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CASE REPORT

Intraductal Papillary Neoplasm of the Bile Duct (IPNB): Case Report and Literature Review of a Challenging Disease to Diagnose

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Introduction

Intraductal papillary neoplasm of the bile duct (IPNB) is defined as a bile duct epithelial tumor characterized by papillary proliferation within the bile duct lumen [1, 2]. It has been established as a precursor lesion towards cholangiocarcinoma and includes previous categories of premalignant biliary lesions. There are certain morphological features of these tumors, especially intraductal papillary growth pattern, that are similar to IPMN of the páncreas. Opposed to cystic mucinous tumors, the IPNB shows communication with the biliary tract and no ovarian like stroma (OLS) in the pathology findings [3].

IPNB develops through the adenoma-carcinoma sequence and usually progresses slowly compared to classic intrahepatic bile duct carcinoma [1, 3, 4]. An invasive component is present in approximately 40–80% of reported cases [5]. These tumors can originate from anywhere along the biliary tree, including intrahepatic and extrahepatic bile ducts.

The main clinical features are intermittent abdominal pain, acute cholangitis, and jaundice but in some patients IPNB remain asymptomatic for a long period of time [3–5].

Due to the unusual presentation of IPNB, its identification represents a diagnostic challenge. Given the malignant potencial, surgical resection with adequate margins is the standard treatment.

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In this case report, we describe the cytologic, histopathologic, clinical features, and surgical treatment of IPNB with invasive adenocarcinoma in a 72-year old male patient.

Case Report

A 72-year old male patient with past medical history of hypertension and tabaquism, was referred to our hospital with epigastric pain associated with jaundice, acholic stools, pruritus, and choluria. On admission, laboratory liver function tests demonstrated: total bilirubin 2.6 mg/dL (reference range 0.2–1.3 mg/dL), direct bilirubin 0.8 mg/dL, alkaline phosphatase 166 UI/L (reference range 38–126 UI/L), AST 364 UI/L (reference range 15–46 UI/L), ALT 90 UI/L (reference range 9–52/L). Viral markers for hepatitis B and C were negative.

An ultrasound was performed showing an heterogeneous and multicystic formation of 71 × 42 mm in the left lobe and microlithiasic gall bladder with intra- and extrahepatic biliary dilatation. A computed tomography (CT) and magnetic resonance (MRI) were carried out revealing microlithiasic gall bladder and a thin-walled multicystic lesion of 76 × 66 mm with isodense homogeneous content located in segments VIII–V–IV in close contact to right and left brunches of the portal vein. The common bile duct was displaced by the cystic formation and dilatation of the intrahepatic biliary duct towards lateral segments was also noted (Fig. 1).

Due to the acute condition of the biliary lithiasis evidenced by abdominal pain and the possibility to evaluate communication with the biliary tract, we decided to perform a laparoscopic cholecystectomy. An intraoperative colangiography was carried out showing communication between the tumor and the left biliary tract making more likely the presumptive diagnosis of IPNB (Fig. 2). No complications were noted during laparoscopic cholecystectomy or postoperative period. Pathology findings evidenced chronic cholecystitis with adenomyosis. Given that we did not want to carry out an

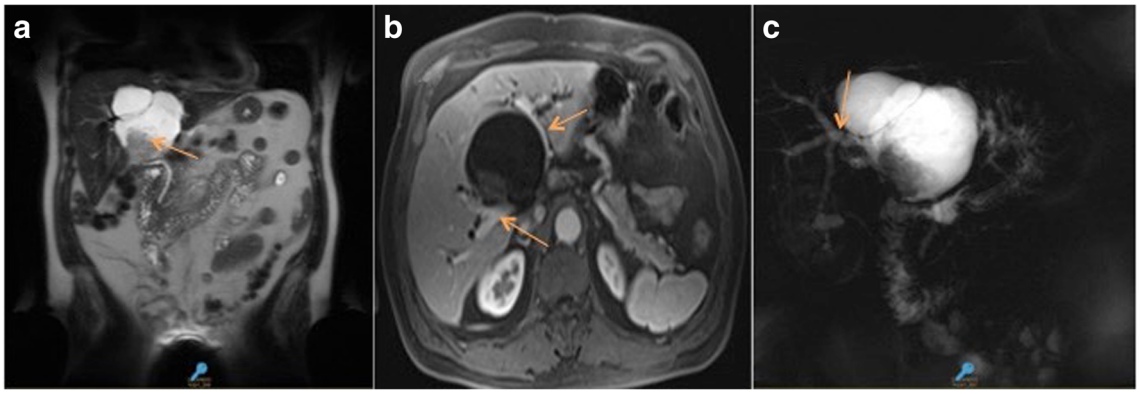

Fig. 1 Magnetic Resonance Imaging. **a** Multicystic lesion of 76 × 66 mm with isodense homogeneous content located in segments VIII–V–IV. **b** The lesion appears in close contact to the right and left brunches of portal vein. **c** The common bile duct is shifted by the cystic formation. Intrahepatic ducts are dilated

enlarged liver resection in a patient with an acute condition of the biliary lithiasis in addition to a greater planning for the elective oncological liver surgery, we decided to use a two-step approach performing first the laparoscopic cholecystectomy and then the major liver resection.

