CASE REPORT

Intraductal oncocytic papillary neoplasm: a benign hepatic cystic neoplasm

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SUMMARY

A 61-year-old Asian man presented with severe right upper quadrant pain which had been worsening for several months. Laboratory results indicated elevated aspartate aminotransferase and alanine aminotransferase. The subsequent ultrasound, CT and MRI showed a large cystic mass with solid components and severe intrahepatic and extrahepatic biliary ductal dilatation. The mass was resected and pathology showed a well-demarcated mucinous cystic lesion with polygonal cells containing ovoid nuclei and abundant pink oncocytic cytoplasm. These findings are characteristic of intraductal oncocytic papillary neoplasm (IOPN), a rare subtype of intraductal papillary neoplasm of the liver. IOPN occurs most frequently in the Asian regions endemic to clonorchiasis and hepatolithiasis; however, cases have been reported in the Western world as well. Patients with IOPN are male or female and typically middle-aged. Treatment is typically resection. Prognosis is favourable and recurrence is rare. The 5-year survival rate is upwards of 80%.

BACKGROUND

There is a broad differential diagnosis for cystic liver lesions, with prognosis spanning from benign indolent lesions to aggressive malignancy. Intraductal oncocytic papillary neoplasm (IOPN) of the biliary ducts is a rare cystic liver mass, which may appear to have aggressive or complex imaging features, however has a favourable prognosis when appropriately managed. Knowledge of this rare entity and recognition of its imaging and pathological appearance can help avoid misdiagnosis and optimise management.

CASE PRESENTATION

A 61-year-old Asian man presented with severe right upper quadrant pain which had been worsening for several months. The patient also had been complaining of non-specific gastrointestinal symptoms over the last 3 years. There was no significant pertinent medical history or family history.

INVESTIGATIONS

Laboratory results indicated elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Initial ultrasound of the liver showed a large cyst with solid components. Further workup with MRI and CT demonstrated a large complex cyst occupying the entire right lobe of the liver. There was extensive intrahepatic biliary ductal

dilatation resulting from both mass effect and from the mucinous production into the biliary ducts by the lesion (figures 1–3). There was also mass effect on the adjacent right kidney, which was displaced across midline to the left (figure 2); the gallbladder, which was displaced inferiorly (figure 1); and the overlying right lung, which was displaced superiorly (figure 1).

A partial right hepatectomy was performed. The right lobe of the liver was received fragmented by the pathology department, measuring 22.0 cm in maximum dimension. A clearly demarcated cystic lesion filled with clear mucoid fluid and composed of friable tan-pink papillary projections was seen (figure 4).

Low-power morphology demonstrated a homogeneous papillary architectural pattern throughout (figure 5). Medium-power morphology demonstrated abundant papillae with fibrovascular cores present as an intraductal proliferation, which was well-circumscribed and separated from non-neoplastic liver (figure 6). High-power cytomorphology demonstrated regular round-ovoid nuclei with conspicuous nucleoli. The cells were polygonal/epithelioid with abundant pink oncocytic granular cytoplasm. Clear mucin can be seen between layers of the oncocytic cells (figure 7).

The radiological and pathological findings are compatible with IOPN of the biliary ducts.

DIFFERENTIAL DIAGNOSIS

Differentials include mucinous cystic neoplasm (biliary cystadenoma/cystadenocarcinoma) and hepatic abscess. The imaging appearance of biliary cystadenoma/cystadenocarcinoma has substantial overlap with IOPNs. Biliary cystadenocarcinomas tend to have more septations and discrete solid components, and because they are characterised pathologically by ovarian-type stroma, occur in female patients. Additionally, mucinous cystic neoplasms have upstream biliary ductal dilatation due to obstruction; however, unlike IOPN, downstream biliary ductal dilatation is absent. Mucinous neoplasms also do not communicate with the bile ducts, although this distinction may not be observable on imaging.

Although hepatic abscesses are complex and have thick septa, they do not produce mucin nor contain papillary solid components. Clinically, patients with hepatic abscess also typically have fever, leucocytosis and/or other symptoms of infection.

