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Atypical Presentation of a Rare Disease: Eosinophilic Cholangitis Posing as a Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1 **Judie Noemie Hoilat**
ABDEF 1 **Gilles Jad Hoilat**
ABDF 2 **Saeed AlQahtani**
BDEF 3 **Hussah F. Alhussaini**
ABDEF 2 **Saleh I. Alabbad**

1 College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
2 Department of Surgery, Section of Liver and Small Bowel Transplantation and Hepatobiliary-Pancreatic Surgery, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
3 Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Corresponding Authors: Judie Noemie Hoilat, e-mail: jhoilat@alfaisal.edu, Saleh Ibrahim Alabbad, e-mail: salehalabbad@kfshrc.edu.sa, Hussah F Alhussaini, e-mail: halhussaini@kfshrc.edu.sa
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Patient: Male, 84
Final Diagnosis: Eosinophilic cholangitis
Symptoms: Abdominal pain • fatigue • fever • loss of appetite • nausea • vomiting • weight loss
Medication: —
Clinical Procedure: Left hepatectomy with caudate lobe resection
Specialty: Gastroenterology and Hepatology

Objective: Rare disease

Background: A variety of benign etiologies of biliary stricture may initially be mistaken for hilar cholangiocarcinoma. Consequently, many patients undergo surgery for a benign disease that could have been treated medically. Eosinophilic cholangitis (EC) is an uncommon, benign, self-limiting disease that should be considered when approaching a case of obstructive jaundice since it causes biliary stricture formation. Transmural eosinophilic infiltration of the biliary tree is characteristic of EC. It may initially be indistinguishable from hilar cholangiocarcinoma.

Case Report: We present a rare case of an 84-year-old male who was referred to our hospital for abdominal mass investigation with the provisional diagnosis of cholangiocarcinoma. During the workup, the index of suspicion for malignancy remained high as the typical laboratory and radiological findings for benign causes of biliary stricture were not present. Hence, the patient underwent left hepatectomy with caudate lobe resection and received a retrograde diagnosis of EC.

Conclusions: This case demonstrates that EC could present in the elderly with cardinal signs of cancer and absence of the typical findings of EC which was not previously reported. Since only 70% of patients present with peripheral eosinophilia, we stress on the importance of implementing diagnostic criteria for EC in the setting where peripheral eosinophilia is absent. Furthermore, this disorder has been reported to respond well to steroid therapy, hence, diagnostic criteria for EC would provide another treatment option for elderly and/or those who are not fit for surgery.

MeSH Keywords: Bile Duct Diseases • Cholangitis • Constriction, Pathologic

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/906130>



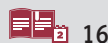
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Background

When approaching a biliary stricture, one must consider benign as well as malignant etiologies since they can be clinically identical. Eosinophilic cholangitis (EC) is an uncommon, benign, self-limiting disease that causes biliary stricture formation in the intra or extrahepatic biliary tract which results in obstructive jaundice. Transmural eosinophilic infiltration of the biliary tree is a characteristic of EC. Even though the age of diagnosis normally ranges between teenage years to late 60s, this disease frequently presents in the fourth to fifth decade [1].

Few reported cases of EC are diagnosed based on reversibility of biliary abnormalities and clinical improvement following a trial of corticosteroid therapy. In the majority of reported cases, malignancy could not exclude based on imaging modalities and biopsies, hence they were treated surgically and received a retrograde diagnosis.

We report a case of an 84-year-old male who had cardinal signs of cancer in the absence of typical findings of EC.

Case Report

A previously healthy 84-year-old Saudi male was referred from a primary care facility for abdominal mass investigation. He presented with a two-month history of abdominal pain (not radiating), fatigue getting worse with time, and generalized body ache. Associated symptoms included nausea, vomiting (minimal amounts, non-bloody), weight loss (by observation; not measured), poor appetite, dysuria, on and off headache and fever. He had no history of smoking, alcohol consumption or allergies.

He had a past medical history of ischemic heart disease status post catheterization around 20-years ago and angioplasty

for single vessel disease. He remained asymptomatic after surgery and not on any medication; he also had benign prostatic hypertrophy and a past surgical history of appendectomy.

On physical examination he was vitally stable with mild bradycardia, afebrile, not jaundiced and had mild epigastric tenderness. To exclude ulcerative colitis, a flexible sigmoidoscopy was performed which revealed no pathology.

