Intrahepatic Biliary Intraductal Oncocytic Papillary Neoplasm/Carcinoma: First Reported Case in Australia and Literature Review

Christopher Chu, M.B.B.S. FRANZCR, William Felbel, M.B.B.S. FRCPA, and Francis Chu, M.B.B.S. FRACS

Biliary (hepatic and extrahepatic) intraductal papillary mucinous neoplasms and intraductal oncocytic papillary neoplasms/carcinoma are rare neoplasms. Classification of biliary intraductal papillary tumors can be confusing and reports in radiology literature are extremely limited. We describe the first reported case of biliary intraductal oncocytic papillary neoplasms/carcinoma in the liver in Australia. The intraductal nature of such neoplasms can be identified on magnetic resonance imaging and magnetic resonance cholangiopancreatography.

Introduction

Despite increasing reported cases and understanding of the pancreatic intraductal papillary mucinous neoplasm (IPMN) [1-4], biliary (hepatic or extrahepatic) IPMN is still rarely encountered. Classification of such intrahepatic biliary IPMN can be confusing. Yamamoto et al classified such tumor as a rare subtype type of peripheral cholangiocarcinoma, which has a better prognosis than the mass forming and periductal forms [5]. Biliary intraductal papillary forms resemble closely to their pancreatic counterpart. Biliary intraductal oncocytic papillary neoplasm (IOPN), probably a subtype of IPMN, is also almost identical to pancreatic IOPN [6].

There have been only few reports of biliary IPMN [7-13]. We found only one extrahepatic and six intrahepatic cases of biliary IOPN in our search of the medical literature [6, 15-18]. We found no reported cases of biliary IOPN...
Intrahepatic Biliary Intraductal Oncocytic Papillary Neoplasm/Carcinoma: First Reported Case in Australia and Literature Review

Case Report

A 56-year-old Caucasian man was noted to have obstructive liver function on a routine blood test with elevated bilirubin, alkaline phosphatase and gamma glutamic transpeptidase. He was otherwise asymptomatic and denied any fever or weight loss. Clinical examination was unremarkable, Ultrasound revealed a complex cystic lesion in segment V of the liver associated with echogenic solid component. (Fig. 1) Computed tomography (CT) confirmed a fluid attenuation lesion with central soft tissue attenuation and intrahepatic biliary dilatation in segments V and VIII (Fig. 2). CT cholangiogram failed to show contrast excretion in the dilated biliary tree. (Fig. 3) MRI and MRCP demonstrated an irregular lesion within an aneurysmally dilated focal cystic structure with an irregular solid lesion, which was intermediate signal on T1 and hypointense on T2 sequences. There was negligible enhancement after dynamic intravenous gadolinium administration in all phases. (Fig. 4) On MRCP, the cystic component appeared to be in continuity with the dilated biliary tree in segments V and VIII. (Fig. 5) The provisional diagnosis of intrahepatic biliary intraductal papillary neoplasm was made radiologically. Patient underwent partial hepatic resection. Pathology specimen revealed a 3.0 x 3.0 x 2.6 cm soft tan to pink neoplasm with mucinous appearance. Microscopically, there were massively dilated interconnecting bile ducts filled by papillary neoplastic proliferation. It has a complex arborizing architecture with fibrovascular cores covered by multiple layers of oncocytic cells, forming occasional cribriform patterns. (Fig. 6A-C) Marked accumulation of mucinous materials was noted. There is superficial pushing invasion of periductal stroma by papillary neoplastic cells. (Fig. 6D) The diagnosis of intrahepatic biliary intraductal oncocytic papillary carcinoma (IOPC) was made. Patient remains disease-free to date.
Intrahepatic Biliary Intraductal Oncocytic Papillary Neoplasm/Carcinoma: First Reported Case in Australia and Literature Review

Figure 4A. Axial T1-weighted MRI of the liver demonstrates the soft tissue component is of intermediate signal.

Figure 4B. Coronal TSE T2-weighted MRI of the liver demonstrates the soft tissue component is hypointense on T2. Note the aneurysmally dilated cystic component communicating with adjacent dilated intrahepatic biliary tree (black arrow).

