Hilar Biliary Obstruction: Malignant Masquerades

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ABSTRACT

Biliary obstruction at the hepatic hilus is most often due to malignancy. Clinically, it can be very difficult to differentiate malignant from benign obstruction when a mass lesion is not evident on cross-sectional imaging. In this article, we describe three cases of benign biliary obstruction due to so-called malignant masquerades to familiarize the reader with the clinical, radiographic, and pathological features of these uncommon but important entities.

KEYWORDS: Biliary obstruction, autoimmune pancreatitis, chemotherapy-induced biliary sclerosis, *Clonorchis sinensis*

Objectives: Upon completion of this article, the reader should know the differential diagnosis of hilar biliary strictures and have an understanding of benign processes that mimic the appearance of cholangiocarcinoma.

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Biliary obstruction at the hepatic hilus is most often due to malignancy. The most common etiology is either primary cholangiocarcinoma or metastatic disease to the liver bile duct or periportal lymph nodes. Clinically, it can be very difficult if not impossible to differentiate malignant from benign obstruction when a mass lesion is not evident on cross-sectional imaging.¹ The cases that follow are examples of benign biliary obstruction due to so-called malignant masquerades,² presented to familiarize the reader with the clinical, radiographic, and pathological features of these uncommon but important entities.

CASE 1

A 65-year-old woman presented with painless jaundice associated with nausea and vomiting. A computed

tomography (CT) scan and endoscopic ultrasound were performed, and they demonstrated biliary obstruction and a 2-cm irregular mass in the head of the pancreas suggestive of pancreatic carcinoma (Fig. 1). A fine-needle biopsy performed at the time of the endoscopic ultrasound was nondiagnostic, and she underwent pancreaticoduodenectomy. Pathology reported chronic pancreatitis with no evidence of malignancy. Twenty lymph nodes with reactive changes were included in the specimen. The patient was discharged on hospital day 8 following an unremarkable postoperative course.

Two months later, the patient again presented with painless jaundice and a serum bilirubin of 32 mg/dL. Contrast-enhanced CT of the abdomen at that time showed peripheral biliary obstruction with a paucity of central bile ducts (Fig. 2). Percutaneous transhepatic cholangiography was performed, and it confirmed the

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Case-Based Interventional Radiology; Guest Editors, Ron C.

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Semin Intervent Radiol 2007;24:3–9. Copyright © 2007 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.
DOI 10.1055/s-2007-971179. ISSN 0739-9529.

Figure 1 (A) Contrast-enhanced computed tomography demonstrates biliary dilation. (B) Although there is no discrete mass, there is fullness in head of pancreas (asterisk). In association with biliary dilation, this was suspicious for pancreatic adenocarcinoma.

Figure 2 (A) and (B) Several weeks after pancreaticoduodenectomy, contrast-enhanced computed tomography demonstrates peripheral biliary dilation with paucity of central ducts. The common duct (not shown) was not dilated.

CT findings. Specifically, central biliary strictures and peripheral biliary dilation were observed (Fig. 3). Because placement of a biliary drainage catheter would only drain a single duct well and could potentially contaminate other poorly drained ducts, no catheter was placed. The serum

IgG₄ level was found to be elevated, measuring 1840 mg/dL. Steroid therapy was initiated, and the jaundice resolved. The patient was discharged in good condition on hospital day 6. Two weeks after discharge, the bilirubin decreased to 3 mg/dL, and the patient was clinically well.

Case 1 Diagnosis Autoimmune pancreatitis.

Case 1 Discussion

Autoimmune pancreatitis (AIP), also known as lymphoplasmacytic sclerosing cholangitis or sclerosing pancreatitis, is an uncommon inflammatory disease that may mimic pancreatic carcinoma.³ The diagnosis is often made postoperatively, as in this case, when instead of adenocarcinoma, the pathological specimen demonstrates periductal T-cell infiltration, fibrosis, and acinar atrophy (Fig. 4) that result in stenosis of the pancreatic duct and/or distal bile duct. Fine-needle and core biopsy often fail to obtain material sufficient for positive pathological diagnosis.

