An oncocytic variant of intraductal papillary neoplasm of the bile duct that formed a giant hepatic cyst

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Abstract

Intraductal papillary neoplasms of the bile duct (IPNB) is the collective term used to refer to papillary bile duct tumors, mucin producing bile duct tumors, and cystic bile duct tumors. Pathologically, these tumors may be considered a highly differentiated adenocarcinoma or a tumor of borderline malignant potential. IPNB is classified into one of four variants based on cell differentiation. The rarest, oncocytic, is characterized by oxyphilic granular cytoplasm and no mucous cell differentiation. The patient, a 59-year old man, was admitted with a complaint of abdominal fullness and a 30×25 cm cystic mass in the right hepatic lobe demonstrated on computed tomography (CT). The mass had no malignant features on CT or magnetic resonance imaging; however, a portion was FDG avid on ^{18}F-fluorodeoxyglucose positron emission tomography scan (FDG-PET). A fenestration operation was performed for the presumed diagnosis of a hepatic cyst. Pathological examination of the cyst contents demonstrated some atypical cells suspicious for malignancy. After eight months of observation, abnormal FDG uptake was again observed at the residual cyst. A partial hepatectomy was performed to excise the cyst. Pathological examination demonstrated adenocarcinoma *in situ* derived from an oncocytic IPNB variant. Following the resection, the patient remained disease free for 40 months. This is an extremely rare case of an oncocytic variant of IPNB that was difficult to distinguish clinically from a solitary hepatic cyst.

Introduction

Intraductal papillary neoplasms of the bile duct (IPNB) collectively refer to papillary bile duct tumors, mucin producing bile duct tumors, and cystic bile duct tumors. They characteristically show a papillary proliferation of dysplastic biliary epithelium, hypersecretion of mucous and biliary duct dilation. Pathologically, these tumor cells represent a highly differentiated adenocarcinoma or tumor of borderline malignant potential. These tumors are analogous to an intraductal papillary mucinous neoplasm (IPMN) of the pancreas and have, therefore, been referred to as IPNB.[1-3] The rarest variant, the oncocytic type, has oxyphilic granular cytoplasm without mucous cell differentiation. Only 9 cases have been reported in the English Language literature. We discuss here the diagnosis and treatment of a rare case of an IPNB that presented as a large cystic hepatic lesion.

Case Report

The patient, a 59-year old man, was admitted with a complaint of abdominal fullness and early satiety and a 30x25 cm cystic mass in the right hepatic lobe, demonstrated on computed tomography (CT) (Figure 1A). The cyst was simple and without malignant features such as septations or wall thickening. On magnetic resonance imaging (MRI), the signal pattern of the cystic contents had low signal intensity on T1-weighted images (Figure 1B) and high intensity on T2-weighted images (Figure 1C). No septations or wall thickening was evident on MRI. Abdominal angiography demonstrated no vascularization in the cyst wall. The tumor markers CA19-9, CA125, AFP and PIVKA-II were all normal. An ^{18}F-fluorodeoxyglucose positron emission tomography scan (FDG-PET) demonstrated an FDG avid area in the cyst wall (Figure 1D). Collectively, these findings were consistent with a low risk of malignancy, as the mass was suspected to be a hepatic cyst. As the patient was highly symptomatic, the decision was made to proceed with fenestration. Laparotomy exposed the cyst which was covering the epigastrium (Figure 2A). The cyst was opened and a small excrescence was present in the area corresponding to the hypermetabolic area on FDG-PET (Figure 2B). This tissue was removed and evaluated by frozen section. Cellular atypia was present; however, no malignancy was identified. The remainder of the cyst wall appeared unremarkable. The patient had an uncomplicated course and was discharged home on Day 15 post surgery. Pathological examination showed most of the cyst wall was composed of a fibrotic tissue (Figure 2C). However, in the permanent sections using frozen tissue for intraoperative diagnosis, papillary proliferation of atypical cells with enlarged nuclei was observed (Figure 2D). The rate of proliferation (MIB-1 index) of these atypical cells was 47%, which suggested that the cystic lesion was possibly malignant. On histology, a biliary cystadenocarcinoma of the oncocytic type or an intraductal papillary neoplasm of the bile duct was suspected. FDG avidity was not detected in the residual cyst following the surgery. Therefore, the patient remained under observation.

