Intraductal papillary neoplasms of bile duct. A distinct entity like its counterpart in pancreas


1Department of Pathology, Zhongshan Hospital, Fudan University, Shanghai, 2Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai and 3Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, China

Summary. To recognize the new entity-intraductal papillary neoplasia of bile duct in liver, the authors reviewed the clinical records of sixteen patients, analyzed the microscopic features, and selected immunohistochemical reactivity (cytokeratins and mucins) that might correlate with classification.

Ten patients were male and six were female, with a mean age of 58 years (range, 21-73 years). According to their cell phenotypes, these papillary tumors were classified as intestinal type (6 cases), pancratobiliary type (4 cases), gastric type (5 cases) and oncocytic type (1 case). Most were located in the left hepatic duct and accompanied with bile duct dilatation (10 cases). Eight showed minimal expansile invasion into the ductal wall and eight were noninvasive. Five patients were treated with a hepatectomy, three underwent segmental resections, and one underwent a left hepatic lobectomy. One patient died of unrelated causes 6 years after operation, and another died of postoperative complications. The remaining 7 patients are alive and disease free 1-5 years after surgery. Because of its distinct clinical, pathological features and a favorable prognosis can be expected after complete surgical resection, we suggested that intraductal papillary neoplasia should be distinguished from other types of peripheral cholangiocarcinoma, as a distinct entity, like its counterparts in the pancreas. Neoexpressed and overexpressed mucins are of clinical value as a marker for supportive diagnosis, prognosis or monitoring therapy.

Key words: Papillary neoplasms, Bile duct, Liver, Mucin

Introduction

The current WHO classification recognizes both benign (biliary papillomatosis, BP) and malignant (papillary cholangiocarcinoma) types of biliary papillary neoplasms. They are uncommon lesions, but their existence has been known for a long time. BP, recognized as papillomatosis in 1976 (Neumann et al., 1976), was a disease characterized by multiple papillary tumors of variable distribution and extent in the intrahepatic and/or extrahepatic biliary tree (Lee et al., 2004). Although BP is basically a collection of benign papillary adenomas, papillary adenocarcinoma can develop within these lesions and has a tendency to spread superficially along the bile duct mucosa (Terada and Nakanuma, 1990). Part of these tumors secret an excessive amount of mucin, which may disturb bile flow and cause severe ductal dilatation. Recent studies revealed striking similarities to intraductal papillary mucinous tumor of the pancreas in its histopathologic features, production of a large amount of mucin, pathophysiologic characteristics, and resultant clinical manifestations. But the concept and nomenclature of intraductal papillary tumor of the bile ducts have continued to evolve.

Within the last decade this entity has been increasingly reported in the liver literature. One recent study (Zéni et al., 2006) has shown that bIPNs may be distinguished into different types showing a different biology according to their mucin pattern. To our knowledge, few reports to date have compared the clinical characteristics, prognosis and mucin pattern of this IPN. In this article, the histopathologic features of intraductal papillary tumor of the intrahepatic bile ducts are described.

Materials and methods

Case selection

The surgical pathology files of Zhongshan Hospital
were screened for intra-hepatic cholangiocarcinoma. They were collected during the period from 2000 to 2005 at the tertiary referral center. A histological review of 5000 liver tumors, revealed 16 (0.32%) possible bIPNs, most originally diagnosed as a papillary cholangiocarcinoma or papilloma of bile duct.

A neoplasm was considered an intrahepatic bIPN only when it met the following criteria: 1) retention of fluid in cystic lesions and/or markedly dilated ducts radiographically; 2) confirmation of the fluid as mucin by percutaneous transhepatic biliary drainage and/or endoscopic retrograde cholangiography and/or in the surgically removed specimens; 3) arising from macroscopically identifiable intrahepatic; and 4) cyst formation and/or dilatation of bile duct, like pancreas.

The noninvasive components of the neoplasm were classified as adenoma, borderline tumor, and carcinoma in situ (CIS) using the WHO classification and, where present, the invasive carcinomas were classified as tubular or colloid (mucinous noncystic) type. When a lesion showed mixed types of IPN or a patient received multiple cholangioscopic biopsies at different sites, the most advanced type was used for final classification.

