ABSTRACT

The intraductal papillary neoplasm of the bile duct (IPNB) is a rare, little-known entity, regarded as the biliary equivalent of intraductal papillary mucinous neoplasm of the pancreas (IPMN-P). It is considered a premalignant lesion, which progresses in a multistep fashion towards invasive cholangiocarcinoma. IPNB can occur in any segment of the bile duct, presenting multiple foci and a variety of symptoms including abdominal pain, dyspepsia, jaundice, repetition cholangitis and weight loss. Between 5% and 29% of patients are asymptomatic. The most common radiological findings are dilatation of the bile duct and the presence of intraductal masses. Free margin resection is the treatment of choice for IPNB regardless of size, location, and initial benign status, since recurrent episodes of cholangitis and obstructive jaundice caused by mucin production may cause serious clinical problems. In patients who are not candidates for surgery, treatment is mainly limited to the creation of a biliary bypass to relieve jaundice and/or cholangitis.

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Key Words: Bile duct; Biliary intraductal tumor; Mucinous; Neoplasm

INTRODUCTION

Intraductal papillary neoplasm of the bile duct (IPNB) is a rare and little known entity, considered the biliary equivalent of intraductal papillary mucinous neoplasm of the pancreas (IPMN-P) [1]. Since 1960 there have been increasing reports of a variety of mucin-secreting papillary and cystic lesions of the intra and extrahepatic bile tract [2]. In 2001, the concept of IPNB was proposed by Chen and Nakanuma, who noted that intraductal papillary neoplasms of the liver, with goblet cells and colon-like metaplasia were associated with an overproduction of mucin and mucobilia [3]. Finally, in 2010, IPNB was included in the classification of the World Health Organization as a distinct clinical pathological entity [4].

In this study we conducted a PubMed search of articles in English and Spanish between 1966 and 2015 with the words "intraductal papillary tumor of the bile duct", "biliary intraductal papillary neoplasm", "biliary papillomatosis" and obtained 75 items. After selecting the papers that focused primarily on IPNB, we reviewed a total of 37. Table 1 compares the most important series of IPNB, although they are very heterogeneous.

DEFINITION OF IPNB

TIPNB is an epithelial exophytic biliary tumor, which appears as a papillary mass in the lumen of the bile duct and presents a prominent intraductal growth pattern [5]. It may induce mucin hypersecretion, which causes cystic dilatation of the bile ducts affected [6]. Lesions that progress to invasive cholangiocarcinoma in a multistep fashion, similar to IPMN-P, are considered premalignant.

IPNB may occur in any segment of the bile duct and presents multiple foci [7]. In some series, IPNBs are most frequently located in the intrahepatic ducts [8], while in others the most frequent location is the...
hepatic hilum\cite{7}. A case of IPNB in the duodenal papilla originating from the bile duct has been described\cite{8}. Most series agree that intrahepatic IPNBs appear more frequently in the left hepatic lobe\cite{3-5,8}.

**ETIOLOGY AND RISK FACTORS**

DIPNBs derive from the normal bile duct epithelium. Due to alterations in gene expression, progressing to dysplasia (initially low-grade, then intermediate, then high-grade) and finally to invasive carcinoma\cite{4}. It has been postulated that chronic inflammation may cause papillary growth of epithelial cells in the bile ducts\cite{9}. One cause of chronic inflammation of the bile ducts is bile stasis, which may occur for several reasons: agenesis of the gallbladder, hepatolithiasis and clonorchiasis (an infectious disease caused by the liver fluke Clonorchis sinensis)\cite{10,9,11}. These risk factors are more prevalent in Eastern countries, where the incidence of IPNB is higher.

**PATHOLOGY**

The term “intraductal papillary neoplasm” was coined in 1994 to refer to a number of entities described in the literature as neoplastic, cystic and mucus-producing lesions\cite{11}. The concept includes malignant and benign forms and the accepted definition of IPN includes mass-forming pre-invasive tumors growing inside the pancreatic ducts\cite{11,12}.

