CASE REPORT

Eosinophilic cholangiopathy: the diagnostic dilemma of a recurrent biliary stricture. Should surgery be offered for all?

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SUMMARY

A 63-year-old man presented with the initial diagnosis of autoimmune pancreatitis with obstructive jaundice. CT of the abdomen revealed an oedematous pancreas and dilated common bile duct (CBD), without gallstones. After failure of initial retrograde cholangiopancreatography, a percutaneous biliary catheter was inserted with good drainage. Subsequent endoscopic retrograde cholangiopancreatography (ERCP) revealed a 2 cm distal CBD stricture. A biliary stent was inserted past the stricture. Biopsy of the stricture, brush cytology of the bile duct and fine needle aspiration of pancreatic head under endoscopic ultrasound guidance were negative for malignancy. Autoimmune screen was negative as well. However, the patient represented with cholangitis requiring repeat ERCP and insertion of a second biliary stent. He finally underwent cholecystectomy with excision of the distal CBD and Roux-En-Y hepaticojejunostomy. Histology revealed diffuse eosinophilic cholecystitis and cholangitis. A retrospective review of the blood results showed persistent eosinophilia in full blood count measurements from presentation and persisting throughout the treatment period.

BACKGROUND

Eosinophilic cholangiopathy is a rare benign disorder of the biliary tract which can cause biliary obstruction. While some cases do respond to steroids, a significant number require surgery for definitive diagnosis and resolution of symptoms. This condition poses a difficult diagnostic challenge as it can masquerade as cholangiocarcinoma, with a histological confirmation of the diagnosis often not possible prior to surgery.

Sharing our experience with this case is also important as there are no clear management guidelines available for this condition so far. We suggest that surgery should be considered for definitive management of these patients, especially when malignancy cannot be excluded or with failed trial of steroids.

CASE PRESENTATION

A 63-year-old Chinese man presented to our institution with epigastric pain and jaundice for 1 week, as well as loss of appetite and loss of weight of 9 kg over the previous 3 months. There was no fever, vomiting or altered bowel habits. He had a medical history of hyperlipidaemia and type 2 diabetes mellitus on oral hypoglycaemic agents, with no family history of malignancy or inflammatory

bowel disease. On examination, he was noted to be jaundiced with mild epigastric tenderness.

INVESTIGATIONS

Blood tests were performed, with total white cell count of $6.24 \times 10^9/L$, serum amylase 289 U/L, total bilirubin 252 $\mu\text{mol/L}$ (normal 5–30 $\mu\text{mol/L}$) with direct bilirubin 136 $\mu\text{mol/L}$ (normal 2–7 $\mu\text{mol/L}$), alkaline phosphatase 652 U/L, aspartate transaminase 298 U/L and alanine transaminase 453 U/L. Hepatitis markers were negative. Contrast-enhanced CT of the abdomen showed acute pancreatitis, with dilation of the CBD, common hepatic duct (CHD) and intrahepatic ducts without radio-opaque biliary or gallbladder stones (figure 1).

DIFFERENTIAL DIAGNOSIS

Initial impression was that of pancreatitis with either reactive oedema of the adjacent bile duct or extrinsic compression by the oedematous pancreatic head. MRI of the pancreas and MR cholangiopancreatography (MRCP) revealed no pancreatic head mass, with the site of obstruction noted at distal CBD just proximal to the ampulla of Vater. Ca 19-9 was elevated at 43.3 U/mL (normal 0–30 U/mL). In view of the possibility of a malignant CBD stricture, an endoscopic retrograde cholangiopancreatography (ERCP) was performed, but the guidewire could not be advanced past the obstruction. Hence, a percutaneous biliary drainage catheter (PTC) was inserted for decompression. Bile cytology from the catheter was negative for malignant cells. Endoscopic ultrasound (EUS) showed an oedematous pancreatic head without a discrete mass. Fine needle aspiration cytology (FNAC) of the pancreatic head was also negative for malignant cells.