Clinical and pathological data collection

Clinical data collected included age, gender, tumor size, and presence of lymph node metastases at presentation.

The pathology of the resected liver tumors was studied and the gross configuration, microscopic growth patterns, and cytologic features were recorded. The presence and extent of an invasive carcinoma was noted. Deparaffinized sections were stained with hematoxylin and eosin and periodic acid-Schiff-Alcian blue (PAS-AB, pH 2.5) double staining. Immunohistochemical analysis was carried out on serial sections cut from the neoplasms employed with DAKO EnVision+ system (Tokyo, Japan). A panel of the primary antibodies was listed in Table 1. The tumor free adjacent liver parenchyma and tissue from common bile duct served as controls.

Immunohistochemical evaluation

Membranous staining for MUC1, cytoplasmic

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Producer</th>
<th>Dilution</th>
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<tr>
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<td>DAKO</td>
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<tr>
<td>Carcinoma Antigen 19-9</td>
<td>Novacastra</td>
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<tr>
<td>Carcinomembryonic Antigen</td>
<td>A0115</td>
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<tr>
<td>MUC1</td>
<td>Ma895</td>
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<td>1:100</td>
</tr>
<tr>
<td>MUC2</td>
<td>Ccp58</td>
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<td>CLH2</td>
<td>Novacastra</td>
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<tr>
<td>MUC6</td>
<td>CLH5</td>
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</tbody>
</table>

IPA, intraductal papillary adenoma; IPB, intraductal papillary borderline neoplasm; IPCiS intraductal papillary carcinoma in situ; IPCa, intraductal papillary carcinoma.

Table 2. Subtype of intraductal papillary neoplasm of intrahepatic bile duct.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Number</th>
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<th>IPB</th>
<th>IPCiS</th>
<th>IPCa</th>
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<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pancreatobiliary</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Oncocytic</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>16</td>
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<td>5</td>
<td>8</td>
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</tbody>
</table>

IPA, 8 (50%); IPCa, 8 (50%).
duct (Fig. 1C). In the cases in which mucin was not found, fine papillary or granular tumor tissue was casted in the dilated peripheral IHD without dilatation of the extrahepatic bile ducts (Fig. 1D).

Microscopic findings

The bIPN tumors were largely exophytic in the cyst lumina and showed variable degrees of architectural complexity, ranging from sparse villiform papillae to a more exuberant growth giving rise to solid areas with slit-like spaces (Fig. 2) Fibrovascular cores were mostly well formed and composed of loosely textured stroma lymphoplasmacytic infiltrated. A distinctive feature was the presence of intraepithelial mucin-containing lumina that gave rise to a cribriform pattern (Fig. 3). The epithelium ranged from a simple cuboidal to columnar epithelium to areas of stratified epithelium with loss of polarization. Cellular clusters were budding from the papillae lined by multilayered epithelium. Mitoses were present and the mitotic count ranged from 1 to 3 per 10 high power fields in most areas.

Classification of papillary patterns

BIPNs were classified into four groups based on the typing of pIPMN in the literature (Table 2).

Intestinal type bIPN (n=6)

These were composed of long finger-like projections (without complex branching) and lined by columnar cells with cigar-shaped nuclei were classified as intestinal type (Fig. 2A). These were morphologically indistinguishable from colonic villous adenomas. The cells contained variable amounts of mucin in the apical

Fig. 1. Cut surface of the surgically resected specimens. A. The bile duct lumen was partly obstructed by mucin; the intra-hepatic duct was lined by a massive papillary proliferation of epithelial cells extending from the bile duct bifurcation. B. Gross appearance of a 13 cm cystic tumor filled with mucin and soft brown mural nodules. Direct communication with the bile ducts is easy to appreciate on gross appearance. C. The cystically dilated bile ducts lined by exuberant papillary projections. D. A grayish fungating mass of 8.5 cm in size with a few mucin in the dilated left bile duct.
cytoplasm. Nuclei were pseudostratified with varying degrees of atypia.