Two months after cholecystectomy, a new MRI was performed showing a slightly increase in tumor's size with an 87 × 84 mm measurement (76 × 66 mm in previous study).

Blood levels of tumor markers, such us CEA and CA 19.9 were within normal parameters and Serology was negative for Echinococcus antibodies.

In order to obtain an intracystic measurement of CA 19.9, a computed tomography guided puncture was performed. CA 19–9 measured in the cystic fluid was 1967 U/ml (reference range 30–100 U/ml). The cytology findings described hepatic cyst of biliary content. No atypic cells were noted.

Based on imaging findings that showed a cystic tumor with communication with the biliary tree and presumptive diagnosis of IPNB, the patient was considered candidate for resection and underwent a left enlarged hepatectomy associated with a caudate lobe resection. Frozen section biopsy of the bile duct was carried out and no malignancy or dysplasia was noted. Operation time was 260 min and intraoperative blood loss was 450 ml. The patient was extubated immediately after surgery. No major postoperative complications were noted and was discharged on the seventh postoperative day. Gross examination of the 535-g partial hepatectomy specimen (15.2 × 14 × 5.5 cm) revealed a 10.2 × 9.5 cm papillary multilocular cystic tumor. The tumor showed connection with intrahepatic biliary tract. The microscopic evaluation revealed a 7 × 2 mm invasive adenocarcinoma (Fig. 3). Ovarian like stroma (OLS) was not identified. The histological subtype described was pancreatobiliary. The immunohistochemical analysis demonstrated negative CDX2, estrogen and progesterone receptors and positive citoqueratine 7 and 19 receptors. Multilocular cystic tumor was fully resected with adequate margins (Fig. 4).

No evidence of recurrent disease were noted by laboratory exams and computed tomography during 12 months follow-up.

Discussion

Intraductal papillary neoplasm of the bile duct (IPNB) is defined as a bile duct epithelial tumor characterized by papillary proliferation within the bile duct lumen and it was first described by Chen and Nakanuma in 2001 [6]. It was adopted in the 2010 World Health Organization classification as a precursor lesion towards cholangiocarcinoma and includes previous categories of premalignant biliary lesions. In this classification, two categories of mucin-producing bile duct tumors of the liver had been established: mucinous cystic neoplasm of the liver (MCN) and intraductal papillary neoplasm of the bile duct (IPNB) [7].

The MCN is characterized for expressing ovarian like stroma (OLS), having a low incidence of communication with the biliary tree and having a female preponderance [3].

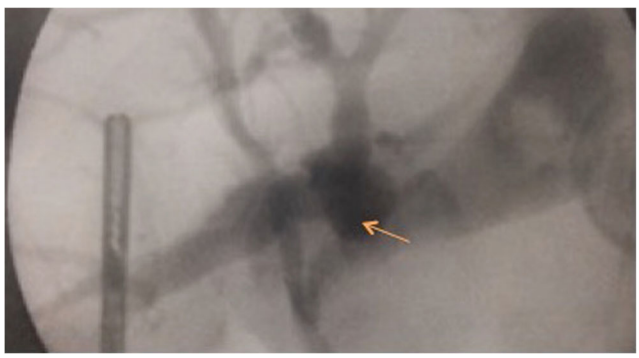

Fig. 2 Intraoperative cholangiography shows communication between the tumor and the left biliary tract