Patients with AIP often present with symptoms similar to pancreatic cancer or pancreatitis, including

Figure 3 Percutaneous transhepatic cholangiogram shows strictures of central intrahepatic bile ducts with peripheral ductal dilation. The common hepatic duct and anastomosis are more normal in caliber.

Figure 4 Hematoxylin and eosin-stained specimens at 10 × (A) and 60 × (B) of resected pancreatic head presented demonstrate T-cell infiltration with periductal infiltration.

painless jaundice, abdominal pain, nausea, and vomiting. The disease presents most often in the fifth or sixth decades and appears to be more common in men than women.^{3,4}

Imaging findings of AIP are nonspecific. CT and magnetic resonance (MR) imaging may demonstrate a focal lesion in the pancreas or focal or diffuse enlargement of the pancreas. Unlike other causes of acute pancreatitis, inflammatory infiltration of the peripancreatic fat, pseudocysts, phlegmonous changes, and calcifications are rare. There may be delayed enhancement of the pancreatic parenchyma due to the presence of fibrosis and inflammation.⁵ Endoscopic retrograde cholangiopancreatography (ERCP) may show diffuse or segmental irregular narrowing of the pancreatic duct with or without associated biliary obstruction.

When the diagnosis of AIP is considered preoperatively, an elevated serum IgG₄ can clinch the diagnosis and potentially avoid major surgery. IgG₄ is the least common of the IgG subclasses, accounting for ~5% in normal patients.⁶ IgG₄ is known to be elevated in a handful of other conditions, including membranous nephropathy, pemphigus, atopic dermatitis, asthma, and some parasitic infections.⁶ Elevated serum IgG₄ has been found to be both sensitive (95%) and specific (97%) in the diagnosis of AIP in the appropriate clinical setting.⁶ The diagnosis may also be made on the basis of immunohistochemistry, as the plasma cell infiltrate stain for anti-IgG₄ monoclonal antibodies.⁷

AIP differs from other forms of pancreatitis because it demonstrates clinical response to corticosteroid therapy. Corticosteroid immunosuppression is usually started at 30 to 40 mg per day. The dose is tapered once response to treatment is confirmed. Treatment results in improvement of strictures in the majority of patients, as in the patient presented, whose recurrence was successfully treated with a course of oral prednisone. IgG₄ levels should decrease after treatment and may be used as a marker for disease activity. Repeat cross-sectional imaging 4 to 6 weeks following initiation of

therapy should be performed to evaluate response. Given the potential consequences of missing a pancreatic carcinoma, a mass or fullness that is unchanged or increases in size on steroid therapy should be considered for definitive surgery.

Recurrence of AIP is not uncommon, occurring in up to a third of patients following surgical resection. Patients with recurrent disease most commonly presented with recurrent jaundice after pancreaticoduodenectomy.² Finally, in a minority of patients, AIP is associated with other autoimmune diseases, including Sjögren's disease, retroperitoneal fibrosis, ulcerative colitis, systemic lupus erythematosus, and primary sclerosing cholangitis.

CASE 2

A 47-year-old man underwent hemicolectomy for invasive adenocarcinoma. Four of five lymph nodes in the resected specimen were involved by tumor, but at the time of surgery there was no evidence of systemic metastases. Contrast-enhanced CT performed 3 months after surgery demonstrated two metastases in the right hemiliver. The patient subsequently underwent six cycles of 5-fluorouracil/leucovorin and CPT-11 with stable disease. Right portal vein embolization was performed, and subsequently a right trisegmentectomy and wedge resection of a segment 2 lesion was performed with curative intent. A hepatic arterial infusion pump (HAIP) was placed for adjuvant chemotherapy.