The tumor was mainly made up of tall columnar cells with occasional mucus secretions and mitoses. Nuclei showed moderate to severe atypia, with coarse chromatin. The ducts were dilated and filled with papillary tumor, mucus and bloody debris. In 7 cases, mucinous carcinoma was visible.

Pancreatobiliary type bIPN (n=4)

BIPNs composed of complex arborizing papillae lined by cuboidal cells, often with round nuclei containing a single prominent eccentric nucleolus, were classified as pancreatobiliary type (Fig. 3A). This classification is based on similarities to a subgroup of papillary neoplasms of the biliary tree.

The cyst or duct was packed with fine papillary tumor, which was composed of aborizing complex branch and abundant micropapillae, lined by pseudostratified, biliary type cells with frequent cytoplasmic mucinous vacuoles and prominent nucleoli. In some areas, the tumor had a solid architecture with cribriform structures, nuclear crowding, and significant cytologic atypia. These atypical zones merged into a pattern of frankly well-differentiated tubular adenocarcinoma, with invasion of the surrounding liver parenchyma.

Gastric type bIPN (n=5)

BIPNs lined by tall columnar cells with abundant pale supranuclear mucin, some with acidophilia, creating a pattern reminiscent of gastric foveolar cells were classified as gastric type (Fig. 4A).

The nuclei were small and centrally located.
Nucleoli were absent in most areas, but focally they were prominent. Pleomorphism was minimal and focal. Mitotic activity was very low (<1/10HPF). Some cells showed mucin production as seen by the intracytoplasmic globules stained for mucicarmine.

**Oncocytic type bIPN (n=1)**

BIPNs similar to pancreatic intraductal oncocytic papillary neoplasms, consisted of cuboidal cells with abundant oxyphilic, granular cytoplasm with intraepithelial lumina, which gave rise to a cribriform pattern of growth. (Fig. 5A).

There was marked papillary proliferation of the lining epithelial cells, showing eosinophilic cytoplasm with edematous and myxoid fibrovascular cores. The cytoplasm of these papillary carcinomas contained fine droplets positive for PAS-AB (pH 2.5). There was no extension of the tumor into the submucosa. This finding is very similar to that of intraductal oncocytic papillary neoplasm of the pancreas. So they were classified as oncocytic subset.

**Histological grading**

In the current study, bIPN was classified into three classes according to the degree of cytologic and structural atypia, including increased nuclear-to-cytoplasmic ratio, loss of polarity, pleomorphism, hyperchromatism, prominent nucleoli, abnormal mitosis, cribriform pattern and multilayering, and presence of invasion. Based on the maximum degree of cytarchitectural atypia in the intraductal component, each bIPN was classified as adenoma, carcinoma or borderline. Two were defined as intraductal papillary adenoma (IPA) showing mild nuclear atypia, focal

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**Fig 3. Pancreatobiliary type.** A. Multiple papillary and villous proliferations of epithelial lining cells. Cytologically, the nuclei are mildly hyperchromatic. The fibrovascular core is thin. HE, x 40. B. MUC1, x 100. C. MUC2, x 40. D. MUC5AC, x 100
multilayering, and no invasion. One was defined as intraductal papillary borderline tumor (IPB) showing moderate nuclear atypia, cribriform pattern, and multilayering. Five were defined as intraductal papillary carcinoma in situ (IPCis), which is characterized by severe nuclear atypia with pleomorphism, atypical mitosis, and occasional necrosis but no stromal invasion. Eight were defined as intraductal papillary carcinoma, with microscopic foci of stromal invasion and invasion into the hepatic parenchyma or a fibromuscular layer of the bile duct wall.

In *intestinal* type, half of the cases had non-invasive lesion (1 IPA, 2 IPCis), the others were intraductal papillary carcinoma (IPCa) (3 cases). All of pancreatobiliary had carcinoma, (one in situs, 3 invasive). In the gastric types, 2 had invasive carcinoma, the other three were adenoma, borderline and IPCis, respectively. The only oncocytic lesion was carcinoma in situ. Invasive carcinoma was of the mucinous type (colloid) in three patients and of the tubular type (conventional ductal adenocarcinoma) in five patients. The tubular carcinoma were observed in pancreatobiliary type invasive carcinoma (3/4) and in gastric type ones (2/5). Colloid carcinoma was only in intestinal subtype (3/6). Superficial spread of tumors was seen in 2 intestinal types but in none of pancreatobiliary type. Lymph node metastasis was detected in one case of pancreatobiliary type.