Biochemical markers of obstructive jaundice improved with external drainage and the PTC was subsequently internalised past the obstruction with an 8 French biliary catheter. Repeat MRCP/MRI pancreas showed significant biliary decompression and resolving pancreatitis. Repeat ERCP was successfully attempted, with the removal of internalised PTC drainage catheter. There was a 2 cm long distal CBD stricture with the proximal CBD dilated to 11 mm (figure 2). The pancreatic duct was not dilated and measured 1.7 mm. Intraductal ultrasound showed circumferential narrowing and thickened walls of the distal bile duct at the site of stricture. Brush cytology $\times 2$ was performed followed by forceps biopsy of the stricture. A 10 French 8 cm CBD stent was inserted with good

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Figure 1 Contrast-enhanced CT of the abdomen showing acute pancreatitis, worse in the pancreatic head, with dilation of the common bile duct, common hepatic duct and intrahepatic ducts. This was initially attributed to reactive oedema of the adjacent bile duct or extrinsic compression by the bulky pancreatic head.

drainage (figure 3). All cytology and biopsy results revealed benign ductal columnar cells. Another repeat EUS and FNAC of the pancreatic head was performed which once again proved benign.

In view of the negative workup for malignancy, an autoimmune cause was considered and a course of oral prednisolone was started with a tapering dose over 3 months' duration. During this period, the liver function test improved. CT pancreas also showed a resolution of the pancreatitis. However, the autoimmune workup including extractable nuclear antigen profile, antinuclear antibody screen and immunoglobulin G subtype 4 were negative.

Three months after cessation of steroids, the patient represented with sepsis, cholangitis and hyperbilirubinaemia. CT of the liver did not show stent migration and there was diffuse mild thickening of the CBD. There was no evidence of recurrent

pancreatitis and serum lipase was normal. Another ERCP was performed with irrigation of the existing stent and insertion of a new 7 French 7 cm CBD stent alongside the existing stent (figure 4) for purpose of stricture dilation.

TREATMENT

After discussion at a hepatobiliary meeting, the patient was offered surgery in view of recurrent stricturing of the bile duct not responsive to conservative management. He underwent open cholecystectomy, excision of supraduodenal CBD and Roux-en-Y hepaticojejunostomy. At laparotomy, a thickened and fibrotic cystic duct was found. The CHD was also noted to be thickened and dilated at 1.5 cm. The frozen section of the excised CBD and cystic duct were negative for malignancy. CBD exploration was performed and choledochoscopy did not reveal any obvious stricture or mucosal lesion.

Histopathology of the gallbladder showed chronic cholecystitis affecting its entire wall from the cystic duct resection margin to the fundus, with predominantly eosinophilic infiltrate intermixed with mature plasma cells, few lymphocytes and rare neutrophils. The distal CBT wall showed fibrosis with severe chronic inflammatory infiltrate predominated by eosinophils and plasma cells (figures 5 and 6). There were no signs of parasitic activity or eosinophilic microabscesses.

OUTCOME AND FOLLOW-UP

A retrospective review of his full blood counts revealed eosinophilia of 9.7% (normal range 0–6%) on initial presentation and persistently elevated percentage eosinophilia and absolute eosinophil count up to a maximum of 25.4% and $1.9 \times 10^3/\mu\text{L}$ (normal range $0.0\text{--}0.4 \times 10^3/\mu\text{L}$), respectively, throughout his treatment period.

Our patient's symptoms resolved with liver function tests normalising during an uneventful recovery period. He was discharged on postoperative day 7. No evidence of disease remains after a follow-up period of 6 months at the time of writing.

Figure 2 Endoscopic retrograde cholangiopancreatography fluoroscopy showing a 2 cm distal common bile duct stricture with proximal dilation of the bile duct to 11 mm.

Figure 3 Endoscopic retrograde cholangiopancreatography fluoroscopy showing a 10 French 8 cm biliary stent inserted past stricture.

Figure 4 Endoscopic retrograde cholangiopancreatography fluoroscopy showing a second stent inserted alongside the old one in order to attempt stricture dilation.

Figure 5 Image displaying $\times 40$ magnification, showing chronic inflammatory infiltrate predominated by eosinophils and plasma cells (above; distal common bile duct wall, H&E stain). Image displaying $\times 20$ magnification, showing fibrosis and chronic inflammation (below). Distinct muscle layers are absent and there are glands or ducts surrounded by similar concentric layers of fibrocollagen showing infiltrates of eosinophils and mature plasma cells. No significant epithelial dysplasia is present and no malignancy is seen. No parasite is seen.