Discussion

Biliary intraductal papillary mucinous neoplasms (IPMN) are very uncommon tumors. Classification and terminology can be confusing. Yamamoto et al considered the intrahepatic form a rare subtype of peripheral cholangiocarcinoma [5]. The reported incidence ranges widely from 8.3 to 29.9% of resected cholangiocarcinoma [10-11, 19-24]. This wide range of reported incidence may reflect the confusion in classification. Of the seven reported cases of biliary IOPN, six were intrahepatic in location and one was extrahepatic in origin [6,15-18]. The first case of intrahepatic biliary IOPN was described as biliary cystadenocarcinoma with oncocytic differentiation. It was later suggested that these tumors probably arose as intraductal papillary neoplasms, and that the cystic portions were secondary phenomenon from intrahepatic cystic biliary dilatation; hence intrahepatic biliary IOPN would be more appropriate terminology [16]. With the increasing description of the pancreatic IPMN, pancreatic IOPN is now regarded as the oncocytic subtype of pancreatic IOPN. Similarities have been noted in the biliary counterpart, based

Figure 4C. Axial T1-weighted post-gadolinium arterial phase MRI of the liver demonstrates negligible enhancement in the lesion.
Intrahepatic Biliary Intraductal Oncocytic Papillary Neoplasm/Carcinoma: First Reported Case in Australia and Literature Review

Figure 4D. Axial T1-weighted post-gadolinium 2-minute delayed phase MRI of the liver demonstrates negligible enhancement in the lesion.

Figure 4E. MRI of the liver demonstrates the soft tissue component is of intermediate signal on T1 and hypointense on T2 and has negligible enhancement. Note the aneurysmally dilated cystic component communicating with adjacent dilated intrahepatic biliary tree (black arrow).

on growth pattern and pathological findings [16, 25]. As bile ducts and pancreatic ducts both arise embryologically from the hepatopancreatic bud of the foregut, biliary intraductal papillary neoplasms are likely to be more closely related to the pancreatic counterpart than cholangiocarcinoma [17]. This suggestion has been further supported by detection of bile duct type cytokines (CK 7, 18 and 19), and pancreatic digestive enzymes in the case reported by Terada et al. [17]. The tumor antigen Ca 19.9, commonly detected in cholangiocarcinoma, has been variably detected in IOPN [6,17]. Other glycoproteins and tumor antigens, including B72.3, CK 20 and HepPar1, have also been implicated in IOPN [6, 17]. Pancreatic IOPN has also been suggested to be distinct from pancreatic adenocarcinoma based on genetic analysis of the tumor [26].

Both IPMN and IOPN are characterised by mucinous production. IPMN is characterised by the presence of oncocyes which are characterised by abundant finely granular eosinophilic cytoplasm which is thought to be due to increased mitochondria [15]. According to Aday et al., the pancreatic IOPN differentiates it from IPMN by less mucin production and the presence of complex arborizing morphology of the papillae [1]. These findings have also been demonstrated in our patient.

The imaging features of biliary IOPN have not been well-described in the radiology literature. The appearance is likely to be similar to biliary IPMN, which may appear as small and flat or fungating intraductal lesion [7-9]. Larger lesions may be depicted on ultrasound, CT or MRI [7-9]. The direct communication of the cystic portion of intrahepatic biliary IOPN with dilated intrahepatic ducts has been confirmed radiologically by ERCP [17]. In our patient, such communication could not be demonstrated initially on CT cholangiogram. This is to be expected in an obstructed biliary system, a known pitfall of CT cholangiogram. However MRCP and MRI were able to demonstrate this communication and intraductal papillary neoplasm was provisionally diagnosed preoperatively based on the MRI and MRCP appearance. PTC or ERCP could have demonstrated this communication with the biliary system although these procedures are more invasive. Smaller or sessile lesions may be difficult or impossible to be visualised on any imaging modality [7-8, 12-13]. Mucin production of the tumor can result in biliary dilatation, which however can be detected radiologically. The portion of biliary tree containing the tumor may show more focal aneurysmal dilatation. This has been suggested to be a characteristic sign of intrahepatic biliary IPMN [7]. In our patients, these findings could also be depicted on imaging pre-operatively.

Patients with biliary IPMN or IOPN most commonly
Intrahepatic Biliary Intraductal Oncocytic Papillary Neoplasm/Carcinoma: First Reported Case in Australia and Literature Review

Figure 5A. Coronal 3D respiratory triggered MRCP sequence followed by MIP demonstrates the cystic component to be communicating with the dilated intrahepatic biliary tree. Note the irregular lesion (white arrows) is clearly situated with the lumen of the cystic component.

Figure 5B. Coronal 3D respiratory triggered MRCP sequence demonstrates the cystic component to be communicating with the dilated intrahepatic biliary tree. Note the irregular lesion (white arrows) is clearly situated with the lumen of the cystic component.

Figure 6A. Light microscopy reveals the tumor with papillary structures and the fibrovascular cores covered by oncocytic cells (original magnification 100x, H and E).