Several publications, mainly from Asia, have suggested the existence of a similar entity to IPNM-P but originating in the bile ducts\cite{13,14}. The common embryonic origin of the pancreas and the bile ducts in the ventral endoderm raised the suspicion that neoplasms in these sites might share common characteristics.

Since 2010, the World Health Organization has recognized IPNB as an independent entity inside digestive tumors. These neoplasms are typically located in distal bile ducts and in most cases have an invasive component. Lymph nodes involvement at the time of diagnosis is also frequent. Surgical treatment usually includes hepatectomy or bile duct resection, according to the extent of the neoplasm. Perioperative mortality is low, ranging from 0% to 6%, and the 5-year survival rate after surgery is around 80% to 90%.
treatment is unusual[7].

These tumors produce large amounts of mucin, especially if there is a carcinoma component, causing blockage of the bile ducts[39].

To define the type of tumor that makes up IPNB, the classification used in intraductal pancreatic tumors is applied[12,16,17]: (1) Pancreatobiliary type, comprising columnar cells with eosinophilic cytoplasm and round nuclei. Oncocytes are included in this group; (2) Intestinal type, characterized by elongated columnar cells resembling intestinal adenomas or adenocarcinoma; (3) Gastric type, comprising columnar cells with high mucin content in their cytoplasm.

Pancreatobiliary and intestinal IPNB are the most frequent variants, which in more than 50% of cases express the membrane mucoprotein MUC1 but not MUC2. These characteristics reflect greater aggressiveness, with malignancy in up to 80% of cases and progression to tubular or mucinous carcinoma[40].

Because of the adenoma-carciinoma sequence, IPNB can be classified according the degree of cytarchitectural atypia (dysplasia) in low, moderate, high dysplasia and finally in invasive carcinoma[4,12].

CLINICAL FEATURES

IPNB occurs most frequently between the ages of 50 and 70[4,14]. Some authors have observed a higher prevalence in males 4 but others report no difference between the sexes[41].

Like cholangiocarcinoma[22], due to their many possible locations IPNBs present a variety of symptoms. The most frequent are abdominal pain[20], dyspepsia[22], jaundice[20,23], cholangitis and weight loss[20]. Between 5% and 29% of patients are asymptomatic[21].

DIAGNOSIS

Laboratory tests

Plncreased liver enzymes may be observed, showing a pattern of cholestasis with elevated bilirubin and alkaline phosphatase[2,3]. However, in some cases tests are normal[21].

Abdominal ultrasound (US)

Abdominal ultrasound is usually the first test performed when a diagnosis of biliary obstruction or liver pathology is suspected[23]. Possible ultrasound findings include polypoid intraluminal masses, which are only visible if they are large or if there are alterations of the bile duct wall, such as thickening, irregularities or nodules[24]. Ultrasound evaluation of mucin is difficult since it is usually anechoic, like bile[24]. When the mucin occludes the papilla (even only incompletely and intermittently) a major dilatation of the entire biliary tree can be seen. If the tumor is located in a hepatic lobar bile duct, biliary dilatation is only segmental[24].

Computed tomography scan (CT)

The most common radiographic finding is bile duct dilatation, which may be diffuse, localized, or cystic[41]. Other possible findings are intraductal masses, bile duct infiltration, intense rim enhancement at the base of the mass (either isodense or hyperintense in relation to the normal liver parenchyma during the late arterial phase and not hyperintense during the portal phase)[24]. For this reason, Owaga et al[41] reported a tendency to overestimate the invasion of vessels and adjacent organs in their series. The attenuation of mucin in CT is the same as that of water, so its presence cannot be adequately evaluated[24].

MRI

As in US and CT, the most frequent finding is biliary dilatation. As we have just noted, the intensity of mucin is the same as the water and is not detectable by MRI[30,31]. Like CT, MRI may reveal an intraductal mass, which appears iso- or hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging[20].