Eight months post surgery, FDG uptake was again noted in the residual cyst. A partial hepatectomy encompassing the cyst and hepatic right middle lobe was performed (Figure 3A). The patient had an uncomplicated post-operative course and was discharged home on Day 15 post surgery. Pathological examination demonstrated papillary atypical epithelium lining portions of the cyst wall (Figure 3B) which was contiguous with the normal bile duct epithelium (Figure 3C), indicating that the cyst originated in the biliary tree. The tumor cells again displayed oxyphilic granular cytoplasm. As there was no evidence of invasion, the diagnosis was an oncocytic variant of high-grade dysplasia from an IPNB. The patient had no evidence of recurrence on either CT or FDG-PET for 40 months.

Discussion

The present case demonstrates the diagnos-

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tic dilemma of a malignant cystic lesion with benign imaging characteristics on CT, MRI, and abdominal angiography. The initial frozen section was also inconclusive for malignancy likely because of the small specimen size and the lack of an invasive component.

The FDG-PET, however, was positive, consistent with a malignant process. There are several reports about the relationship between cholangiocarcinoma and hypermetabolic activity on FDG-PET.[4,5] PET is highly sensitive and specific for the detection and localization of cholangiocarcinomas (sensitivity 92.3%; specificity 92.6%) 2 cm or over in size.[6] No reports have evaluated the use of FG-PET in smaller tumors. FDG-PET, however, has a high false positive rate in patients with mucinous cholangiocarcinoma.[7] No reports have addressed the imaging characteristics of IPNB on FDG-PET. In this case, the tumor was under 2 cm in size and pathologically *in situ*. Therefore, its FDG-avidity was unexpected.

Indications for surgical management of hepatic cysts include thickening and enhancement of portions of the cyst wall, an increase in size, and whether the patient is symptomatic. A solitary hepatic cyst may be managed with one of the following surgical procedures: percutaneous drainage, fenestration, and hepatectomy.[8,9] Partial hepatectomy is reserved for tumors with high suspicion of malignancy as it is a highly invasive procedure. Thus, in the present case, fenestration was initially performed. As a bile duct neoplasm rather than a hepatic cyst was identified on initial pathology, partial hepatectomy was elected for the second procedure.IPNB are characterized by papillary proliferation of dysplastic biliary epithelium with mucous hypersecretion and biliary duct dilation. Pathologically these tumor cells are composed of highly differentiated adenocarcinoma or borderline malignant cells. They are assumed to be the precursor lesion of an intrahepatic cholangiocarcinoma.[10] The discrimination of biliary cystadenomas and cystadenocarcinomas from IPNB is sometimes challenging. In this case, the tumor did not have an ovarian-type stroma in the cyst wall, and the presence of the normal bile epithelium that was contiguous with the cystic lesion determined the final diagnosis of IPNB. IPNB has four variants: pancreatobiliary, intestinal, gastric, and oncocytic. In this case, the tumor cells had an oxyphilic granular cytoplasm without mucous cell differentiation, consistent with the oncocytic variant.[11] The oncocytic papillary neoplasm of the bile duct was first reported by Wolf *et al*.[12] and is the rarest variant.[13] Only 9 cases have been reported in the English Language literature.[14] The usual presentation is abdominal pain in a middle-aged man with previously reported tumors ranging from 3 to 21 cm in size.[15] Cysts may be uni- or multilocular. No recurrence or metastatic spread has been

