Case Report and Review of the Literature

The Great Imposture: Eosinophilic Cholangitis

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A B S T R A C T

Eosinophilic Cholangitis (EC) is a rare, benign disease often mistaken for cholangiocarcinoma as clinically and radiologically EC resembles cholangiocarcinoma. Often, extensive hepatobiliary resections for a presumed malignancy are completed; however, with appropriate diagnosis EC can be managed medically. We present two cases of EC with a comprehensive literature review and a proposed diagnostic decision algorithm for EC by which to evaluate suspicious lesions with biliary obstruction and potentially avoid surgery for this benign disease.

Introduction

Eosinophilic Cholangitis (EC) is described as an eosinophilic infiltrative process of the biliary tree resulting in fibrosis, stricture, obstruction and often presenting with a tumor-like appearance. EC is primarily identified as an isolated lesion and may also present with concomitant peripheral eosinophilia and/or extra-biliary involvement of the kidneys, ureters, pancreas or lymph nodes [1]. These rare lesions are often mistaken clinically and radiologically for cholangiocarcinoma, resulting in patients undergoing extensive surgical resections for presumed malignancy [2]. If a diagnosis can be confirmed, however, patients may be successfully medically managed [1].

Case Reports

A 49-year old Caucasian male presented with epigastric/right-upper quadrant (RUQ) pain; all labs, including WBC, LFTs, AFP, CA 19-9 and CEA, were within normal limits. Eosinophil count on differential was 3.4% (normal value between 1-6%). Intrahepatic biliary stricture (Figure 1a) in the left lobe of the liver was identified on CT and an

infiltrative "mass" within liver segments 4a and 4b extending into segments 2 and 3 was noted on MRI. Additionally, the obstruction and delayed contrast extravasation was noted (Figure 1b) suggesting cholangiocarcinoma and precluding any further workup. A left hepatic lobectomy with portal lymph node dissection and cholecystectomy was completed. Pathology identified a lymphocytic inflammatory cell infiltrate within the left lobe of the liver with an increased number of eosinophils. Foamy macrophages were present in the lamina propria. Additionally, in the extensive sampling of the bile ducts, fibrosis and eosinophils were present with a minimal amount of inflammation (Figure 2). Following surgery, the patient experienced an uncomplicated recovery and has remained symptom free 6-months post-op.

Our second patient is a 47-year old Caucasian female who presented with pruritis over 2-months. Total bilirubin was elevated (3.8; normal values 0.3-1.9mg/dl) as was the AST (260; normal range 10-40U/L). WBC and eosinophil (1.2%) counts were normal. CT and MRI showed severe intra-hepatic biliary dilation secondary to obstruction at the hepatic hilum. ERCP with sphincterotomy and stent placement in the common hepatic duct were completed (Figure 3) and a brush cytology was

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procured. Pathology identified non-diagnostic reactive ductal epithelium. Due to diagnostic uncertainty and concern for a cholangiocarcinoma, a left hepatic lobectomy with common bile duct resection and roux-en-Y hepaticojejunostomy was performed. Pathology reported a dense periductal infiltrate rich in eosinophils with associated reactive epithelial changes and periductal fibrosis along the left hepatic duct, consistent with eosinophilic cholangitis (Figure 4). At 5-year follow-up, the patient has remained disease free.
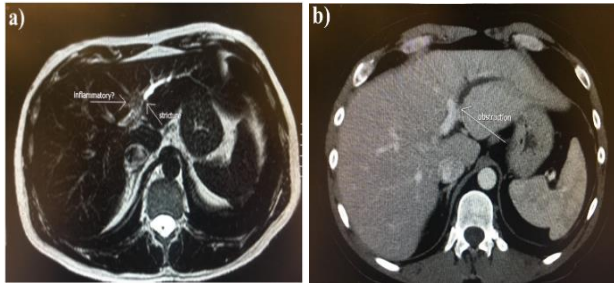