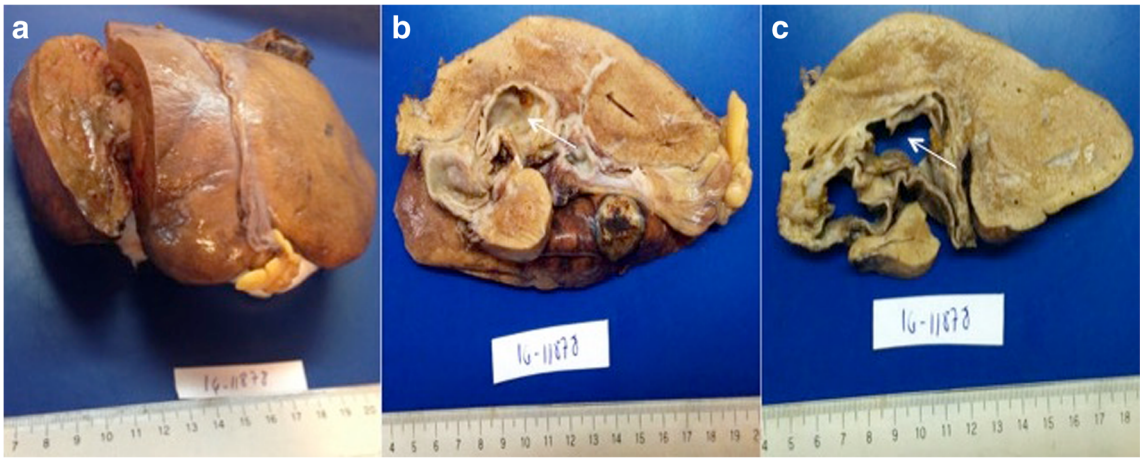

Fig. 3 Gross appearance of the resected specimen. **a** Specimen of left enlarged hepatectomy which measured 15.2 × 14 × 5.5 cm and weighted 535 g. **b** The lesion appears as a multilocular cystic formation that measured 9.5 × 10.2 cm (white arrow). **c** The surface of the resected specimen shows papillary growth (white arrow)

On the other hand, the IPNB lacks OLS in the cyst wall, usually shows luminal communication with the bile duct and a slight male preponderance was noted in the development of these tumors [3]. Kubota et al. reported in their series of 128 mucin-producing bile ducts tumors that 103 of the 119 IPNBs showed communication to the bile duct, while seven of the nine MCNs had no such communication [1–3]. Despite the fact that the presence or absence of communication with the bile duct becomes an important attribute for differential diagnostic, the main condition to differentiate between them is the absence of expression of OLS in IPNB [3]. Like other authors have suggested, an important number of cases reported previously as biliary MCN without OLS are now thought to be IPNB [6–8].

These tumors can originate from anywhere along the biliary tree, including both intrahepatic and extrahepatic bile ducts. They are developed through the adenoma-carcinoma sequence and tend to progress slowly compared to classic intrahepatic bile duct carcinoma [1–5]. An invasive component is present in approximately 40% of reported cases. Kubota et al. published 43 invasive carcinoma in their series of 119 patients [3].

Reported series evidenced that most patients are between 50 and 70 years of age and show a slight male predominance [9]. Although the etiology is unknown, hepatolithiasis seems to be an associated factor in the development of IPNB. So far, there have already been several reports evidencing biliary stones as a concomitant factor in around 30% of patients [9].

There are certain morphological features of these tumors, especially intraductal papillary growth pattern, that are similar to intraductal papillary neoplasms (IPMN) of the páncreas. Based on histological findings, IPNB can be classified into gastric, intestinal, pancreatobiliary or oncocytic subtypes. Kubota et al. reported in their series of 119 patients, 42% of pancreatobiliary type (PT), 28% of intestinal type (IT), 20% of oncocytic type (OT), and 10% were the gastric type (GT). An invasive component is most often present in the pancreatobiliary subtype [3, 4].