Figure 6B. The characteristic oncocyes with brightly eosinophilic granular cytoplasm and enlarged regular nuclei with prominent single nucleoli are present (original magnification 200x, H and E).
Intrahepatic Biliary Intraductal Oncocytic Papillary Neoplasm/Carcinoma: First Reported Case in Australia and Literature Review

Figure 6C. The proliferating oncocyes are arranged in a cribriform architecture (original magnification 400x, H and E).

Figure 6D. There is expansive invasion into the periductal stroma (original magnification 40x, H and E).

present with recurrent symptoms, including abdominal pain, fever and jaundice or less commonly disseminated disease. The age of presentation of the seven previously reported cases of biliary (intrahepatic and extrahepatic) IOPN ranges from 39 to 71 years with a median age of 52 years. All of the patients were male. Our patient also belongs to similar demographics suggesting the tumor may have strong predilection to men and are most common in their 6th decade. Size of the tumor can vary from 1.7 cm to 22 cm depending on the time of presentation which may be determined by the location of tumor with respect to how central or peripheral the tumor is in the biliary tree. The central tumor presents earlier with more extensive biliary obstruction and hence smaller size at time of presentation. It has been suggested that pancreatic IOPN may be subdivided into adenomas, borderline tumors and adenocarcinoma although most displayed sufficient cytoarchitectural atypia to warrant the term intraductal oncocytic papillary carcinoma (IOPC) [1]. The first two reported patients presented with carcinomatosis died of progressive disease. The five patients in the subsequent reported cases underwent resection, one of whom had recurrence and the other four patients remained disease free on follow up. Our patient also presented early with a relatively small tumor at time of resection. Although there was early superficial invasion into periductal stroma, hence the diagnosis of IOPC, there was no evidence of disseminated disease as opposed to the cases reported by Wolf et al and Sudo et al. [15, 16]. Our patient remains disease free after surgical resection. Complete resection is likely to offer the best chance of long term survival for IOPN [6].

In conclusion, biliary papillary neoplasms are rare. Classification can be confusing. Due to the similarities between such tumors with the pancreatic counterpart and the common embryological origin, these neoplasms are likely to be closed related and IPMN and IOPN/IOPC are more appropriate terminologies, with the latter being the oncocytic subtype of IPMN. MRI and MRCP offer non-invasive assessment of the biliary intraductal tumors and the intraductal location of such neoplasms may be identified especially if the tumors are large and fungating. Focal aneurysmal biliary dilatation is thought to be characteristic. With the limited number of cases, the behavior of such neoplasms is difficult to be determined. However, prognosis so far seems to depend on size, location and resectability. Complete surgical resection appears to offer the best hope of cure.

References

1. Adsay NV, Longnecker DS, Klimstra DS. Pancreatic tumors with cystic dilatation of the ducts: intraductal papillary mucinous neoplasms and intraductal oncocytic papillary neoplasms. Semin Diagn Pathol. 2000; 17: 16-30. [PubMed]

2. Adsay NV, Conlon K, Zee SY, Brennan MF, Klimstra DS. Intraductal papillary-mucinous neoplasms of the pancreas. Cancer 2002; 94: 62-77. [PubMed]
Intrahepatic Biliary Intraductal Oncocytic Papillary Neoplasm/Carcinoma: First Reported Case in Australia and Literature Review

3. Nagai E, Ueki T, Chijiiwa K, Tanaka M, Tsuneyoshi M. Intraductal papillary mucinous neoplasms of the pancreas associated with so-called mucinous ductal ectasia. Histochemo-

ical and immunohistochemical analysis of 29 cases. Am J Surg Pathol. 1995; 19: 576-589. [PubMed]

4. Azar C, Van de Stadt J, Rickaert F, et al. Intraductal papillary mucinous tumours of the pancreas. Clinical and therapeutic issues in 32 patients. Gut. 1996; 39: 457-464. [PubMed]

5. Yamamoto J, Kosuge T, Takayama T, et al. Surgical treatment of intrahepatic cholangiocarcinoma: 4 patients surviving more than 5 years. Surgery 1992; 111:617-622. [PubMed]

6. Martin RC, Klimstra DS, Schwartz L, Yilmaz A, Blumgart LH, Jarnagin W. Hepatic intraductal oncocytic papillary carcinoma. Cancer 2002; 95: 2180-87. [PubMed]

7. Lim JH, Yoon KH, Kim SH, Kim HY, Lim HK, Song SY, Nam KJ. Intraductal Papillary mucinous tumour of the bile ducts. Radiographics.2004;24:53-66. [PubMed]