Figure 1: Intrahepatic biliary dilation. Abdominal MRI of patient #1 in our case series demonstrating a) stricture and apparent mass or inflammation in the bile duct b) evidence of the obstruction; note the apparent enhancement exhibiting delayed contrast extravasation.
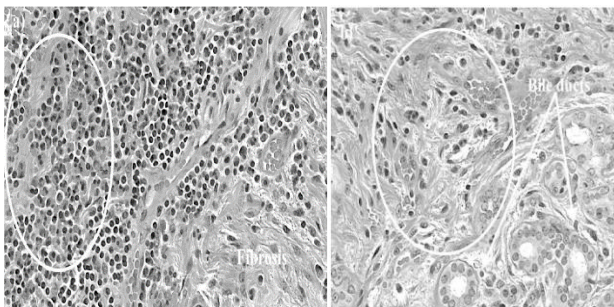

Figure 2: EC identified on a resection specimen. Histology from patient #1 exhibiting a) extensive eosinophils with the bi-lobed nuclei and extensive granules as noted (circled) along with fibrosis; visualized at 40x. b) eosinophilia with limited inflammation (circled), extensive fibrosis and multiple sections of the bile duct; visualized at 40x.
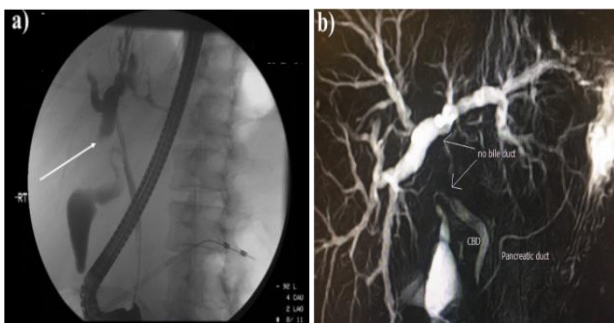

Figure 3. Biliary dilation. Imaging from patient #2 in our case series illustrating a) dilated left biliary system as imaged by ERCP. Note the stent in the CBD and the stricture along the common hepatic duct proximal to bifurcation of left and right hepatic ducts. Dilation of the right and left hepatic ducts proximal to the stricture help to confirm presence of obstruction. b) the stricture appears to be present at the hilum of the common bile duct (CBD); no definitive stricture in the right hepatic duct is noted.
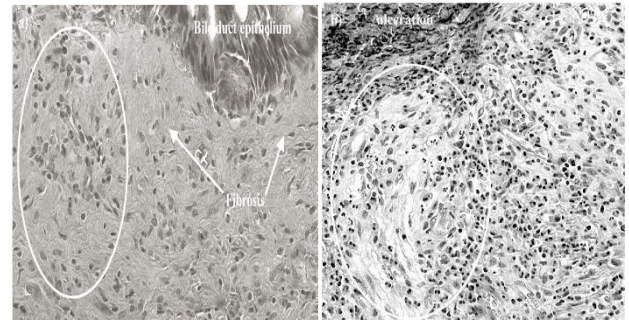

Figure 4: H&E stain of EC. Specimens from patient #2 highlighting eosinophilic infiltrate and fibrosis. a) biliary ductal endothelium surrounded by underlying mononuclear inflammatory cells with eosinophils and fibrosis, hallmarks of ECC (20x image). b) ulceration of the duct proximal to fibrosis and eosinophilic infiltrate (20x image).

Discussion

Eosinophilic Cholangitis (EC) is a rare, benign disease of transmural eosinophilic infiltration of the biliary tree leading to stricture formation and obstruction [1, 3]. Most cases present as a focal process within the biliary system, although there have been a few reported cases of concomitant disease in the kidneys, ureters and pericardium [4]. EC was first officially reported by Leegaard et. al. in 1980, who coined the term "eosinophilic cholangitis", and subsequently by Butler et. al. in 1985 who reported a case of a thickened gallbladder wall and stenosis of intrahepatic bile ducts with eosinophilic infiltration in the cystic duct, gallbladder, lymph nodes and bone marrow, consistent with EC [4, 5].

EC is hypothesized to originate from increased IgE, IL-5 levels leading to diffuse eosinophilic infiltration of the biliary system with TGF-ß produced by eosinophils leading to fibrosis and subsequent stricture formation of the biliary tract [1, 6, 7]. While the inciting cause is unknown, EC has also been proposed as a possible extension of cholecystitis secondary to infections caused by *Enterobacter aerogenes* or *Candida albicans* [8]. A history of allergies has also been associated with peripheral eosinophilia, which may contribute to the higher incidence of EC in Western countries and Japan [9].

