Chapter

Eosinophilic Cholangitis

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Abstract

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. We worked on a case of a patient who was referred to our hospital for jaundice and 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. The 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. 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.

Keywords: bile duct diseases, cholangitis, constriction, pathologic, stricture

1. Introduction

While approaching a patient with jaundice, it is important to understand the different types and approach towards jaundice in order to reach the correct diagnosis. Similarly, when approaching a biliary stricture, one must consider benign as well as malignant etiologies since they can be clinically identical. Eosinophilic cholangitis (EC) is a rare benign disorder of the biliary tract which can cause biliary obstruction.

This is the first book that has a specific chapter for a very rare disease, eosinophilic cholangitis. In this chapter, we will briefly discuss the approach towards jaundice before jumping to the main topic of eosinophilic cholangitis. We hope that you will find the information provided informative.

2. Approach to jaundice

Jaundice (i.e., icterus) is the buildup of bilirubin; a waste product stemmed from the metabolism of aging/destruction of red blood cells (RBCs), causing a yellowish

discoloration in tissues that are filled with elastic collagen, such as skin, sclera, and mucus membranes, etc. [1].

Let us take some cases here to further understand how jaundice can present.

2.1 Case-1

A 14-year-old (y/o) African-American male presented to the emergency department (ED) with severe abdominal pain, swelling of both hands and jaundice. Family history includes two uncles that suffer from "blood problems." Blood tests showed normal alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin was 3.2 mg/dL (2.8 indirect). On peripheral blood smear, sickling was found. Hemoglobin electrophoresis confirmed SS hemoglobin and patient was diagnosed with sickle cell anemia (SCA).

2.2 Case-2

A 42-year-old Caucasian male presented to the office with 2 months of jaundice and abdominal pain. The patient had a blood transfusion in 1988 at the age of 15.

Type of jaundice	Differential diagnosis
Pre-hepatic (hemolytic)	• Excess aged/destroyed RBCs (e.g., hemolysis, blood transfusion) • Decreased hepatic uptake (e.g., portosystemic shunt, drugs) • Decreased conjugation (e.g., Gilbert's syndrome)
Hepatic (hepatocellular)	• Excretion defect (Dubin-Johnson syndrome, Rotor syndrome) • Viral hepatitis • Hepatic steatosis • Alcoholic hepatitis • Non-alcoholic steatohepatitis • Autoimmune hepatitis • Ischemic hepatitis • Drug-induced hepatitis • Hemochromatosis • Wilson's disease
Post-hepatic (obstructive)	• Biliary tract disease (primary sclerosing cholangitis, primary biliary cirrhosis, eosinophilic cholangitis, etc.) • Biliary tract obstruction (gallstones, cholangiocarcinoma, pancreatic or liver cancer, pancreatic pseudocyst, etc.)

Table 1.
Types of Jaundice [2, 3].

Lab findings	AST + ALT	ALP	Conjugated bilirubin (CB)	Unconjugated bilirubin (UCB)	Total bilirubin	Conjugated bilirubin in urine
Pre-hepatic (hemolytic)	Normal	Normal	Normal	Normal/↑	Normal/↑	Negative
Hepatic (hepatocellular)	↑	↑	↑	↑	↑	Positive
Post-hepatic (obstructive)	↑	↑	↑	Normal	↑	Positive

Table 2.
Lab findings depending on type of jaundice [4].

Clinical findings	Urine color	Stool color	Large spleen
Pre-hepatic (hemolytic)	Normal	Brown	Positive
Hepatic (hepatocellular)	Dark (combination of CB + urobilinogen)	Slightly pale	Positive
Post-hepatic (obstructive)	Dark (CB)	Pale	Negative

Table 3.
Clinical findings depending on type of jaundice [4].