A much less likely differential consideration is the solitary bile duct cyst. Unlike IOPNs, they are

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Figure 1 CT of the abdomen and pelvis with intravenous contrast. Coronal image shows a large cystic lesion with multiple enhancing solid papillary soft tissue projections. Although there is mild intrahepatic ductal dilatation of the left lobe of the liver, the liver parenchyma is grossly normal.

typically simple cysts or have thin septations and do not produce mucin. They also are not associated with downstream biliary ductal dilatation.

TREATMENT

Due to the risk of malignant degeneration of the IOPN to adenocarcinoma and also the large size of the hepatic lesion, which exhibited mass effect on adjacent organs, our patient underwent a right hepatectomy. No adjuvant therapy was administered.

OUTCOME AND FOLLOW-UP

After surgical treatment, the patient's presenting symptoms resolved. One year follow-up showed no evidence of recurrence.

Figure 2 CT of the abdomen and pelvis with intravenous contrast. Axial image of the inferior aspect of the right lobe of the liver shows dilated intrahepatic duct. The dilated ducts were found to contain mucin intraoperatively.

Figure 3 Axial T1 postcontrast image with fat suppression shows multiple solid papillary projections.

DISCUSSION

Hepatic intraductal papillary neoplasms (IPN) are tumours that arise from the epithelium of bile ducts and exhibit a papillary growth pattern into the bile duct lumen. They often produce an abundance of mucin, which may disrupt bile flow and cause biliary obstruction.¹ Although histologically related to intraductal papillary mucinous neoplasms (IPMN) of the pancreas, there has been controversy whether they are the same tumours occurring in different locations or if they are different tumours all together.²⁻⁴

Hepatic IPNs have been described as a subtype or precursor to cholangiocarcinoma. Two other described growth patterns of cholangiocarcinoma include mass-like growth and periductal growth, both of which carry a worse prognosis than IPNs.⁵ IPNs are generally well differentiated and have three histological grades including low grade (cellular dysplasia), high grade (in situ adenocarcinoma) and invasive grade (invasion into the biliary duct wall or to adjacent structures).⁶

IPNs are also categorised into four histological variants, including gastric, intestinal, pancreaticobiliary and oncocytic types.⁷ The gastric variant contains columnar cells with abundant cytoplasmic mucin. The intestinal type resembles intestinal mucosa with stratified columnar cells interspersed with goblet

Figure 4 Right lobe of the liver (partial hepatectomy) received fragmented, measuring 22.0 cm in maximum dimension. A clearly demarcated cystic lesion is composed of friable tan-pink papillary projections.

Figure 5 Low-power morphology demonstrates a homogeneous papillary architectural pattern throughout.

cells. The pancreaticobiliary variant is characterised by cuboidal to short columnar cells containing pale eosinophilic cytoplasm and round nuclei. The oncocytic variant exhibits large cells with abundant eosinophilic cytoplasm and round nuclei due to the accumulation of altered mitochondria.^{8,9} Of these, the oncocytic variant, IOPN, is the least common as oncocytic conversion of biliary cells is rare.⁷

Each IPN variant tends to express specific mucin core proteins (MUC), which may predict prognosis. Although there have only been a few studies on the expression of MUC in hepatic IPNs, there have been more rigorous studies on the MUC expression in pancreatic IPMNs. It has been shown that MUC1-positive pancreatic IPMNs tend to progress rapidly leading to poorer prognosis.¹⁰ IPMNs that express MUC5AC alone tend to have better prognosis.¹¹ Rouzbahman *et al*¹² investigated the MUC expression in four cases of hepatic IOPN and discovered that the two cases with invasive qualities showed MUC1 expression, although there was no difference in MUC1 expression between the invasive and non-invasive portions of the lesions. MUC5AC was expressed in all of the four cases. Another study showed that in a group of six cases, five of six expressed MUC5AC. One of the six cases had a poor outcome, which showed MUC2 expression, although it also had MUC5AC expression.⁹ MUC1 or MUC2 expression may indicate worse prognosis, and MUC5AC expression alone may indicate more favourable prognosis. Thus, there may be a correlation between MUC expression and the prognosis of IOPN; however, due to the rarity of the tumour, closer examination will need to be made to establish more conclusive results.