Studies have aimed to find a correlation between hypereosinophilic syndrome (HES), described as peripheral eosinophilia (≥1500 cells/µl for greater than 6 months) without a secondary cause, and involvement of one or more organs. However, no statistically significant correlation exists [1]. Additionally, EC may resemble primary sclerosing cholangitis (PSC), but no true association has been identified [10].

EC presents a diagnostic challenge with a differential diagnosis that includes cholangiocarcinoma, portal biliopathy, idiopathic benign focal stricture, Mirizzi syndrome, inflammatory processes secondary to choledocholithiasis, HIV cholangitis, parasitic infection, primary sclerosing cholantitis (PSC), autoimmune pancreatitis, and IgG4 cholangitis [3,6,10]. As such, it is important to exclude entities from the differential and assure appropriate treatment sequentially through appropriate imaging and laboratory testing. To facilitate a better understanding of how EC presents and begin developing a diagnostic algorithm as to appropriately exclude disease entities besides EC, the specific data points associated with each report of EC, including the two cases presented here, are detailed in Table I and summarized in Table II [1-5, 8-36].
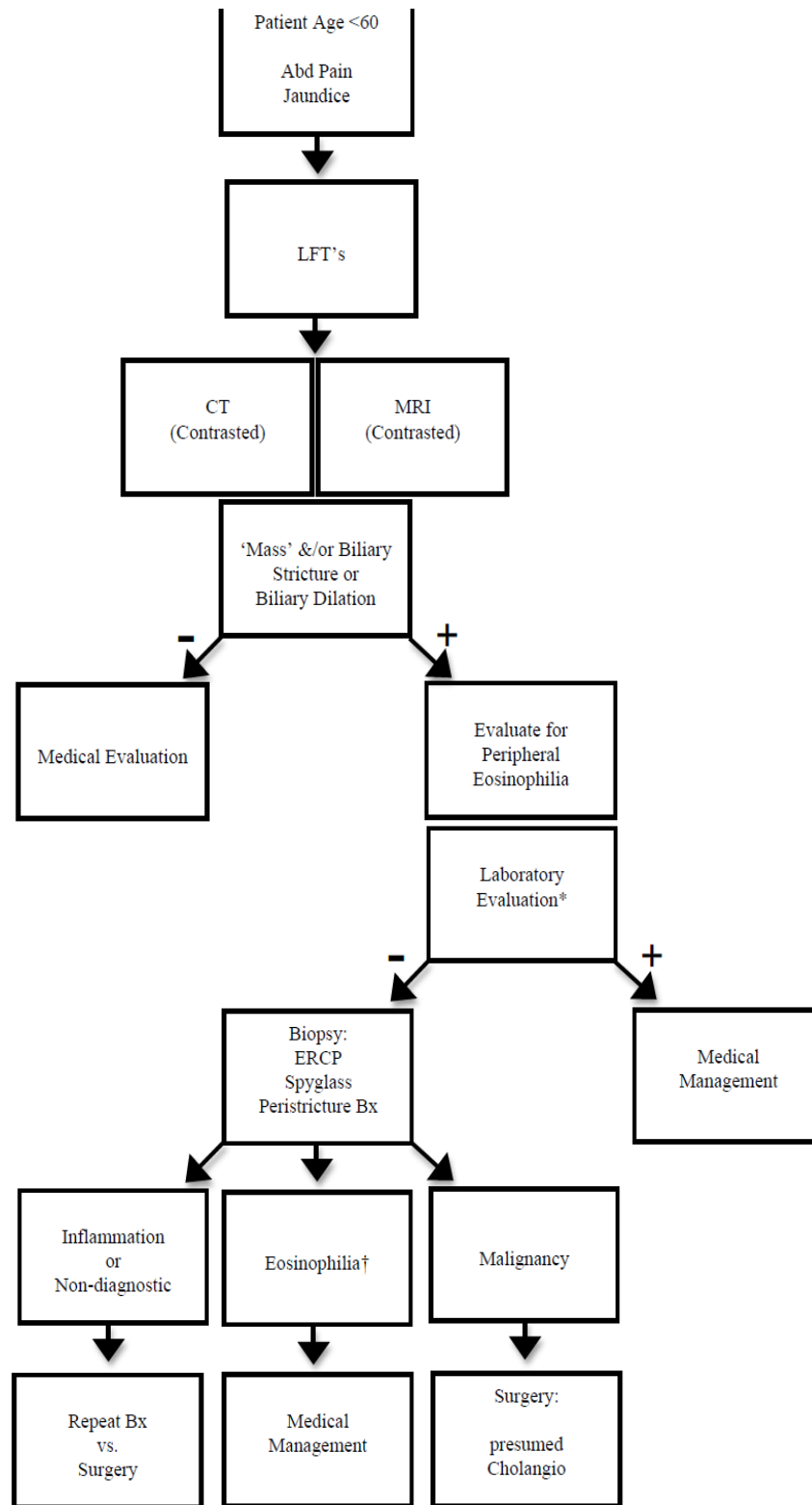
Figure 5: Differential Algorithm to delineate EC from Cholangiocarcinoma. Imaging can determine anatomic abnormalities to include cholangiocarcinoma, portal biliopathy, idiopathic benign focal stricture, Mirizzi syndrome, inflammatory processes secondary to choledocholithiasis, HIV cholangitis, parasitic infection. Definitive diagnoses of these entities may involve biopsies. *Laboratory evaluation includes blood work to address diseases within the differential. LFTs will differentiate EC from PSC. Other lab tests to exclude diseases from the differential are, but are not limited to, HIV, parasitic identification and IgG4 (autoimmune pancreatitis, IgG4 sclerosing cholangitis). †most pathologists will recognize and acknowledge a prominent compliment of this cell type.