8. Lee JW, Han JK, Kim TK, et al. CT features of intraductal intrahepatic cholangiocarcinoma. AJR Am J Roentgenol 2000; 175:721-725. [PubMed]

9. Yoon KH, Ha HK, Kim CG, et al. Malignant papillary neoplasms of the intrahepatic bile ducts: CT and histopathology features. AJR Am J Roentgenol 2000; 175:1135-1139. [PubMed]

10. Kim HJ, Kim MH, Lee SK, et al. Mucin-hypersecreting bile duct tumour characterized by a striking homology with an intraductal papillary mucinous tumour (IPMT) of the pancreas. Endoscopy 2000; 32:389-393. [PubMed]

11. Chow LT, Ahuja AT, Kwong KH, et al. Mucinous cholangiocarcinoma: an unusual complication of hepatolithiasis and recurrent pyogenic cholangitis. Histopathology 1997; 30:491-494. [PubMed]

12. Kokubo T, Itai Y, Ohtomo K, Itoh K, Kawachi N, Minami M. Mucin-hypersecreting intrahepatic biliary neoplasms. Radiology 1988; 168:609-614. [PubMed]

13. Lim JH, Kim YI, Park CK. Intraductal mucosal-spreading mucin-producing peripheral cholangiocarcinoma of the liver. Abdom Imaging 2000; 25:89-92 [PubMed]

14. Lim JH, Yi CA, Lim HK, Lee WJ, Lee SJ, Kim SH. Radiological spectrum of intraductal papillary tumors of the bile ducts. Korean J Radiol 2002; 3:57-63. [PubMed]

15. Wolf HK, Garcia JA, Bossen EH. Oncocytic differentiation in intrahepatic biliary cystadenocarcinoma. Mod Pathol. 1992; 5: 665-668. [PubMed]

16. Sudo Y, Harada K, Tsuneyama K, Katayanagi K, Zen Y, Nakanuma Y. Oncocytic biliary cystadenocarcinoma is a form of intraductal oncocytic papillary neoplasm of the liver. Mod Pathol. 2001; 14: 1304-1309. [PubMed]

17. Terada T, Taniguchi M. Intraductal Oncocytic Papillary Neoplasm of Liver (Case report). Pathology International. 2004; 54(2), 116-123. [PubMed]

18. Spector SA, Bejarano PA, Amortegui JD, Renfrow MR, Livingstone A. Intraductal Oncocytic Papillary neoplasm of the extrahepatic biliary tree: first report. The American Surgeon 2004; 70 (1), 55-58. [PubMed]

19. Suh K.S, Roh HR, Koh YT, Lee KU, Park YH, Kim SW. Clinicopathological features of intraductal growth type of peripheral cholangiocarcinoma. Heparatology 2000; 31:12-7. [PubMed]

20. Isogai M, Nimura Y, Hayakawa N. A case of mucus producing cholangiocarcinoma with superficial spread. Jpn J Gastroenterol Surg. 1986; 19: 710-713. [PubMed]

21. Taoka H, Kawarada Y. [Intrahepatic bile duct carcinoma (cholangiocarcinoma)]. Nippon Geka Gakkai Zasshi. 1997; 98: 484-490. [PubMed]

22. Yamamoto M, Takasaki K, Ootsubo T, Yoshikawa T, Nakamura M, Hanyu F. [Gross appearance and corresponding clinicopathological features of cholangiocellular carcinoma]. Jpn J Gastroenterol Surg. 1994; 27: 52-55. [Online at http://www.jsgs.or.jp/journal/abstract/027010052_e.html accessed June 3, 2007]

23. Ohashi K, Nakajima Y, Kanehiro H, et al. Ki-ras mutations and p53 protein expressions in intrahepatic cholangiocarcinomas: relation to gross tumour morphology. Gastroenterology. 1995; 109:1612-7. [PubMed]
Intrahepatic Biliary Intraductal Oncocytic Papillary Neoplasm/Carcinoma: First Reported Case in Australia and Literature Review

24. Yeh CN, Jan YY, Yeh TS, Hwang TL, Chen MF. Hepatic Resection of intraductal Papillary type cholangiocarcinoma. Ann Surg Oncol 2004; 11(6): 606-611. [PubMed]

25. Adsay NV, Adair CF, Heffess CS, Klimstra DS. Intaductal oncocytic papillary neoplasms of the pancreas. Am J Surg Pathol. 1996; 20:980-994. [PubMed]

26. Patel SA, Adams R, Goldstein M, Moskaluk C. Genetic Analysis of Invasive carcinoma arising in intraductal oncocytic papillary neoplasm of the pancreas (case reports). Am J Surg Pathol 2002;26(8):1071-1077. [PubMed]