Postoperatively, the patient underwent 2 months of pump chemotherapy with floxuridine (FUDR) in addition to systemic chemotherapy before his liver enzymes and bilirubin were noted to be elevated, precluding further pump treatment. The HAIP was filled with Decadron, but the bilirubin continued to rise. CT at that time demonstrated no evidence of metastatic disease to the liver (Fig. 5). ERCP was performed and revealed smooth strictures in the central bile ducts. Percutaneous biliary drainage (Fig. 6) and

Figure 5 (A) Representative image from contrast-enhanced computed tomography demonstrates postoperative hypertrophy of left liver, biliary ductal dilation, and no evidence of tumor recurrence. (B) Hepatic arterial infusion pump in left upper quadrant with catheter tip positioned in gastroduodenal artery.

percutaneous biopsy with forceps followed, but despite adequate drainage, the patient had progressive liver failure over the following 4 years. During this time, he had no evidence of tumor recurrence, and he was listed for a liver transplant. Five years after his hepatic resection, he underwent orthotopic liver transplantation. At last follow up almost 2 years later, the patient remains well and free of disease.

Case 2 Diagnosis Chemotherapy-induced biliary sclerosis.

Case 2 Discussion

Over 50% of patients with colorectal cancer develop hepatic metastases in the course of their disease. Disease is frequently limited to the liver and the cause of mortal-

ity in the majority of such patients. Therefore, strategies for regional control of liver metastases have played a large role in the treatment of this disease.

The placement of HAIPs or catheters allows the delivery of a high concentration of chemotherapy to the liver tumors to enhance antitumor effect while limiting systemic toxicity. HAIP chemotherapy improves both disease-free and overall survival in patients with unresectable colon cancer metastases limited to the liver compared with systemic chemotherapy alone⁸ and as adjuvant therapy following resection.⁹

Arterial infusion is an attractive strategy because liver tumors are supplied almost exclusively by hepatic arterial branches, in contrast to the normal liver parenchyma that derives the majority of nutrient flow from branches of the portal vein. Unfortunately, the bile ducts also receive most of their blood supply from the hepatic

Figure 6 (A) Endoscopic retrograde cholangiopancreatography with patient prone shows central stricture involving left hepatic duct (arrow). The common hepatic duct and common bile duct are normal in caliber (arrowheads). (B) Cholangiography at time of palliative percutaneous drainage.

artery, subjecting them to a high concentration of chemotherapy during chemoinfusion. This toxicity manifests as chemotherapy-induced biliary sclerosis (CIBS), which resembles idiopathic sclerosing cholangitis and occurs in 5 to 29% of patients.¹⁰⁻¹²

Concomitant infusion of dexamethasone or systemic therapy with the COX-2 inhibitor celecoxib decreases but does not eliminate the incidence of CIBS.^{13,14} Although cessation of pump chemotherapy may normalize hyperbilirubinemia, some patients require biliary drainage by endoscopic or percutaneous techniques.

The diagnosis of CIBS is challenging because it always occurs in patients with not only a cancer history but a history of liver metastases. The possibility of extrinsic compression from liver or nodal metastases, therefore, should be entertained as should the uncommon occurrence of a metastasis to the bile duct epithelium itself.

The clinical diagnosis is based on the appearance and location of the stricture, the absence of known recurrent disease involving the bile ducts or periductal hepatic parenchyma, and a transductal or percutaneous biopsy of the stricture that is negative for malignant cells. Common features of CIBS include a predominant involvement of the common hepatic duct and bifurcation with sparing of the distal common duct.¹⁵ Periductal fibrosis, cholestasis, and epithelial membrane blebbing, suggestive of large duct obstruction with minimal hepatocyte injury, are the typical findings at pathology.¹⁶

Treatment presents yet another challenge for patients and their physicians alike. Elevation of the serum bilirubin or alkaline phosphatase requires cessation of chemoinfusion. Endoscopic or percutaneous drainage may be performed in patients with signs or symptoms, including cholangitis, pruritus, or elevated bilirubin precluding systemic chemotherapy. Similar to idiopathic sclerosing cholangitis, the strictures are often resistant to balloon dilation and often require long-term catheterization.