Investigations

Pertinent laboratory tests revealed a full white blood cell count of $3.57 \times 10^9/L$ (normal range 3.90×10^9 to $11 \times 10^9/L$) with a differential of 47% neutrophils, 30% lymphocytes, and 9% eosinophils. The rest of the complete blood count showed hemoglobin level of 144 g/L, hematocrit level of 41.7%, and platelet count of $349 \times 10^9/L$.

Liver function tests showed a total bilirubin level of 5.4 $\mu\text{mol/L}$ (normal range 0 to 21 $\mu\text{mol/L}$); direct bilirubin, 2.8 $\mu\text{mol/L}$ (normal range 0 to 5 $\mu\text{mol/L}$); alanine transaminase (ALT), 22 U/L (normal range 10 to 45 U/L); aspartate transaminase (AST), 16.8 U/L (normal range 10 to 45 U/L). Alkaline phosphatase and gamma glutamyl transferase (GGT) were markedly elevated with values of 132.7 U/L (normal range 50 to 116 U/L) and 214 IU/L (normal range 11 to 49 IU/L), respectively. Serum amylase and lipase levels were within normal limits.

Tumor markers showed elevated levels of carcinoembryonic antigen (CEA), 71.050 U/mL (normal range 0 to 27 U/mL), whereas carbohydrate antigen 19-9 (CA19-9) and alfa-fetoprotein (AFP) levels were unremarkable.

Ferritin level was markedly elevated, 889.9 $\mu\text{g/L}$ (normal range 30 to 400 $\mu\text{g/L}$). Coagulation profile as well as blood chemistry values were all normal. Urinalysis revealed elevated pH 7.5

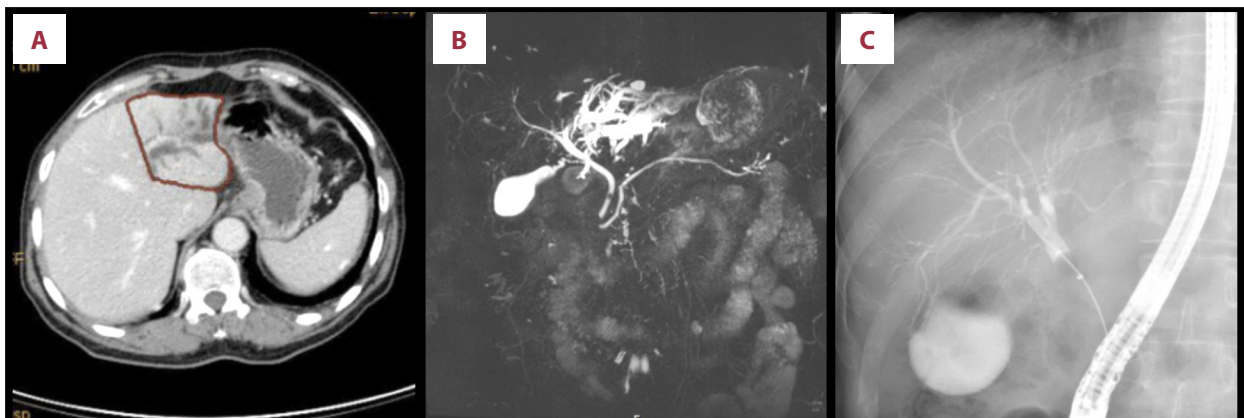


Figure 1. (A) Computed tomography of abdomen and pelvis (CT); (B) magnetic resonance cholangiopancreatography (MRCP), and (C) endoscopic retrograde cholangiopancreatography (ERCP) showing a focal dilation of the biliary tree to the left lobe through the suggestion of subtle ill-defined enhancing mass lesion at the level of the liver hilum.



Figure 2. Positron emission tomography–computed tomography (PET/CT) showing no hypermetabolic lesions.

(normal range 4 to 7), with other results unremarkable and culture was negative.

Computed tomography (CT) (Figure 1A) of abdomen and pelvis revealed focal dilation of the biliary tree to the left lobe through the suggestion of subtle ill-defined enhancing mass lesion at the level of the liver hilum, suggestive of cholangiocarcinoma; several small low attenuation lesions in segment 2, 4A, 6; the largest was segment 2 measuring about 10 mm in maximum diameter, benign in nature, no definite liver metastasis, several prominent, but not enlarged porta hepatis lymph nodes; the largest seen anterior to the portal vein measuring about 7 mm in short axis. The spleen appeared unremarkable with several areas of calcification, but no focal lesions. The pancreas, gallbladder, adrenal glands, and both kidneys appeared

unremarkable. Evidence of soft tissue stranding was seen within the omentum in the midline, but no obvious disease. No distant metastasis and no gastric masses. These findings were confirmed by a magnetic resonance cholangiopancreatography (MRCP) (Figure 1B), which additionally revealed a left main duct stricture and surrounding soft tissue enhancement, concerning for cholangiocarcinoma in the left hepatic lobe.