Mucin production in IOPN may also be predicted using examination of MUC expression. Although there is no intracellular mucin in the oncocytic cells of IOPN, there is a variable amount

Figure 6 Medium-power morphology demonstrates abundant papillae with fibrovascular cores present as an intraductal proliferation, well-circumscribed and separated from non-neoplastic liver.

Figure 7 High-power cytomorphology demonstrates regular round-ovoid nuclei with conspicuous nucleoli. The cells are polygonal/epithelioid with abundant pink oncocytic granular cytoplasm. Extracellular clear mucoïd fluid was seen elsewhere on high power between the layers of oncocytic cells.

of mucin secretion into the bile ducts. One study showed only 4 of 19 cases of IOPN exhibited mucin hypersecretion characteristics.⁶ However, another study examined the MUC expressions, which emulated the gastric phenotype of pancreatic IPMN. This suggests that the oncocytic cells of IOPN tumours that secrete mucin, such as in our case, may be transformed gastric phenotype cells.⁹

Patients with IOPN present with non-specific right upper quadrant pain, episodes of acute cholangitis and obstructive jaundice, though some are asymptomatic and the result of incidental findings. Acute cholangitis is also a less common presentation. Laboratory values reflect biliary obstruction and include elevation of ALT, AST, total bilirubin, direct bilirubin, gamma-glutamyl transpeptidase and alkaline phosphatase. Cancer antigen 19-9 is variably increased in a percentage of patients; however, it is not a universal finding.¹³

On imaging, IOPN appears as cystic lesions with direct communication to dilated intrahepatic and occasionally extrahepatic biliary ducts. These lesions may be incidentally discovered on imaging if their growth has not yet caused obstructive symptoms. Ultrasound demonstrates cystic structures with papillary projections into the cyst. Contrast-enhanced CT and MRI demonstrate enhancing papillary solid components within the cystic structures, an appearance that may be identical to biliary cystadenoma/cystadenocarcinoma.⁵ Although imaging can determine the extent of growth, the cystic nature and the papillary growth pattern of IOPNs, it is difficult for imaging to determine whether there are mucinous secretions as mucin and simple fluid may appear identical on ultrasound, CT and MRI.⁷

IOPN lesions have favourable prognosis. Treatment of IOPN includes surgical resection, which is usually curative. If the disease is multifocal, it indicates possible superficial spread of disease over the biliary ducts, increasing difficulty in obtaining clear margins during resection. Liver transplantation may be the only completely curative option.¹⁴ In patients in whom surgical options are not feasible, palliative treatments with cyst drainage may be performed to alleviate jaundice, cholangitis and other biliary obstructive symptoms.^{14,15}

It is important to consider IOPNs in the differential for hepatic cystic lesions, as prognosis is generally good after surgical resection. This is especially true for male patients because initial instinct may point towards aggressive and malignant processes as the more common benign cystadenomas tend to only occur in female patients.¹⁶

Learning points

- ▶ Intraductal oncocytic papillary neoplasm (IOPN) of the biliary ducts is a very rare cystic hepatic lesion with a male predominance.
- ▶ Although there is substantial overlap in the imaging appearance with biliary cystadenoma, they are histologically distinct entities. Biliary IOPNs occur in higher frequency in men and is pathologically almost identical to pancreatic IOPNs.
- ▶ IOPN imaging characteristics include complex cystic lesion with solid components and characteristic upstream and downstream biliary ductal dilatation due to intraductal mucin or obstruction.
- ▶ IOPN has a distinct pathological appearance of well-circumscribed lesion with papillary architecture and polyploid cells with ovoid nuclei and abundant oncocytic cytoplasm.
- ▶ Treatment of IOPN is surgical resection due to the potential for malignant degeneration of the lesion, which typically results in an excellent prognosis.

Contributors AG is the supervising physician in the case, and contributed towards the editing of the radiological aspects of the case. AT contributed towards coordinating patient information, writing and editing. GV contributed towards acquiring patient consent and editing the clinical section of the case. AB contributed towards editing the pathology section of the case.

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