The addition of diffusion-weighted imaging to gadoxetic acid-enhanced MRI may be beneficial in the depiction of intraductal tumors and may also be helpful in determining tumor invasiveness, though not tumor extent[20].

Cholangiography / MRCP

Yeh et al[25] proposed a series of patterns of cholangiographic findings for classifying IPN-B in order to facilitate management and processing: type I A, hepatolithiasis with biliary stricture; type I B, fusiform biliary tree with amorphous floating filling defects in absence of discernible neoplasia; type I C, disproportional biliary dilatation in absence of neoplasia; type II A, intrahepatic polypoid or cystic neoplasia; type II B, intrahepatic polypoid or cystic neoplasia extending to the extrahepatic bile duct; type III A, type I or II with operable concomitant malignancy; type III B, type I or II with inoperable concomitant malignancy.

Endoscopic retrograde cholangiopancreatography (ERCP)

The most characteristic finding for the diagnosis of IPN-B is mucobilia[20], which is difficult to characterize in MRCP 23. ERCP reveals a dilated papillary orifice with mucin after the performance of sphincterotomy[27]. Its disadvantage is that the viscous mucin filling the dilated biliary tree makes it difficult to diagnose and locate tumors[27]. After evacuating the mucin by means of endoscopy, relatively large nodules may be seen in the wall of the bile duct[22].

Cholangioscopy

Determination of the tumor is difficult because of the abundant mucin secreted by the tumor or because of the superficial mucosal spread of the tumor along the bile duct[25]. In this situation, cholangioscopy is useful because it allows direct vision. Percutaneous transhepatic cholangioscopy (PTCS) can be performed through a transhepatic biliary drainage (PTBD) or via a retrograde approach with peroral cholangioscopy (POCS)[29], allowing biopsies to be performed in order to confirm bile duct histology and to assess the extent of the tumor[41].

PTCS presents certain complications such as the risk of tumor seeding in the sinus tract of the puncture[29], catheter dislodgement or hemobilia[41]. The main advantage is its feasibility even in patients with difficult anatomy, in lesions above the bifurcation or upstream from strictures[29], and in cases with abundant mucin production[27].

Sakai et al[30] demonstrated the clinical utility of PTCS for decision-making regarding treatment for IPNB, finding that its assessment agreed with the results of tumor staging in the cases analyzed.

Intraductal sonography (IDUS)

IDUS has been described as a simple method for patient staging and for assessing the extent of bile duct tumors[24]. Its fine probe can pass through the hilum into the intraduodenal peripheral bile duct, and clear images can be obtained of the depth of tumor invasion even in the presence of viscous mucin[27]. The problem with this technique is the difficulty of assessing the superficial extent of the tumor in cases of cholangitis or previous catheter placement in which the duct wall is thickened[21], or in cases with coexisting biliary sludge, which may simulate an elevated tumor[27].
DIFFERENTIAL DIAGNOSIS

The differential diagnosis of IPNB includes recurrent pyogenic cholangitis, cholangiocarcinoma associated with choledochal cyst, and biliary mucinous cystic neoplasm (MCN-B) [33].

IPNB can easily be confused with recurrent pyogenic cholangitis, since the two entities can cause intermittent obstruction of the papilla and the mucin plugs can be mistaken for stones [31]. For differential diagnosis, invasive methods are required, such as ERCP or cholangioscopy to demonstrate the presence of mucin [27].

IPNBs are distinguished from other cholangiocarcinomas by their appearance on CT and/or MRI as diffuse or segmental biliary dilatations with or without a visible mass, or stenosis, and may be single or multiple. Other cholangiocarcinomas appear as nodular masses or segmental stenosis of the bile duct with proximal dilatation [20].

The difference between IPNBs and MCN-Bs lies in the fact that the latter have an ovarian-like stroma, lack any communication with the bile ducts, and are usually found exclusively inside the cyst [3, 23].