Positron emission tomography-computed tomography (PET/CT) (Figure 2) in conjunction with previous MRI, revealed a soft tissue lesions within the main left biliary duct but did not show any FDG activity; however, that does not exclude cholangiocarcinoma. There was an 8 mm mildly active porta hepatis lymph node. The remaining full body was unremarkable.

An endoscopic retrograde cholangiopancreatography (ERCP) (Figure 1C) was performed at which time a Brush biopsy was obtained revealing no malignant cells.

Endoscopic ultrasound-guided fine needle aspiration (EUS guided FNA) was then performed revealing the presence of rare benign ductal epithelium and benign mesothelial cells, as well as a background of mixed inflammation including many eosinophils in the liver hilum bile duct.

Treatment

Since the index of suspicion for malignancy remained high, the patient underwent abdominal exploration and there was no evidence of peritoneal deposit or liver metastasis. After mobilization of the left lobe, multiple lesions were found especially in segment #3, #4b, and #5 and a big lymph node was identified along the proper hepatic artery as well as localized peritoneal deposit over the porta hepatis.

Frozen section of proper hepatic lymph node, right hepatic lobe, peritoneal deposit, and a Tru-Cut biopsy from the segment #4b and #5 revealed no evidence of malignancy. Hence, the patient underwent left hepatectomy with caudate lobe resection. To restore drainage of the right system, Roux-en-Y hepaticojejunostomy was performed. The patient's surgery was uneventful, and he was discharged home on postoperative day 8.

Pathology report

The resected left lobe weighed 266 g and measured 13×9×4 cm. The cut surface of the liver tissue revealed white scattered spots in the area of portal tracts involving most of the liver parenchyma. However, no definite masses were noted. The microscopic examination showed classical features of sclerosing cholangitis with typical onion-skin fibrosis around most of the large and medium sized bile ducts as seen in Figures 3 and 4. The periductal fibrosis was heavily infiltrated by sheets of

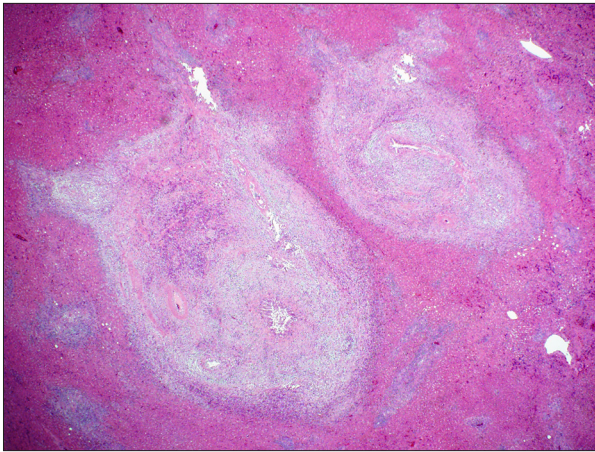


Figure 3. Severe degree of periductal onion skin fibrosis (hematoxylin and eosin stain displaying 2× magnification).