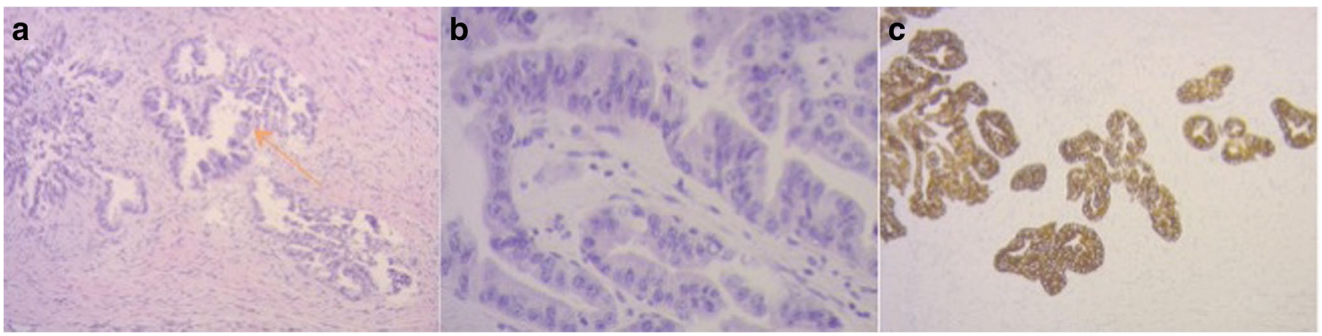

Fig. 4 Microscopic findings from the resected specimen. **a** Hematoxylin and eosin staining (magnification × 40) evidencing a multilocular cystic formation with papillary proliferations covered endoluminaly by columnar cells. **b** Hematoxylin and eosin staining (magnification × 100) evidencing adenocarcinoma with stromal invasion. **c** Inmunohistochemistry: The tumor cells were negative for CDX2, estrogen, and progesterone receptors and positive for cytokeratin 7 and 19

However, important differences exists between IPNB and IPMN of the páncreas, the most remarkables are that in IPNB is often found an invasive component (40–80%) and the pancreatobiliary type is the most common histological pattern [4–9]. On the other hand, the frequency of malignancy is approximately 20–30% in main duct IPMN (type I) and 3–5% in brunch duct IPMN (type II). Another important difference is regarding mucin hypersecretion property that both tumors possess. Mucin is macroscopically identifiable in most cases of IPMN but in only one third of IPNB cases [1].

The most common clinical features of IPNB are intermittent abdominal pain, obstructive jaundice, and fever due to the production of large quantity of mucus which causes cholangitis [cita]. However, 5–30% of the patients presented no symptoms and are discovered during routine medical examination and image studies [cita]. Such symptoms seems to be related with tumor's mucin-producing activity which causes bile duct obstruction. Tumor's most common location varies according to published evidence. Some reports showed that the majority of IPNB was located at the intrahepatic bile duct, whereas the other evidenced that the most common location of IPNB was the hepatic hilum. Nevertheless, the most frequent location seems to be in the left-side of the biliary tree, as we described in this case [1].

The diagnosis of IPNB is still challenging because of its low incidence especially in western countries. The most common radiologic findings in order of frequency are cystic dilatation of the bile duct, multilocular cyst, and simple cyst [cita]. On CT scan, compared to normal hepatic parenchyma, it is described as isodense or hyperdense during arterial phase and not hyperdense during portal-venous and delayed phase. In MRI, it is described as hypointense mass on T1 and hyperintense mass on T2. Opposed to IPNB, MCN was demonstrated as a multilocular cyst in most reported cases [10].

Tumor markers such us CA 19–9 tends to be more increased in patients with mucinous neoplasm compared to patients with simple cysts, especially in intracystic measurements. Nevertheless, published evidence suggests that CA 19–9 cannot be relied on differentiation of benign from malignant tumors. Therefore, intracystic measurements CA 19–9 can be used as an accessory method of establishing the differential diagnosis between mucinous tumors and simple cysts. [11, 12].

Published evidence showed that the standard treatment of IPNB, without distant metastasis, is radical surgical resection with adequate margins due to the potential risk of malignant transformation inside the cystic lesion [3–13]. The strategy employed must be the similar than in other intrahepatic cholangiocarcinomas. This includes a major hepatectomy in most cases with frozen section biopsy of the bile duct in order to verify the grade of displasia present and if there is tumor involvement of the resection margin. This is of crucial importance since IPNB often involves biliary epithelium diffusely or multifocally [1–9].

The discussion on whether to perform systematic resection of the bile duct or not still remains open. Nevertheless, Kubota et al. have reported no statistically significant difference in overall survival rate when analyzing outcome of patients with and without resection of extrahepatic bile duct [3]. Therefore, due to the low but still present morbidity that accompanies this procedure and having in mind that resection of the extrahepatic bile duct did not influence long-term survival, we decided not to perform resection of the extrahepatic bile duct. We suggest resection of the extrahepatic bile duct when frozen section of the biliary tree is involved either by dysplasia or carcinoma.

Determination of the optimal surgical strategy depends on the site and extent of the lesions. Procedures such us pancreaticoduodenectomy may be performed based on tumor's location in order to get optimal resection margins. Jarnagin et al. suggest regional lymphadenectomy for tumors localized in the hilium or distal bile duct but not for intrahepatic lesions [2].

Palliative treatments for patients with distant metastasis includes chemotherapy and percutaneous transhepatic drainage [2–9].

