had intraductal papillary adenocarcinoma with underlying biliary papillomatosis (7: Class 5, 1: Class 3, Fig.3), three patients had papillomatosis with high grade dysplasia (Class 2), and one patient had papillomatosis with villous adenoma (Class 1).

The mean duration of follow-up was 24 months (range 6–84 months). For patients who underwent surgery (n=8), the mean follow-up was 30 months (range 6–73 months). For patients who underwent only biopsy (n=5), the mean follow-up was 18 months (range 6–84 months). No patient experienced disease recurrence at the site of surgical resection.
DISCUSSION

Biliary papillomatosis or IPNB are intraluminal papillary tumours of the intrahepatic and/or extrahepatic ducts. Papillomatosis, or papillary carcinomatosis, refers to a disease in which multiple tumours occur along the bile duct. Biliary papillomatosis was first described by Caroli in 1973 and is a rare disease characterised by multiple papillary adenomas in the biliary tree [7].

Tumours cause bile duct dilatation and obstruction and manifest clinically as intermittent obstructive jaundice and repeated episodes of acute cholangitis. Acute cholangitis is not a common manifestation of typical cholangiocarcinoma but is common in biliary papillomatosis or IPNB. It may be due to tumour emboli that are friable and easily detach from their origin, thus leading to an acute obstruction of the bile duct that resembles bile duct stone obstruction [8]. The major concern is malignant transformation of the tumour into adenocarcinoma, which occurs in up to 83% of cases [8]. Biliary papillomatosis or IPNB are more common in men in the sixth to seventh decades of life, as shown in this and previous studies [8].

Papillary cholangiocarcinoma is rare, comprising approximately 3–5% of cholangiocarcinomas. It can occur in any portion of the intrahepatic bile duct and tends to have a polypoid growth pattern [1]. These papillary tumours are less aggressive than traditional cholangiocarcinomas. There is no consensus regarding the proper classification of the disease, and there are overlaps in the definitions of the pancreas counterpart of intraductal papillary mucin-producing tumours, intraductal mucin-producing cholangiocarcinoma, and the intraductal variant of cholangiocarcinoma.

Recently, Shibahara et al [9] and Zen et al [10] contributed to the understanding of papillary tumours in the bile duct that resemble intraductal papillary mucinous neoplasm of the pancreas (IPMN-P) and pancreatic intraepithelial neoplasia. These bile duct tumours show papillary proliferation in the bile duct with mucin secretion and are considered IPNB, the biliary counterpart of IPMN-P [11,12].

In pathologic analysis, biliary papillomatosis or IPNB is visualised as innumerable nodular or flat papillary frond-like infoldings. The columnar epithelial cells surrounding the slender fibrovascular stalks are supported by connective tissue from the laminar propria and spread along the mucosal surface to invade the duct wall or its outer surface. Various histologic patterns frequently coexist [13]. On abdominal ultrasonography, biliary papillomatosis or IPNB is usually visible as a nonshadowing echogenic mass or as material within a dilated common bile duct or intrahepatic bile ducts [2]. The echogenic bile duct wall is usually intact because the tumours are confined within the bile duct. However, the detection of mucin secretion may be difficult, and an obstructing mass is not usually detected with ultrasonography.
On CT scans, poorly-defined hypo- or iso-attenuating nodular lesions with variable degrees of intrahepatic and extrahepatic bile duct dilatation and focal segmental thickening of the bile duct walls are visible. However, a relatively smooth and clear outer margin of the thickened wall can be identified but is not always visible due to its small size. In one report, the detection rate of intraductal masses by ultrasonography and CT was only 41.2% and 50%, respectively [8]. When intraductal masses were not detected by ultrasonography or CT, they were diagnosed as biliary stones, clonorchiasis, and benign biliary strictures.

In a previous report on CT findings in 15 patients with malignant papillary neoplasms of the intrahepatic bile ducts by Yoon et al [14], solitary papillary tumours had a size range of 1.0 to 4.5 cm (mean 2.5 cm), and multiple papillomatosis had a size range of 0.5 to 2.0 cm (most were < 1.0 cm) on gross specimens. The most common CT finding was the presence of intraductal lesions, which occurred in 87% of cases (67% had a single nodule, and 20% had multiple nodules). The tumour margins were more often well-defined (53%) than poorly-defined (33%), hypoattenuation of the tumour was common (73%), and bile duct dilatation was mainly localised (80%).

Several cases of peripheral cholangiocarcinoma that spread along the luminal surface of the intrahepatic bile ducts have been reported. Ohta et al [15] reported four cases of cholangiocarcinoma that arose from the periphery of the stone-containing bile ducts and spread along the luminal surface of the bile duct epithelium. Microscopically, the tumour showed papillary proliferation. Kim et al [16] described a case of peripheral cholangiocarcinoma that arose from the small intrahepatic bile ducts and spread along the luminal surface of the peripheral bile duct tributaries. The bile ducts were plugged with gray-white, finely granular and friable tumour tissue, some of which was necrotic. The tumours were multicentric, confined within the duct lumen, and could be removed easily from the ducts.

In our study, diffuse biliary dilatation with amorphous filling defects was a characteristic finding on ERCP or PTC. Biliary obstruction was usually partial, and the papillary surface of the tumour had fine surface irregularities and velvety or serrated contours. On PTC, multifocal filling defects with a variable degree of intrahepatic bile duct stricture were present.