CASE 3

A 74-year-old man from Singapore presented with painless jaundice and pruritus. Medical history included diabetes, hypertension, atrial fibrillation, coronary artery disease, and a depressed left ventricular ejection fraction. On presentation, serum bilirubin measured 11.5 mg/dL, alkaline phosphatase was 177, and serum glutamic-oxaloacetic transaminase/serum glutamic pyruvic transaminase (SGOT/SGPT) was 214/207. The white cell count was normal. Contrast-enhanced CT (Fig. 7) and MR imaging demonstrated biliary obstruction at the hilus without a discrete mass lesion. The working diagnosis was cholangiocarcinoma. Due to his multiple comorbidities, he was determined to be at high risk for surgical resection.

Figure 7 Contrast-enhanced computed tomography in patient with pruritus shows marked dilation of intrahepatic bile ducts with no discrete mass lesion.

Over the next 2 weeks, the patient's symptoms improved, and the serum bilirubin decreased to 2.5 mg/dL. One month later, his symptoms and hyperbilirubinemia recurred, and ERCP demonstrated smooth tapered narrowing of the central hepatic ducts with isolation of right posterior sectoral ducts from the remainder of the biliary tree. Right posterior biliary drainage and subsequently left-sided drainage (Fig. 8) were performed, and a specimen of clear green bile was sent for culture and cytology. The cytology was positive for numerous oval forms (Fig. 9) consistent with parasitic disease that was confirmed by culture to represent *Clonorchis sinensis* ova. No malignant cells were identified.

The patient underwent systemic therapy with Praziquantel and returned to his native Singapore with the drainage catheter in place. He is alive 2.5 years after the diagnosis.

Case 3 Diagnosis *Clonorchis sinensis* infection.

Case 3 Discussion

Infection with *Clonorchis sinensis*, or oriental liver fluke, is prevalent in Southeast Asia. Both humans and animals (dogs, pigs, cats, and rats) act as the definitive hosts. Adult worms deposit eggs into the bile ducts that enter the intestine and pass in the stool. In fresh water, eggs are ingested by snails. The eggs undergo metamorphosis and shed new parasites into the water that penetrate the scales of fish. The parasites become encysted in the muscle, and when a human or mammal eats the infected fish, the parasites encyst in the duodenum, finally migrating to the bile duct where they mature into adult worms that range in length from 10 to 25 mm. The fluke's life span is 20 to 25 years.

In the biliary tree, the fluke causes biliary hyperplasia and periductal fibrosis with sparing of the portal tracts. The complications of infection are

Figure 8 (A) Patient underwent drainage of isolated right posterior sector showing smooth tapered occlusion of right hepatic duct (arrow). (B) Left-sided drainage performed shows dilated left-sided ducts and confirms isolation from right bile ducts at the hilus.

Figure 9 Numerous oval forms (arrows) were found in cytology specimen, proven by culture to represent ova of *Clonorchis sinensis*.

most commonly related to biliary obstruction and bacterial superinfection. In addition to inflammation and fibrosis, the eggs and reactive mucin act as a nidus for stone formation and bacterial superinfection.

Clinical manifestations of clonorchiasis range from asymptomatic infestation to nonspecific abdominal pain and diarrhea to recurrent pyogenic cholangitis with biliary calculi and obstruction, and most recently with multiple liver nodules mimicking metastases.¹⁷ Peripheral eosinophilia is common. Several studies have demonstrated a causative relationship between infestation with *Clonorchis* and the development of cholangiocarcinoma.¹⁸

Cholangiographic findings include dilation of the intrahepatic bile ducts with sparing of the distal bile ducts. Oval filling defects representing adult worms are occasionally seen. The diagnosis is clinched by the presence of *Clonorchis sinensis* ova in the stool or biliary washings.

CONCLUSION

Many processes at the confluence of the right and left hepatic bile ducts can create a clinical malignant masquerade. The purpose of presenting these cases here was to highlight some of the uncommon, benign processes that can present a diagnostic challenge even to the most experienced physicians. In a minority of such cases, a definitive benign diagnosis can be made without operation on the basis of diagnostic tests, as in the case of AIP with elevated serum IgG₄ levels and a clinical and radiographic response to steroid treatment. Because it can be difficult to confirm a benign preoperative diagnosis in many cases, however, surgical resection is often indicated to avoid the potentially devastating consequences of missing a treatable cholangiocarcinoma.^{2,19}

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