EC typically presents in a demographic with a mean age of 42, while those younger than 40 representing the minority of cases (21%; 8/38; Table 1); males are 1.4 times more likely to develop EC as females (Tables 1 and 2). Symptoms at presentation are most often epigastric pain (24/38; 63%), jaundice (20/38; 53%) and fatigue (Tables 1 and 2) [1, 3].An examination of liver function indicators (LFTs) typically demonstrate elevated total bilirubin and complete blood count may indicate elevated eosinophil count with normal WBC (66% Table 1) however, as was seen in the two patients in our case series, the peripheral eosinophilic value may be normal (33%; Table 1) [10].

Diagnostic tests such as CEA, AFP and CA 19-9, and the autoimmune markers ASMA and ANA, have not shown to discriminate EC from any other diagnosis, suggesting limited utility [1]. Other markers, such as IgG4, which would differentiate EC from IgG4 cholangitis, may have limited utility for institutions for which this test must be sent out and may not be an expeditious option. For the cases presented here, IgG4 would not have added information which would have altered disease management.

Imaging includes abdominal CT, liver MRI and MRCP, all of which may demonstrate biliary wall thickening, biliary strictures and intrahepatic biliary dilation, with the presence of "beading" or "focal disease" more concerning for PSC or cholangiocarcinoma [2, 10]. For the cases of EC identified from the literature, imaging revealed strictures most commonly in the CBD (22/38; 58%) and IHBD (18/38; 47%; Table 1). Mass effect, proximal dilation and atrophy were not consistently documented in the literature. The two cases represented here both identified intrahepatic biliary dilation by MRI, unfortunately, imaging was not conclusive as EC and cholangiocarcinoma both often demonstrate this focal effect.

Endoscopic retrograde cholangiopancreaticogram (ERCP) can aid in diagnosis by identifying biliary strictures and allowing for specimen collection. The use of FISH (fluorescent-labeled DNA probes) to detect chromosomal alterations of malignant cells has been found to be more specific for the detection of malignant strictures compared with routine cytology brushing (98% vs 91%, respectively) however, for most institutions, FISH analysis delays the diagnosis and may not be cost effective [3].

EC is often mistaken for cholangiocarcinoma, leading to unnecessary surgical intervention including, but not limited to, liver resection, cholecystectomy, common bile duct resection, and hepaticojejunostomy or pancreaticoduodenectomy [10]. In our review of the literature, 66% of the cases had surgery, with 52% of those being successfully treated with surgery alone. Currently, 10-24% of all liver resections result in benign biliary pathology [1, 3]. Matsumoto et al, describes diagnostic criteria for EC as 1) wall thickening and stenosis of biliary system on imaging, 2) eosinophilic infiltration on pathology (either biopsy or resection), and 3) reversibility of symptoms with steroids [3,9]. To prevent unnecessary surgical resection, EC should be diagnosed by non-resectional biopsy and since individual case studies of EC have shown the benefit of high-dose steroids (prednisone 60mg daily for 2 weeks and then tapered over 6 months) with biliary stenting as needed for obstructive symptoms, the goal would-be disease-free survival without resection [1, 9]. Unfortunately, the dire consequences of missing a malignant disease cannot be ignored. Thus, many cases fall to surgical resection due to diagnostic uncertainty.