TREATMENT

All patients with IPNB require treatment even if the tumors are considered benign, due to the recurrent episodes of cholangitis and obstructive jaundice caused by mucin production [6]. Possible treatment options include:

Surgery

Surgical treatment of IPNB is based on free margin resection of the tumor. In many cases, differentiating an IPNB from a non-papillary cholangiocarcinoma is difficult. Because of the similarities between the two entities, the indication is single or multiple segmentectomy, depending on the anatomical location. In large tumors, hemihepatectomies may be mandatory. In tumors arising in the main bile duct, treatment includes bile duct resection and biliary-digestive anastomoses. If the distal bile duct is involved, a duodenopancreatectomy may even be performed to obtain a free margin [23].

Radical lymphadenectomy is not indicated except in the presence of lymph nodes with pathological appearance, which are shown to be tumoral during intraoperative analysis [32, 33].

The mortality rate published in the series is 3%, with morbidity up to 40%. These results are similar to those recorded in cholangiocarcinoma series. Due to the good results obtained after surgery, with survival rates of up to 85% at 5 years, free margin resection is the treatment of choice for IPNB regardless of size and location [3, 23, 34].

OTHER

Endoscopic drainage

In patients who are not candidates for surgery, treatment is mainly limited to biliary drainage in order to improve jaundice or cholangitis [27]. Some authors consider that endoscopic nasobiliary drainage is better than plastic or metal biliary drainage for elderly patients and for patients with comorbidities [12].

N-Acetyl-Cysteine (NAC)

N-Acetyl-cysteine is a mucolytic agent that decreases the viscosity of mucus. It is useful in diseases such as idiopathic pulmonary fibrosis and also for dissolving kidney stones via irrigation in percutaneous nephrostomies [1]. Its use in the treatment of IPNB in patients not suitable for surgery has recently been described [6, 35].

NAC infusion diluted in saline solution through a nasobiliary catheter proved effective for resolving a biliary obstruction caused by IPNB in a patient who refused surgery [22]. In another case, intermittent infusion of 300 mg of NAC three times a day for 10 days through a transhepatic biliary drainage catheter obtained an improvement in abdominal pain and jaundice [21].

Chemotherapy

The literature on cancer treatment in these tumors is scarce. Valente et al. [20] recently presented the first case of IPNB and IPMN-P simultaneously managed conservatively with chemotherapy and radiotherapy, achieving a reduction in tumor size and resolving jaundice. The patient required 26 cycles of chemotherapy (one first line with 5-Fluoruracine together with radiotherapy, and a second line with gemcitabine) with a survival longer than 36 months [30].

PROGNOSIS AND FOLLOW-UP

Although biologically IPNBs appear to be less aggressive, with slower growth [6, 7] and a tendency towards a better prognosis than other bile duct carcinomas [23], this may be due to the high prevalence of early-stage tumors reported in the series analyzed [6]. In both Eastern [21] and Western [33] series the anatomical location of the IPNB does not influence survival, since it does not affect the course of the disease or its prognosis.

As regards histological subtypes, the pancreatobiliary subtype has a poorer prognosis than gastric and intestinal forms; it is more often associated with invasive carcinoma and has a higher cumulative recurrence rate [3, 23]. Recurrences have been described in IPNB after resection, even in non-invasive tumors. Therefore, follow-up is recommended even after apparently complete resection [6], especially in the pancreatobiliary subtype [7].

In conclusion, given the difficulty in many cases of differentiating IPNB from cholangiocarcinoma, its status as a premalignant lesion, which progresses to an invasive cholangiocarcinoma, and the good results in terms of survival obtained with surgery, free margin resection of the tumor is the treatment of choice. In patients who are not candidates for surgery, biliary drainage with or without chemoradiation or N-acetyl-cysteine is required for resolution of the jaundice or cholangitis. Although IPNBs tend to have a better prognosis than other types of carcinomas of the bile ducts, they may present recurrences after resection, and so follow-up is recommended. The pancreatobiliary subtype has the highest rate of recurrence, the worst prognosis, and the highest rate of invasive carcinoma.

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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