In all bIPN cases, communication with the duct system was histologically confirmed. Elements of tumor extended beyond the gross tumor capsule into dilated peripheral bile ducts. A transition between the tumoral epithelium and the nonneoplastic epithelium of the bile ducts was identified. In one case, there was minimal focus of invasive carcinoma extending into the cyst wall without invasion of liver parenchyma. The resection

![Fig 4. Gastric type. A. Numerous papillary structures that project into the lumen. The fibrotic wall of the common bile duct is intact. HE, x 100. B. MUC5AC, x 40. C. MUC1, x 100. D. MUC6, x 200](image_url)
margins were free of tumor in all cases.

**Immunohistochemical findings**

**Mucins (Table 3)**

In bIPN, MUC1 had luminal surface staining and/or intracytoplasmic diffuse staining. The apical side of pancreaticobiliary type tumor cells was strongly positive for MUC1, while no intestinal bIPN were positive for MUC1.

Supranuclear MUC2 localization with granular staining or perinuclear staining was observed in intestinal subtype bIPN. MUC5AC had intracytoplasmic granular staining with supra- and perinuclear localization in gastric and pancreaticobiliary subtype. The MUC6

| Table 3. Immunohistochemical data of intraductal papillary neoplasm of intrahepatic bile duct. |
|------------------|---|---|---|---|---|---|---|---|---|
| Subtype         | N | MUC1 | MUC2 | MUC5AC | MUC6 | CEA | CA19-9 | CK7 | CK20 |
| Intestinal      | 6 | 0   | 6    | 1      | 0    | 0   | 2     | 3   | 2    |
| Pancreatobiliary| 4 | 4   | 0    | 4      | 4    | 1   | 2     | 4   | 0    |
| Gastric         | 5 | 1   | 0    | 4      | 1    | 1   | 2     | 4   | 0    |
| Oncocytic       | 1 | 1   | 0    | 1      | 1    | 0   | 1     | 1   | 0    |
| bIPN            | 16| 6   | 6    | 10     | 6    | 2   | 7     | 12  | 2    |

**Fig. 5. Oncocytic type.**

A. The most predominant cells of the lining epithelium were columnar cells with oncocytic features showing abundant eosinophilic granular cytoplasm and centrally located nuclei with prominent nucleoli. HE, x 40.

B. PAS, x 100.

C. MUC5AC, x 40.

D. MUC6, x 200.
expression pattern was granular in the entire cytoplasm of the oncocytic subtype (Fig. 3b) or relatively diffuse in the cytoplasm of the pancreatobiliary subtype.

The intestinal type consistently expressed MUC2 but not MUC1. When this bIPN subtype becomes invasive, the invasive tumor component shows a colloid pattern with consistent positivity for MUC2, MUC5AC and negativity for MUC1. The pancreatobiliary type of bIPN was positive for MUC1 but negative for MUC2. The gastric type of bIPN usually expressed MUC5AC but were negative for MUC1 and MUC2. The oncocytic type of bIPN consistently expressed MUC5AC and expressed MUC1 focally but was negative for MUC2.

Also, the normal duct tissues were faintly and focally positive for MUC5AC, not only in the ductules of liver but also on the apical side of the periductal glands of large bile ducts. However, MUC2 was completely negative in them.

There was also correlation between MUC1 and MUC5AC expression in pancreatobiliary type and gastric type bIPN. As shown in figures 2-5, MUC1 expression was much higher in pancreatobiliary type than in intestinal type bIPN. In contrast, MUC2 expression was lower in pancreatobiliary type than in intestinal type bIPN.

Follow-up

All bIPN patients were followed up. The duration of follow-up ranged from 17 months to 78 months (median 35±20). Out of the 16 patients, 14 remain alive and 12 of these are free of disease at the time of writing. One died of heart disease. The cumulative 2-year survival rate was 87.5%. Two have lived for more than 5 years after surgery without recurrence. Recurrence developed in two patients who had undergone subsegmentectomy, despite initial negative resection margin. An intrahepatic recurrence adjacent to the main lesion developed in one patient 46 months after lobectomy. The patient expired 37 months after resection. One patient who had a positive resection margin is still alive at 27 months, with multiple intrahepatic metastases of remnant liver after left lobectomy.