We reviewed 36 case reports of patients who were diagnosed with EC and evaluated the literature along with the two cases reported here. The most common presentation included abdominal pain (23 of 38 patients, 61%), with 55% (12 out of 22 patients) having concomitant jaundice. Jaundice alone at initial presentation was reported in 6 out of 38 patients (16%). Less commonly, patients presented with associated fever (16%) or pruritis (15%). Imaging was discussed in 28 of the 38 case reports and bile duct stenosis was identified in 22 patients (78%), suggesting mass effect (Table 1 and 2). Other abnormalities included unspecified intrahepatic ductal dilation in 6 patients, and biliary dilation alone in 1 patient. Surgical intervention was completed on 25 patients, including wedge biopsy, roux-en Y hepaticojejunostomy, cholecystectomy or pancreaticoduodenectomy. Of these, 12 underwent additional post-surgical management that included corticosteroids, ursodiol, hydroxurea, azathioprine, benzafibrate or mesalazine. Medical management was the only treatment in 11 patients. Of the 38 cases, 31 commented on recurrence of which 21 reported actual follow-up times (2 months to 14 years; Table 1). In the 31 patients in whom recurrence was commented on, 26 (84%) had no recurrence. This group included 9 patients treated with surgery only, 9 patients that had surgery and medical treatment, and 7 patients with medical intervention only. A small subset (5/31; 16%; Table 1) were identified as having recurrent disease.

To date, we have completed the most comprehensive literature review comparing age, race, gender, presenting symptoms, presence of eosinophilic infiltrate and biliary stricture, as well as comparisons of surgery versus medical management with corresponding outcomes (Table 1). This review has prompted the development of a decision algorithm concerning appropriate management of possible EC patients (Figure 5). The conventional demographic profile of an EC patient is middle-aged (<60) presenting with abdominal pain and jaundice. An evaluation of liver function (LFTs) and imaging should be completed. If LFTs are within normal limits and a mass and/or biliary stricture/dilation is identified, peripheral eosinophilia should be assessed. Presence of peripheral eosinophilia dictates medical management; however, absence of peripheral eosinophilia is suggestive pathologic evaluation through biopsy. Histologic structure and specific staining can differentiate inflammation, eosinophilia and malignancy, suggesting the appropriate treatment for the patient while avoiding unnecessary surgical resections.

Table I. Literature Review (n=38)

Author	Yr	Age	Race	Gender	Presenting Symptoms	PRHE	PREI	REI	PE	Stricture site	Surgery	Medical Tx	Outcomes
Leegaard *4	1980	46	-	M	Abdominal pain, jaundice--			Y		CBD	CE	CS	No recurrence at 18 mo
Butler*5	1985	32	B	M	Abdominal pain			Y	Y	CBD	CE	-	No recurrence at 24mo
Rosengart[11]	1990	48	W	M	Abdominal pain, jaundice	N		Y	N	CHD	CE	-	No recurrence at 9 mo
Platt[12]	1990	56	A	F	Jaundice/Ut reteric obs	Y	E	Y	N	CBD	CE	-	Recurrence 14y as ureteritis
Scheurlen[13]	1992	28	-	M	Abdominal pain, diarrhea	Y	E	Y	Y	CBD/IHBD	-	Hydroxurea	No recurrence
Grauer[14]	1993	41	H	M	Abdominal pain, jaundice, fever	Y	E	Y	Y	EHBD†	-	CS, Ursodiol	Recurrence in kidney
Schoonbroodt[15]	1995	20	-	M	Jaundice, fever	Y	E	Y	Y	IHBD	CE	CS	Recurrence in stomach
Tenner[16]	1997	38	-	F	Abdominal pain	Y	I	Y	Y	CBD/IHBD	CE	CS	No recurrence 3mo
Song[17]	1997	48	-	F	Abdominal pain	Y'	NMCP	Y	Y	CBD	CE, T-tube	-	No recurrence at 9mo
Al-Abdulla[18]	2000	42	-	F	Abdominal Pain, jaundice	N		Y	Y	IHBD	CE	CS	
Rodgers[8]	2001	50	W	F	Epigastric pain, Nausea, Vomiting	Y'	I	Y	N	CBD	Roux-en-Y/CE	-	No recurrence at 2 mo
Shanti[19]	2001	33	B	M	Abdominal pain, jaundice	N		Y	N	IHBD (bilat)	CE, hepatojejunostomy	-	No recurrence 3mo
Shanti[19]	2001	57	B	F	Abdominal pain, jaundice	Y	I	Y	N	CBD	Roux-en-Y	-	No recurrence 6mo
Vauthey[2]	2003	44	-	M	Abdominal pain, jaundice	Y	NMCP	Y	Y	CBD (distal)	-	CS	No recurrence 18mo
Jimenez-Saenz[20]	2003	67	-	F	Abdominal pain, jaundice	Y	E	Y	Y	IHBD/EHBD†	CE	CS	No recurrence 12mo
Duseja[21]	2005	16	-	F	Abdominal Pain, jaundice	Y	NMECP	Y	Y	CBD	-	CS	No recurrence 12mo
Matsumoto[9]	2007	38	A	F	Abdominal Pain, jaundice	Y	E	Y	Y	IHBD	-	CS	No recurrence 5mo