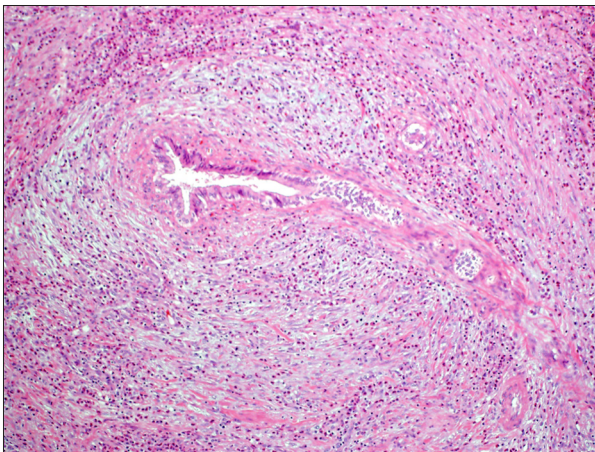
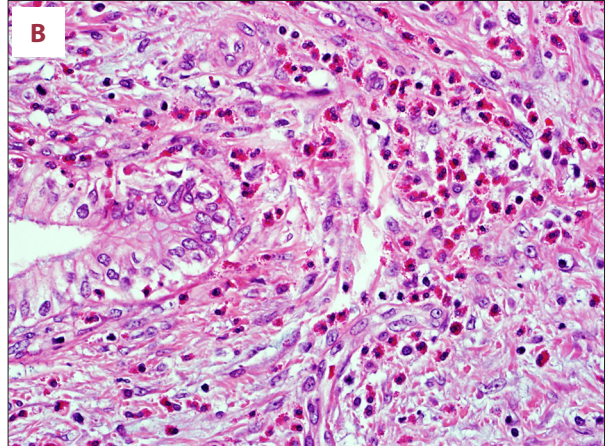
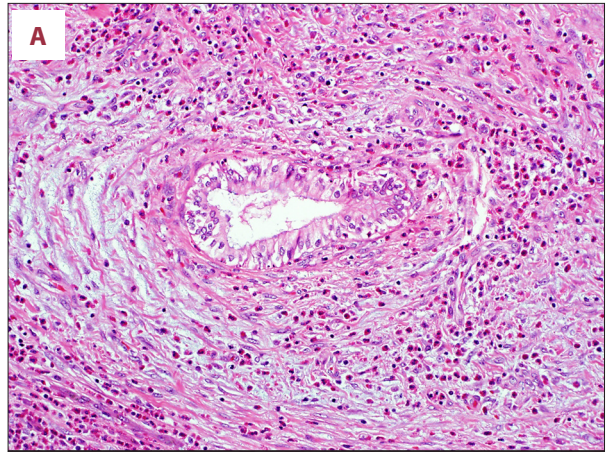


Figure 4. The inflammatory infiltrates around the partially damaged bile duct are mostly eosinophilic cells (hematoxylin and eosin stain displaying 10× magnification).

eosinophilic cells which accounted for more than 40 cells per high-power field (HPF). The cells were focally infiltrating the bile duct epithelium, as seen in Figure 5A, 5B. In places, the damaged bile duct contained cholesterol rich stones which were blocking most of the lumen, as seen in Figure 6.

Follow-up

At six-months follow-up, the patient did not complain of any symptoms and his liver function tests (LFTs) were within normal limits. The MRCP performed at that time showed normal liver parenchyma without any suspicious lesions or bile duct dilation.



Figures 5. (A, B) The eosinophilic count exceed 40 cells per HPF (hematoxylin and eosin stain displaying 40× magnification).

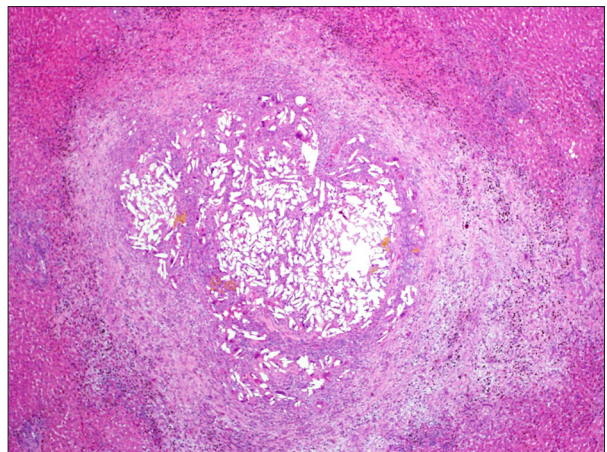


Figure 6. The damaged bile ducts contain cholesterol rich stones which are blocking most of the bile duct lumen as shown (hematoxylin and eosin stain displaying 4× magnification).

Discussion

Eosinophilic cholangitis (EC) is an uncommon, benign, self-limiting cause of biliary stricture characterized by transmural eosinophilic infiltration of the biliary tree which may result in obstructive jaundice. The severity and prognosis vary considerably, and it may affect part or the entire biliary tree. In 2003, Vauthy et al. found only four cases with confined involvement of the biliary tree reported in the literature [2]. Rapidly progressing EC may lead to hepatotoxicity and fibrosis leaving liver transplantation as the only cure [3]. Its pathogenesis remains poorly understood [4].

Albot et al. described eosinophilic cholecystitis in 1949 [5] but it was not until 1980 that Leegaard et al. reported the first case of EC [6]. Nashed et al. conducted a study where they collected around 23 cases of EC revealing that this disease was slightly more prevalent in men M: F (1.6: 1) and that the most common presenting symptom was abdominal pain followed by jaundice. Around 69.6% of patients demonstrated peripheral eosinophilia and 30.4% had normal serum eosinophil counts [4].