Of the 8 patients with invasive carcinoma, 2 of 3 patients with colloid type tumors were free of tumor at a median of 39 months. Of the 5 patients with tubular type invasive carcinoma, one patient died of other causes, and three patients were alive (two were free of disease, and one experienced disease recurrence and was treated by liver transplantation) at an average follow-up of 2.5 years.

Discussion

Peripheral cholangiocarcinoma (PCC) is the second most common malignant tumor of the liver. Various terminologies and classifications have been used to describe the pathologic and radiologic appearance of cholangiocarcinoma, and each describes a specific aspect of the tumor. The Liver Cancer Study Group of Japan has proposed a new classification based on growth characteristics, with tumors being identified as mass-forming, periductal-infiltrating, and intraductal-growing types (Yamamoto et al., 1998). This classification is considered to be the most reasonable because it describes the gross appearance, growing characteristics, biologic behavior, and prognostic implication for patients, and because it is helpful for radiologic interpretation. The prognosis for mass-forming and periductal-infiltrating cholangiocarcinomas is generally unfavorable, whereas the prognosis for intraductal-growing cholangiocarcinoma is much better (or excellent) after surgical resection (Isaji et al., 1999). Chen et al. proposed the term “intraductal papillary neoplasia of the liver” for such lesions, implying that IPN may be the hepatobiliary equivalent of pIPMN (Chen et al., 2001).

Recent studies on pIPMNs have shown that they are heterogeneous. On the basis of their histology and mucin type and expression, Ban et al. (2006) proposed two histopathologic categories, as columnar type and cuboidal type. Adsay preferred the terms villous-intestinal, pancreatobiliary and null types, respectively in pancreas. IPMNs contain three pathologically and biologically distinct epithelial subtypes: intestinal (35%), pancreatobiliary (22%), and null (31%). The null type referred to the papillae lined by tall columnar cells that have basally located nuclei and abundant apical mucin with various degrees of chromophilia, resembling gastric foveolar epithelium. Furthermore, Furukawa et al. (2005) recognised 4 subtypes of IPMN, including intestinal, pancreatobiliary, gastric and oncocytic type. Kloppel and Kosmahl (2006) suggested that bIPN paralleled to its counterpart, including 4 subtypes. According to their criteria, in the present study, 6 cases were classified as intestinal type, 4 cases as pancreatobiliary type, 5 cases as gastric type and 1 case as oncocytic type.

The alterations in quality and quantity of mucins have been demonstrated in pIPMNs. Adsay et al. (2004) reported that all the pancreatobiliary type pIPMNs were carcinoma and 7 in 12 pIPMNs, which expressed MUC1, were pancreatobiliary type. Also, in our study, all 4 pancreatobiliary type were carcinoma and showed expression of MUC1 in all of the cases. When invasive, this subtype presents as a tubular adenocarcinoma with positivity for MUC1 and negativity for MUC2. MUC2 was only expressed in intestinal type. MUC5AC showed very high expression in both pancreatobiliary type and gastric type but no difference between non-invasive and invasive lesion. In contrast, MUC6 showed higher expression rates in non-invasive lesions than in invasive carcinomas. Interestingly, this MUC6 expression pattern is contrary to the MUC1 expression pattern described above. MUC6 seems to be related with the tumor formation process of pancreatobiliary type (Nakanuma et al., 2002). The conspicuous difference in the expression pattern of MUC2 in intestinal type and MUC6 in
pancreatobiliary type is an interesting future area of study. In the current study, MUC1 was expressed in none of the gastric type adenomas but in half of the intestinal type IPCa and pancreatobiliary type IPCa. Thus, MUC1 is a useful marker for a differential diagnosis between adenoma and carcinoma.