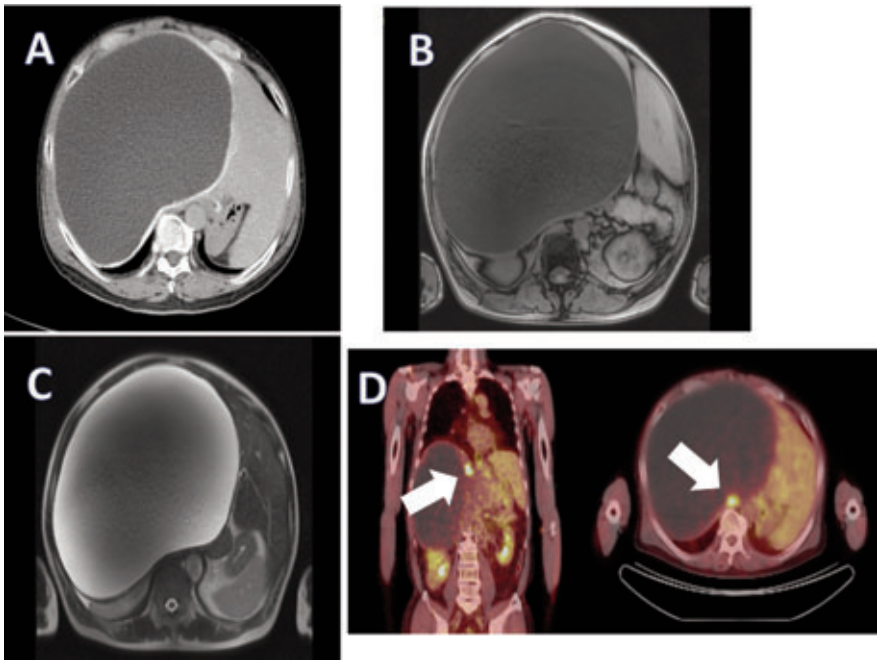

Figure 1. Computed tomography scan (A) and magnetic resonance imaging (B, C) demonstrating an extremely large, cystic mass in the right hepatic lobe. T1-weighted images (B) and T2-weighted images (C). ^{18}F-fluorodeoxyglucose positron emission tomography scan with an area of FDG avidity (arrow) in the cyst wall (D).