Jeyamani [22]	2007	13	-	M	Abdominal Pain	Y	E	Y	Y	CBD	-	CS	Recurrence in liver
Jeyamani [22]	2007	26	-	M	Fever, pruritis	Y	E	Y	Y	CBD/CHD/IHBD	Biliary sphincter otomy	CS	No recurrence 6mo
Sussman [23]	2008	52	W	M	Abdominal pain, pruritis	Y	E	Y	Y	Liver sinusoids	-	CS, AZT, UDCA	No recurrence
Horiuchi [24]	2009	45	A	M	Liver dysfunction	Y	E	Y	Y	IHBD	-	UDCA, Bezafibrate	
Miura [10]	2009	46	A	M	Jaundice	N		Y	N	IHBD/EHBD†	Pylorus preserving pancreatoduodenectomy; wedge liver biopsy;	-	
Chen [25]	2009	55	-	M	Jaundice	Y	NMCP	Y	Y	IHBD (bilat)/CBD/CHD	Roux-en-Y, CE	CS	No recurrence 9mo
Raptou [26]	2009	24	-	M	Abdominal Pain	N		Y	Y	IHBD	Cyst removal; wedge bx	Albendazole	No recurrence
Iwamuro [27]	2009	66	A	F	Jaundice	Y	I	Y	Y	IHBD/EHBD†	-	CS	
Nashed [3]	2010	33	W	M	Jaundice, Pruritis,	Y	NMCP	Y	N	CHD	Roux-en-Y/CE, CBD resect,	-	No recurrence 40mo
Dubay [28]	2010	29	W	F	Abdominal pain, nausea, pruritis	Y	NMCP	Y	Y	CBD	Roux-en-Y	-	
Ling [29]	2011	58	-	F	Abdominal pain, icterus, nausea	Y	E	Y	Y	CBD	-	-	Spontaneous remission
Kroemer [30]	2012	49	-	M	Abdominal pain, jaundice	Y	I	Y	N	CPD/CBD	Pancreatoduodenectomy	-	
Kimura* [31]	2013	48	-	M	Eosinophilia	Y	E	Y	Y	Almost normal liver and BD	CE	CS	
Hokuto [32]	2014	73	A	M	Incidental finding	Y	NMCP	Y	Y	CBD	CE	CS	No recurrence
Gunji [33]	2014	39	A	M	Abdominal Pain	Y	E	Y	Y	IHBD (bilat)/CBD	-	CS, UDCA, mesalazine, benzafibrat	Multiple recurrences
Seow-En [34]	2014	63	A	M	Epigastric Pain, Jaundice	Y	NMCP	Y	Y	CBD/CHD	open cholecystectomy, excision	CS	No recurrence 6mo