In the present study, pancreatobiliary type showed the superficial spread along the bile duct in 3 of the 4 cases examined, whereas gastric type showed no superficial spread in 5 cases examined. These pathologic differences between gastric type and pancreatobiliary type may cause the difference in outcome of the patients. In the 8 carcinoma cases, invasive growth beyond the basal layer was significantly frequent in pancreatobiliary type bIPN (3 of 4) but low in gastric type (2 of 5). In addition, between the oncocytic type and pancreatobiliary type, there was significant resemblance in the clinicopathologic factors besides mucin profiles. So we proposed oncocytic subtype may be a unique style of pancreatobiliary type.

bIPN comprise a histologic spectrum that ranges from adenoma to invasive carcinoma with different degrees of aggressiveness (Kim et al., 2004). Not infrequently, varying degrees of cytoarchitectural atypia are seen in the same tumor, and current thinking is that all IPNs with invasive carcinoma progressed from an adenoma that underwent transformation, perhaps reflecting stepwise molecular genetic changes. In our study, a significant age difference of 7.5 years was found between patients with invasive carcinoma and those with benign or in situ or borderline tumors, and there was a stepwise age increase between patients with adenomas, borderline and in situ tumors, and those with invasive carcinoma (47, 55, and 60.8 years, respectively). This is the first time a significant difference in age has been described, and although not useful for diagnosis or exclusion of malignancy, given the large overlap between groups, it does give insight into the time required for progression into malignant transformation. Interestingly, a similar age differential has been described in pIPMN, which share many phenotypical and genetic alterations with bIPNs.

None of the 8 patients with adenomas, borderline tumors, or carcinoma in situ died as a consequence of the disease (although one of them died of other causes during follow-up), and the survival of the 8 patients with invasive cancer was a remarkable 87.5% at 2 years. The overall survival of the bIPN patient population is very favorable, with several large reported series having a 5-year survival rate in excess of 80% (Suh et al., 2000). As in our experience, Lee et al. (2004) report that after curative resection the 5-year survival rate is 81%, while in patients undergoing palliative drainage the mean survival is 37 months, significantly longer than that of cholangiocarcinoma (Tajima et al., 2004). Presumably, the favorable prognosis reflects the absence of a significant invasive component. While the infiltration into surrounding liver and extrahepatic metastases are rare, this tumor is potentially malignant, and the potential for growth and spread along and within the biliary tree is great. The noninvasive histology also results in large lesions that often require large hepatic resections. Resection is the treatment of choice when bIPN is localized according to preoperative imaging workup and with the support of intraoperative ultrasound or cholangioscopy (Cox et al., 2005). If the patient cannot withstand or is not willing to undergo major surgery, local ablation, stenting or drainage palliative procedures are considered (Yeung et al., 2003). In the case of bIPN liver transplantation is the treatment of choice (Beavers et al., 2001; Dumortier et al., 2001). The multicentricity and diffuse pattern of bIPN explains the high recurrence rate after surgical resection of the underlying lesion. Thus, bilobar or recurrent disease, as well as the high risk of malignant transformation should favor total hepatectomy and liver transplantation to be considered as the ultimate curative approach.

bIPN bears a striking similarity to intraductal papillary mucinous tumor of the pancreas in its histopathologic features, production of a large amount of mucin, pathophysiologic characteristics, and resultant clinical manifestations. Because of the shared origins of the biliary tract and pancreas, the two systems may have a homologous pathologic condition. However, overproduction of extracellular intraductal mucin may not be as common in bIPN as in pIPMNs. It therefore seems appropriate to call the biliary papillary tumors “intraductal papillary neoplasm” in analogy to their pancreatic counterpart.

The reclassification of biliary carcinoma may have value in determining prognosis and treatment methods. bIPN should be distinguished from other types of PCC because a favorable prognosis can be expected after complete surgical resection. The excellent prognosis of these bIPNs is in sharp contrast with the poor 5-year survival rate of the most common conventional adenocarcinomas of the PCC, and therefore warrant histologic separation.

Conclusion

Because of its different clinical, pathological features and the fact that a favorable prognosis can be expected after complete surgical resection, we suggested that bIPN should be distinguished from other type of PCC, as a distinct entity, like its counterparts in the pancreas.

References


Intraductal papillary neoplasms of bile duct


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