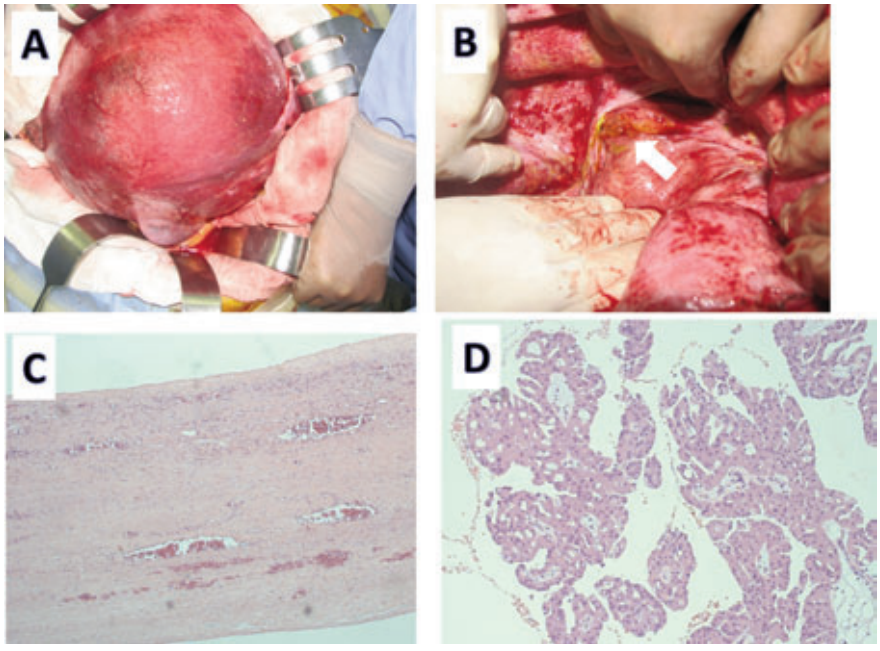

Figure 2. Intraoperative findings. The cyst occupied the epigastrium (A). A small excrescence (arrow) was observed in the cystic wall in the area of FDG avidity (B). Histopathological findings of the cyst removed during the first surgery. The wall was composed of fibrotic tissue (C). Papillary tissue was evident in the frozen section, and cellular abnormalities were observed (D).

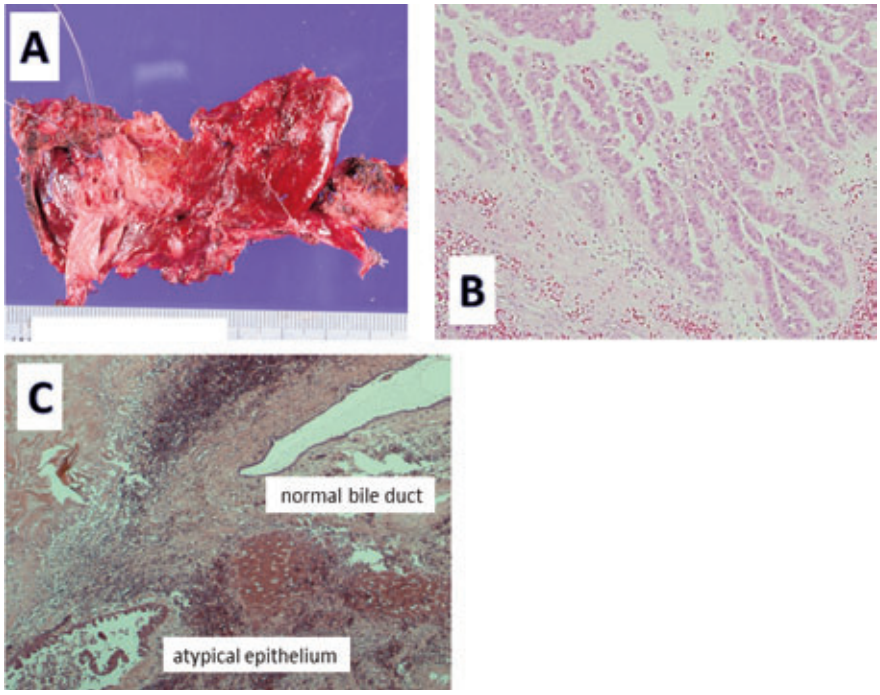

Figure 3. The residual cyst was removed along with the right hepatic lobe (A). Atypical papillary epithelium (B). The atypical epithelium was contiguous with the normal bile duct epithelium (C).

reported for the oncocytic variant, consistent with its benign histological appearance and lack of invasion.[16-18] Although the case reported here had the above-mentioned features, diagnosis was difficult as the tumor only formed a small component of the cyst. Lee *et al*. reported 2 cases of oncocytic IPNB contained within unilocular cysts. These tumors showed an obvious nodular mass in the cyst wall.[19,20] In the present case the IPNB had also formed a small nodule within an extremely large cyst. Therefore, this case had an unprecedented form compared with the previous reports.

Flavio *et al.* reported outcomes of IPNB.[20] The factors associated with a worse median survival are depth of tumor invasion, margin positive resection, and expression of MUC1 and CEA. The present tumor was an *in situ* lesion that was completely resected. It is not surprising, therefore, that the patient has not had a recurrence.

Conclusions

The present report describes a case of IPNB that resembled a hepatic cyst. Despite the utilization of multiple imaging modalities, the diagnosis of malignancy was not established until final pathological examination. Unlike hepatic cysts that may be managed conservatively, the recommended treatment of a suspected IPNB is complete resection.