Author	Year	Age	Race	Gender	Symptoms					Stricture location	Surgery	Medical Therapy	Outcome
											of supraduodenal CBD, Roux-en-Y hepaticojejunostomy		
Vainer[35]	2014	15	-	F	Jaundice	Y	E	Y		IHBD (bilat)	Laproscopic CE	CS/azathiprine	No recurrence 12mo
Fragulidis[1]	2015	27	W	F	Abdominal pain, jaundice	Y	I	Y	Y	IHBD	-	CS	No recurrence 18mo
Walter[36]	2017	41	-	F	Abdominal pain, icterus	Y	E	Y	N	CBD	-	CS	No recurrence
Krishna	2017	49	W	M	Abdominal pain	N		Y	N	IHBD	Left Hepatic Lobectomy	-	No recurrence 6mo
Krishna	2017	47	W	F	Pruritis	N		Y	N	IHBD	R Hepatic Lobectomy	-	No recurrence 5y

PRHE is the pre-resection histologic evaluation of tissue by biopsy, frozen section, FNA, or brushings; PREI refers to the identification of eosinophilic infiltrate on the pre-resection specimen; REI indicates the state of eosinophilic infiltrate on the resection specimen; PE refers to the identification of eosinophilia in the peripheral blood; *=denotes that the original article was not available or in a language other than English; Greyed boxes indicate that the information was not available.

Eos infiltrate indicates eosinophilic infiltrate on the biopsy or specimen; Abn PE=abnormal peripheral eosinophilia; Stricture site denotes identification on imaging; Stricture location denotations are as follows: CBD=Common Bile Duct, CHD=Common Hepatic Duct, IHBD=Intra-hepatic Bile Duct, †EHBD=Extrahepatic Bile Duct (authors did not differentiate CHD from CBD), CPD=Common Pancreatic Duct; CE = Cholecystectomy; Medical Therapy is denoted as follows: CS = Corticosteroids, AZT = Azathioprine, UDCA = Ursodeoxycholic Acid; grey boxes indicate information was not given.

Table II. Summary of the Literature

n=38		
Age		
	Mean	42
	Median	44.5
	Range	13-73
Gender		
	Male	22 (58%)
	Female	16 (42%)
Race		
	White	8 (21%)
	Black	3 (8%)
	Hispanic	1 (3%)
	Asian	8 (21%)
	Not reported	18 (47%)
Symptoms		
	Abd. pain	24 (63%)
	Jaundice	20 (53%)
	Other	13 (34%)
	Incidental Finding	1 (3%)
PE		
	Yes	25 (66%)

	No	11 (29%)	
	Unknown	2 (5%)	
Location of Stricture			
	CBD	20 (53%)	
	CHD	5 (13%)	
	IHBD	17 (45%)	
	EHBD	4 (11%)	
	Multiple	10 (26%)	
	Other	3 (8%)	
PRHE (n=36)			
	Yes	29 (77%)	
	Eosinophils	15 (52%)	
	Surg	1 (7%)	
	Med	8 (53%)	
	S+M	5 (33%)	
	Inflammation	6 (16%)	
	Surg	3 (50%)	
	Med	2 (33%)	
	S+M	1 (17%)	
	'no malignant cells'	8 (21%)	
	Surg	3 (38%)	
	Med	2 (25%)	
	S+M	3 (38%)	
	No	7 (18%)	
	Not reported	2 (5%)	
REI			
	Yes	38 (100%)	
	No	0	
Treatment			
	Surgery	25 (66%)	
	Surg only	13 (52%)	
	Medical	24 (63%)	87.5% CS*
	Med Only	12 (50%)	
	Surg + Med	12 (32%)	
	No tx	1 (3%)	
Outcomes			
	Recurrence	5 (13%)	
	Surg	1 (20%)	
	Med	3 (60%)	
	Both	1 (20%)	
	No Recurrence	25 (66%)	
	Surg	9 (36%)	
	Med	7 (28%)	
	Both	9 (36%)	
	†Spontaneous	1 (3%)	
	Not reported	7 (18%)	

PRHE=pre-resection histologic evaluation; REI=resection eosinophilic infiltrate; PE=peripheral
Eosinophilia; *the primary medical treatment was reported to be corticosteroids;
†case report indicated no surgical or medical management of the patient and the case was
 reported as a spontaneous remission

Conclusions

Eosinophilic Cholangitis is a rare, benign biliary pathology often mistaken for cholangiocarcinoma, leading to extensive surgical resections and increased morbidity and mortality. Therefore, it is important to keep EC in addition to other benign biliary diseases in mind when working up obstructive biliary disease.

Disclosures

The authors report that there is nothing to disclose.

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