Figure 6 The gallbladder measured $8.0 \times 3.0 \times 2.0$ cm, showing chronic cholecystitis affecting its entire wall from the cystic duct resection margin to the fundus. The inflammatory infiltrate is composed of large numbers of eosinophils well intermixed with mature plasma cells, a few lymphocytes and rare neutrophils. Many of the eosinophils are degranulated; however, eosinophilic microabscess formation is not seen. Reactive fibrosis is present and rings of collagen fibres surround Rokitansky-Aschoff sinuses. No significant epithelial dysplasia is present. Mucous gland metaplasia is noted. There is no parasite seen. The cystic duct with thickened walls is noted measuring 7.0 mm in diameter with the cystic duct opening measuring 2.0 mm in diameter (above image—gallbladder wall; below image—cystic duct margin, $\times 20$ magnification, H&E stain).

DISCUSSION

Eosinophilic cholangiopathy is a rare benign disorder of the biliary tract and encompasses the entities of eosinophilic cholecystitis and eosinophilic cholangitis, characterised by diffuse eosinophilic infiltration of the gallbladder wall and bile ducts, respectively. Eosinophils can sometimes be present among the inflammatory infiltrate of the gallbladder wall, but it is unusual for it to be the predominant cell type and rarely will there be almost pure eosinophilia. This rare cause of acute cholecystitis cannot be distinguished clinically from other forms of cholecystitis.

Occasionally, there may be associated eosinophilic cholangitis with symptoms of obstructive jaundice. To our knowledge, isolated eosinophilic cholangitis without cholecystitis has not been previously documented.

First described by Leegard¹ in 1980, only 25 cases of eosinophilic cholangiopathy have been published in the literature since then, including this study. The exact cause for this disease

Table 1 Reported cases of eosinophilic cholangitis managed with biliary resection and Roux-en-Y

Study	Patient	Imaging findings	Laparotomy findings	Surgery	Follow-up (months)
Rodgers <i>et al</i> ²	50F	MRI: 2 cm CHD stricture extending into RHD, with 2 cm mass	Thickening of CBD, CHD, RHD LHD and GB	Cholecystectomy, excision of extrahepatic biliary tree, bilateral Roux-en-Y HJ	2
Shanti <i>et al</i> ¹⁴	33M	ERCP: stricture of RHD, LHD MRCP: 3×4 cm mass at biliary confluence	Multilobulated mass involving porta hepatis and GB fundus, encasing and obstructing the CHD Multiple similar masses in the GB wall	Cholecystectomy, excision of extrahepatic biliary tree, bilateral Roux-en-Y HJ	3
Shanti <i>et al</i> ¹⁴	57F	ERCP: irregularity of extrahepatic biliary tree, small corkscrew bile duct	Narrowed CBD with surrounding 5×3 cm fibrous mass encasing porta hepatis	CBD with mass dissected up to proximal CHD and excised. Roux-en-Y HJ	6
Chen <i>et al</i> ¹¹	55M	ERCP: multiple strictures of IHDs, hilum, CBD MRCP: thickened wall of distal CBD	4×5×4 cm mass involving the distal CBD, pancreatic head, and mesenteric root	Cholecystectomy, Roux-en-Y HJ	19
Nashed <i>et al</i> ⁷	33M	MRCP: focal stricture of CHD at level of cystic duct entry EUS: mass in proximal CHD with wall thickness 4.7 mm	Not stated	Cholecystectomy, portal lymphadenopathy, en bloc CBD resection, Roux-en-Y HJ	40
This study (2013)	63M	ERCP: 2 cm distal CBD stricture, proximal bile duct dilated to 11 mm. EUS: thick-walled distal CBD at site of stricture	Thickened, fibrotic cystic duct. CHD thickened and dilated at 1.5 cm. Choleldochoscopy: no stricture or mucosal lesion seen	Cholecystectomy, Excision of supraduodenal CBD, CBD exploration, Roux-en-Y HJ	6