References

1. Chen TC, Nakanuma Y, Zen Y, et al. Intraductal papillary neoplasia of the liver associated with hepatolithiasis. Hepatology 2001;34:651-8.
2. Zen Y, Sasaki M, Fujii T, et al. Different expression patterns of mucin core proteins and cytokeratins during intrahepatic cholangiocarcinogenesis from biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct-an immunohistochemical study of 110 cases of hepatolithiasis. J Hepatol 2006;44:350-8.
3. Nakanuma Y, Sato Y, Harada K, et al. Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. World J Hepatol 2010;2:419-27.
4. Weber A, Schmid RM, Prinz C. Diagnostic approaches for cholangiocarcinoma. World J Gastroenterol 2008;14:4131-6.
5. Lee SW, Kim HJ, Park JH, et al. Clinical usefulness of 18F-FDG PET-CT for patients with gallbladder cancer and cholangiocarcinoma. J Gastroenterol 2010;45:560-6.
6. Kluge R, Schmidt F, Caca K, et al. Positron emission tomography with [(18)F]fluoro-2-deoxy-D-glucose for diagnosis and staging of bile duct cancer. Hepatology 2001;33:1029-35.
7. Fritscher-Ravens A, Bohuslavizki KH, Broering DC, et al. FDG PET in the diagnosis of hilar cholangiocarcinoma. Nuclear medicine communications. 2001;22:1277-85.
8. Madariaga JR, Iwatsuki S, Starzl TE, et al. Hepatic resection for cystic lesions of the liver. Ann Surg 1993;218:610-4.
9. Tan YM, Chung A, Mack P, et al. Role of fenestration and resection for symptomatic solitary liver cysts. ANZ J Surg 2005;75: 577-80.
10. Nakanuma Y, Sasaki M, Sato Y, et al. Multistep carcinogenesis of perihilar cholangiocarcinoma arising in the intrahepatic large bile ducts. World J Hepatol 2009;1:35-42.
11. Martin RC, Klimstra DS, Schwartz L, et al. Hepatic intraductal oncocytic papillary carcinoma. Cancer 2002;95:2180-7.
12. Wolf HK, Garcia JA, Bossen EH. Oncocytic differentiation in intrahepatic biliary cystadenocarcinoma. Mod Pathol 1992;5:665-8.
13. Nakanishi Y, Zen Y, Hirano S, et al. Intraductal oncocytic papillary neoplasm of the bile duct: the first case of peribiliary gland origin. J Hepatobiliary Pancreat Surg 2009;16:869-73.
14. Cocieru A, Kesha K, El-Fanek H, Saldinger PF. Hepatic intraductal oncocytic papillary carcinoma. Am J Surg 2010;199:e57-8.
15. Terada T, Taniguchi M. Intraductal oncocytic papillary neoplasm of the liver. Pathol Internat 2004;54:116-23.
16. Tabibian JH, Lassman CR, Margolis DJ, et al. Intraductal oncocytic papillary neoplasm of the liver: case and review of a rare variant. Ann Hepatol 2008;7:168-73.
17. Tanaka M, Fukushima N, Noda N, et al. Intraductal oncocytic papillary neoplasm of the bile duct: clinicopathologic and immunohistochemical characteristics of 6 cases. Hum Pathol 2009;40:1543-52.
18. Jarnagin WR, Bowne W, Klimstra DS, et al. Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. Ann Surg 2005;241:703-12.
19. Lee S, Kim YS, Lee WJ, Jang KT. Intraductal oncocytic papillary neoplasm of the bile duct: ultrasonography and CT findings with pathological correlations. Clin Radiol 2009;64:841-4.
20. Rocha FG, Lee H, Katabi N, et al. Intraductal papillary neoplasm of the bile duct: a biliary equivalent to intraductal papillary mucinous neoplasm of the pancreas? Hepatology 2012;56:1352-60.