A few tumours with irregular, beaded stricture patterns of the intrahepatic bile duct were noted, which is similar to the observations obtained in a previous report [2]. However, the high mucin secretion and obstruction by mucin-hypersecreting type tumours prevent the thorough opacification of the entire biliary tract; therefore, ductal evaluation by ERCP or PTC can be suboptimal. In addition, ERCP occasionally fails to detect dilated bile ducts because the tumours and mucin inhibit the adequate inflow of the contrast material into the dilated bile ducts. Therefore, small papillomas may be obscured and left undetected by conventional radiologic modalities.

As recently reported by Jung et al [17], MRCP improved the visualisation of the biliary system in biliary papillomatosis (86%) better than ERCP (48.9%) because MRCP allows the visualisation of the biliary system without overlooking the ducts. Biliary papillomatosis was identified with MRCP as multiple round, oval, or papillary signal void lesions within the lumen or attached at the wall of the bile duct [16]. In our
Although the origin of cystadenoma and cystadenocarcinoma cells produce mucin, which fills the cystic space, but the in a cystic manner, forming single or multilocular cysts combined with bile duct stones and atrophic parenchyma. Dilatation of the intrahepatic and extrahepatic bile ducts cholangitis, mucinous cystadenoma, and cystadenocarcinoma.

Fluoroscopically guided biopsies [18]. These results are significantly better than those reported for a sensitivity of 96% for diagnosing cholangiocarcinoma. Sensitivity of 82.4% for the diagnosis of cholangiocarcinoma improve biopsy accuracy [18-20]. Cancers [18]. Several reports have suggested that PTCS can in intrahepatic calculi removal, the dilatation of intrahepatic further enhanced the application of this technique. PTCS has been utilised to manage a variety of biliary tract disorders [18]. The introduction of small-calibre flexible cholangioscopes in 1976 by Yamakawa et al further enhanced the application of this technique. PTCS has been used to manage diverse biliary tract disorders, including intrahepatic calculi removal, the dilatation of intrahepatic biliary strictures, and the evaluation of suspected bile duct cancers [18]. Several reports have suggested that PTCS can improve biopsy accuracy [18-20].

One large study reported that the PTCS biopsy has a sensitivity of 82.4% for the diagnosis of cholangiocarcinoma [19]. Nimura [20] reported that a PTCS-directed biopsy has a sensitivity of 96% for diagnosing cholangiocarcinoma. These results are significantly better than those reported for fluoroscopically guided biopsies [18].

The differential diagnosis of IPNB is recurrent pyogenic cholangitis, mucinous cystadenoma, and cystadenocarcinoma. Recurrent pyogenic cholangitis usually involves the irregular dilatation of the intrahepatic and extrahepatic bile ducts combined with bile duct stones and atrophic parenchyma. In cystadenoma or cystadenocarcinoma, the tumour grows in a cystic manner, forming single or multilocular cysts with internal septations and solid mural nodules. Tumour cells produce mucin, which fills the cystic space, but the cystic space does not communicate with the bile ducts [21]. Although the origin of cystadenoma and cystadenocarcinoma may be the same as that of intraductal mucosal spreading cholangiocarcinoma, they are considered to be a limited form of disease. In contrast, intraductal mucosal spreading cholangiocarcinoma spreads along the intraluminal surface of the bile ducts. Hilar cholangiocarcinoma is usually apparent on CT and cholangiography as an ill-defined infiltrating tumour at the porta hepatitis [22]. However, this tumour can appear on CT as a well-defined, nodular mass located at the porta hepatitis with characteristics similar to those of some malignant papillary neoplasms of the intrahepatic bile duct. Therefore, in some tumours located near the porta hepatitis, it may be difficult or impossible to differentiate papillary cholangiocarcinoma from a nodular growing type of ductal adenocarcinoma.

The management of IPNB is difficult because of the wide distribution and progressive nature of the lesions. Because the risk of malignancy is considerable, therapeutic options include partial hepatectomy and liver transplantation. The survival rate is improved after curative surgery. The average survival time of biliary papillomatosis patients is in the range of 28 [23] to 32 months [24]. Yeung et al [24] reviewed 78 cases of biliary papillomatosis and postulated a median survival of 28 months after radical resection, irrespective of histological signs of dysplasia. In contrast, the median survival time was only 11 months when no radical resection was performed.

When surgery was not an option, local ablation with photodynamic therapy or laser via an endoscopic procedure was reported for the palliative treatment of malignant neoplasms of the bile duct [25, 26]. Intraluminal brachytherapy with Iridium-192 has also been applied [27].

**CONCLUSIONS**

Radiologic techniques, especially multi-detector CT imaging are useful for detecting IPNB causing obstruction. However, IPNB is clinically challenging to diagnose because the resolution is limited for detecting its fine features. PTCS is an effective approach for diagnosing IPNB, which allows the direct visualisation and tissue confirmation of growing papillary tumours. When intraductal masses or nodules are observed with localised dilatation of the intrahepatic bile duct on multi-detector CT, malignant papillary tumours of the intrahepatic bile duct should be included in the differential diagnosis.

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