Complete resection of IPNB provides a good prognosis, even in patients with an associated invasive component. Compared to MCN, IPNB has worse survival rates, 84% 5-year survival versus 100% 5-year survival of the MCN [3–5]. The long-term survival is determinated by two main factors: cellular type of IPNB and margins of oncologic resection. The highest survival rate has been seen in the gastric subtype and the worst in the pancreaticobiliary. Recent studies demonstrated that although the survival rates of IPNB patients with invasive carcinoma tended to become worse than those of patients with only dysplasia, there were no statistically significant differences among these groups. Kim et al. demonstrated in their multivariate only R1-resections was the only prognostic factor for tumor recurrence and patient survival [1]. Therefore, we emphasize the importance of performing a resection with adequate oncological margins.

Conclusion

In summary, we conclude that IPNB is a rare pathology with good prognosis that must be taken into account in the differential diagnosis of cystic liver lesions such as echinococcosis, mucinous cystic neoplasm, complicated simple cyst, and metastasis from gastrointestinal stromal tumors. Surgical resection is the treatment of choice and since R1 resection seem to be the greatest enemy in patient's survival, we must emphasize the importance of a resection with adequate oncological margins.

Compliance with Ethical Standards

Conflict of Interests The authors declare that they have no conflict of interest.

References

1. Jung G, Park KM, Lee SS, Yu E, Hong SM, Kim J. Long-term clinical outcome of the surgically resected intraductal papillary neoplasm of the bile duct. J Hepatol. 2012;57:787–93.
2. Rocha FG, Lee H, Katabi N, RP DM, Fong Y, D'Angelica MI, et al. Intraductal papillary neoplasm of the bile duct: a biliary equivalent to intraductal papillary mucinous neoplasm of the pancreas? Hepatology. 2012;56(4):1352–60.
3. Kubota K, Nakanuma Y, Kondo F, Hachiya H, Miyazaki M, Nagino M, et al. Clinicopathological features and prognosis of mucin-producing bile duct tumor and mucinous cystic tumor of the liver: a multi-institutional study by the Japan Biliary Association. J Hepatobiliary Pancreat Sci. 2014;21(3):176–85. https://doi.org/10.1002/jhbp.23.
4. Zen Y, Fujii T, Itatsu K, Nakamura K, Minato H, Kasashima S, et al. Biliary papillary tumors share pathological features with intraductal papillary mucinous neoplasm of the pancreas. Hepatology. 2006;44(5):1333–43. https://doi.org/10.1002/hep.21387.
5. Barton JG, Barrett DA, Maricevich MA, Schnelldorfer T, Wood CM, Smyrk TC, et al. Intraductal papillary mucinous neoplasm of the biliary tract: a real disease? HPB. 2009;11(8):684–91. https://doi.org/10.1111/j.1477-2574.2009.00122.x.
6. Nakanuma Y, Sato Y, Harada K, Sasaki M, Xu J, Ikeda H. Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. World J Hepatol. 2010;2(12):419–27. https://doi.org/10.4254/wjh.v2.i12.419.
7. WHO classification of tumours of the Digestive System. 4th Edition. 2010.
8. Nakanuma Y, Zen Y, Harada K, Ikeda H, Sato Y, Uehara T, et al. Tumorigenesis and phenotypic characteristics of mucin-producing bile duct tumors: an immunohistochemical approach. J Hepatobiliary Pancreat Sci. 2010;17(3):211–22. https://doi.org/10.1007/s00534-009-0158-7.
9. Wang X, Cai YQ, Chen YH, Liu XB. Biliary tract intraductal papillary mucinous neoplasm: report of 19 cases. World J Gastroenterol. 2015;21(14):4261–7. https://doi.org/10.3748/wjg.v21.i14.4261.
10. Hong GS, Byun JH, Kim JH, et al. Thread sign in biliary intraductal papillary mucinous neoplasm: a novel specific finding for MRI. Eur Radiol. 2016;26(9):3112–20. https://doi.org/10.1007/s00330-015-4158-5.
11. Aljebreen AM, Romagnuolo J, Perini R, Sutherland F. Utility of endoscopic ultrasound, cytology and fluid carcinoembryonic antigen and CA 19-9 levels in pancreatic cystic lesions. World Journal of Gastroenterology : WJG. 2007;13(29):3962–6. https://doi.org/10.3748/wjg.v13.i29.3962.
12. Talar-Wojnarowska R, Pazurek M, Durko L, et al. Pancreatic cyst fluid analysis for differential diagnosis between benign and malignant lesions. Oncol Lett. 2013;5(2):613–6. https://doi.org/10.3892/ol.2012.1071.
13. Yang J, Wang W, Yan L. The clinicopathological features of intraductal papillary neoplasms of the bile duct in a Chinese population. Digest Liver Dis. 2012;44(3):251–6. https://doi.org/10.1016/j.dld.2011.08.014.