A wide range of biliary diseases can mimic cholangiocarcinoma (CCA); benign diseases are found in about 10% of patients who undergo surgery because of hepatic hilar strictures [7].

The diagnosis of EC is based entirely on histological findings. Although the presence of peripheral eosinophilia may aid in the diagnosis, it is absent in 30% of the reported cases and is neither specific nor sensitive for EC. Presence of elevated levels of eosinophils in the blood along with stricture in the biliary tree are common findings of parasitic infections (i.e., *Ascaris* spp) which could easily be ruled out by culturing parasites obtained from stool [4,8]. EC causes a diagnostic challenge because histological confirmation of the diagnosis is often not possible prior to surgery [7].

Certain laboratory tests help distinguish between benign and malignant causes of biliary obstruction; i.e., elevated tumor markers in the serum points towards a malignant etiology. However, it has been reported that CA19-9 may also be elevated in benign conditions such as ascending cholangitis and pancreatitis [9,10].

There are many available imaging modalities that are helpful in visualizing and evaluating the biliary system. Noninvasive imaging modalities can demonstrate common nonspecific findings of EC such as bile duct wall thickening (segmental or diffuse) on US, and contrast enhanced CT and MRCP with or without biliary dilation. These findings can also be seen in malignant processes, hence the need to obtain a brush cytology and tissue biopsy by means of performing invasive imaging modalities such as ERCP [11].

While MRCP is useful in demonstrating an irregular narrowing of the bile duct, ERCP and percutaneous transhepatic cholangiography (PTC) provide additional information such as irregularities of the common bile duct and the intrahepatic ducts as well as the length and site of biliary stricture [2,12].

The single operator spyglass system has been shown to be a powerful tool to differentiate between benign and malignant strictures. Kurland et al. conducted a study of 17 patients who were primarily diagnosed to have a biliary stricture of benign etiology based on cytology. After performing a spyglass-directed biopsy on these patients, four of them were found to have strictures of malignant etiologies [11].

Matsumoto et al. revealed a characteristic feature of EC that helped rule out malignancy: staining of a parenchymal echo in the bile duct wall on contrast-enhanced ultrasound (CEUS). However, they suggested the following requirements to accurately diagnose EC: 1) thickening of the biliary wall or narrowing of the biliary tree; 2) eosinophilic infiltration on histopathology; and 3) regression of the stricture or resolution of other biliary abnormalities in the absence of treatment or subsequent steroid therapy [4,13].

Even though EC is a self-limiting disease, it has a variable course, making precise treatment recommendations difficult. The challenge remains to exclude malignancy, which is not always possible with various imaging modalities and biopsies. Hence, mandatory surgical intervention is an effective and definitive measure of treating EC if there is diagnostic uncertainty. According to the literature, two cases of EC described a stricture in the common hepatic duct that regressed spontaneously without any medical intervention within three weeks [14,15], but most of the published cases of EC were treated surgically and received a retrograde diagnosis, as in the present case [4].

Seow-En et al. suggested that the best option to simultaneously treat a stricture, exclude malignancy, and attain a definite diagnosis of EC is surgical intervention. They also described the advantages of surgery over medical therapy, indicating that medical treatment does not eradicate the chance of recurrence and that it could put patients at risk of complications of repeated steroid therapy.

Butler et al. suggested that prior to undergoing surgery, a diagnostic trial of oral corticosteroid should be considered. However, the dose and duration of treatment are yet to be determined due to the poor understanding of its natural course [8,14,15].

Our case was an elderly man with the cardinal findings of cancer in the absence of the typical findings of EC (jaundice, elevated bilirubin levels, and peripheral eosinophilia) which made it challenging to exclude malignancy by clinical and radiological

findings. Hence it was imperative for this patient to undergo surgical exploration.

Conclusions

In conclusion, EC is an uncommon, benign, and self-limiting cause of biliary stricture. Although this disease has a good response to corticosteroid therapy, it often mimics cholangiocarcinoma which makes reaching a definite diagnosis by clinical and radiological findings difficult. Hence most cases are treated surgically and receive a retrograde diagnosis. Since only 70% of patients present with peripheral eosinophilia, we stress the importance of implementing diagnostic criteria for EC in a setting where peripheral eosinophilia is absent, as in the present case.

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Conflict of interest

None.