CBD, common bile duct; CHD, common hepatic duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; F, female; GB, gallbladder; HJ, hepaticojunostomy; IHD, intrahepatic duct; LHD, left hepatic duct; M, male; MRCP, MR cholangiopancreatography; RHD right hepatic duct.

remains unknown, but there has been previously reported association with cholelithiasis,² idiopathic hypereosinophilic syndrome,³ parasitic infection^{4 5} and allergy.⁶ Symptomatic eosinophilic infiltration of organs other than the biliary tree has also been reported to occur in association, either presenting simultaneously or up to 14 years after treatment of eosinophilic cholangiopathy. These include the stomach,^{7 8} kidneys,³ ureters⁹ and pericardium.¹⁰

Eosinophilic cholangitis remains a diagnostic dilemma as it can mimic cholangiocarcinoma or autoimmune cholangiopathy in causing biliary obstruction. Rodgers *et al*² accurately stated that eosinophilic cholangiopathy is a 'malignant masquerade'. Considerable effort is often employed to exclude malignancy in such cases, similar to our experience. Peripheral eosinophilia is present in most patients,⁷ and bone marrow biopsy can demonstrate eosinophilic infiltration as well.^{8 11} Although this may provide a diagnostic clue to the astute physician, its presence is neither sensitive nor specific and malignancy itself may also lead to eosinophilia.¹²

Matsumoto *et al*¹³ proposed the diagnostic criteria of (1) wall thickening or stenosis of the biliary system; (2) histopathological findings of eosinophilic infiltration; and (3) reversibility of biliary abnormalities without treatment or following steroid treatment. However, histological confirmation of eosinophilia prior to surgery is often not possible with EUS, bile duct biopsies and brushings usually being non-diagnostic. There have been reports of successful response to oral corticosteroids.^{7 13} Previously, Butler *et al*¹⁰ proposed that a 'diagnostic' trial of steroids may be considered prior to surgical intervention. No diagnostic dose of oral corticosteroids, nor treatment dose or duration, has been recommended for this condition thus far.

The surgical treatment for eosinophilic cholecystitis is cholecystectomy, which can be performed laparoscopically, with uniformly good results and symptomatic relief.⁷ As for eosinophilic cholangiopathy, only six patients^{2 7 11 14} (table 1) have been documented in the literature to undergo surgery. All these patients underwent extrahepatic bile duct excision with Roux-en-Y hepaticojunostomy in order to rule out either cholangiocarcinoma or to definitely treat recurrent biliary

strictures. Only postoperatively was the diagnosis of eosinophilic cholangiopathy confirmed on histology. No evidence of malignancy was found. Nevertheless, these patients had uneventful postoperative periods and did not have recurrence of disease for a follow-up period ranging from 2 months to 40 months. Raptou *et al*⁵ described a case of eosinophilic cholangitis secondary to hydatid disease surgically treated by lobectomy with Roux-en-Y hepaticojunostomy and is not included in this table.

While a diagnostic trial of steroids can be attempted, from our experience and the available literature, a definitive treatment with surgery seems to be the best option for achieving definite diagnosis as well as prevention of recurrence. Furthermore, this will allow avoidance of complications of repeated steroid treatment and also definitely exclude malignancy. Also, patients who undergo treatment should be followed up long term to ensure no recurrence of the disease or manifestations in other organs.

Learning points

- ▶ Eosinophilic cholangitis is a rare cause of biliary obstruction, and should be considered as a differential in cases of obstructive jaundice with peripheral eosinophilia.
- ▶ Considerable effort and resource may be employed to elucidate the cause of biliary stricture and to rule out malignancy, but definitive diagnosis can often only be made after surgery.
- ▶ Surgery seems to be the best option for management of eosinophilic cholangitis and prevention of recurrence, as well as to avoid complications of long-term steroid treatment.

Contributors IS-E performed the literature search on the subject and wrote the draft. He was also involved in the patient's follow-up care. AKHC and SST were involved in the patient's initial care, surgical and perioperative management. AKHC is the guarantor and revised the draft. WTP provided histopathological analysis of the specimens.

Competing interests None.

Patient consent Obtained.

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