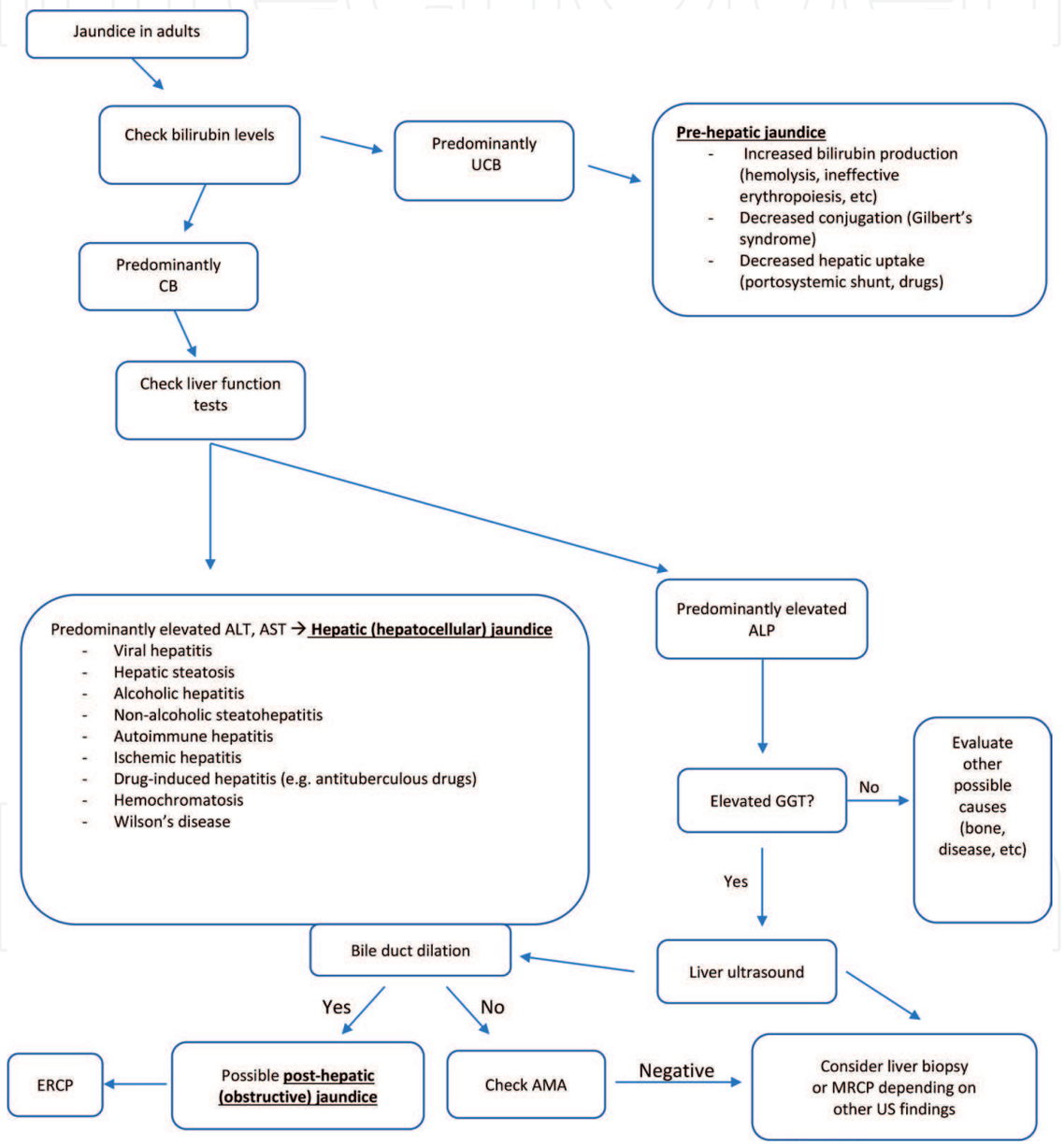

Figure 1.
Approach to Jaundice.

Physical exam showed typical signs of cirrhosis. Labs showed an ALP of 200, ALT 2810, AST 2670 U/L, normal gamma-glutamyl transferase (GGT), bilirubin of 3.3 mg/dL (2 direct, 1.3 indirect), and normal iron and copper levels. Patient was positive for hepatitis C, attributed to his previous blood transfusion. Alpha feto-protein (AFP) levels were elevated and patient was scheduled for a liver ultrasound (US) and biopsy to rule out hepatocellular carcinoma (HCC).

2.3 Case-3

A 39-year-old Caucasian female with a body mass index (BMI) of 36 and a history of hamishoto's thyroiditis, presented to the ED with worsening itching and jaundice. Patient's thyroid function tests were within normal range. Cholesterol was 310 mg/dL, ALP 318, ALT 24, AST 21, and GGT 1120 U/L. Liver US showed no signs of bile duct dilation. Anti-mitochondrial antibody (AMA) titers were elevated. Patient was diagnosed with primary biliary cholangitis (PBC) and was started on ursodiol.

Now what do we take from these three different cases, all of whom presented or were seen to have jaundice? To understand the different presentations of jaundice, let us classify it.

The causes of jaundice can be classified in different ways such as pre-hepatic (hemolytic), hepatic (hepatocellular), and post-hepatic (obstructive) (see **Table 1**). Now, we can differentiate between them in many laboratory and clinical findings (see **Tables 2** and **3**) and know how to approach it (see **Figure 1**).

Understanding the classification, differentiating lab results and approach towards jaundice is important. **Figure 1** can help you as a guide in term of what to do and what to expect. It is helpful to keep it in mind as we go through the chapter.

3. Approach to eosinophilic cholangitis

3.1 Introduction

Now that we have established the approach towards obstructive jaundice. We will dig deeper into eosinophilic cholangitis.

EC is an uncommon, benign, self-limiting cause of biliary structure characterized by transmural eosinophilic infiltration of the biliary tree which may result in obstructive jaundice. The severity and prognosis vary considerably and may affect part or the entire biliary tree mimicking malignancy [5].

3.2 Pathogenesis

The exact pathogenesis is poorly understood.

The cause of eosinophilic cholangitis is unknown. In some reports, hypereosinophilic syndrome (HES) has been mentioned as possible cause. The diagnosis of hypereosinophilic syndrome is based on the following criteria [6]:

1. Sustained eosinophilia (more than 1500 eosinophils per cubic millimeter) for more than 6 months.

2. The absence of other causes of eosinophilia, including parasitic infections and allergies.

3. Signs and symptoms of organ involvement.

Since all reported cases do not appear to have completely met the criteria for HES, the relationship between eosinophilic cholangitis and HES is uncertain.

An allergic mechanism is thought to play a key role in the development of eosinophilic cholangitis, hence the name. In most reported cases, there was an increased level of IgE, interleukin 5, or eosinophilic cationic protein. The latter is one of the major cationic granules released by activated eosinophils and is the most

widely used clinical biomarker of eosinophil in atopic diseases. Furthermore, it has been it has been demonstrated that eosinophils produce transforming growth factor-beta, a cytokine known to stimulate fibrosis, a devastating effect that may leave liver transplantation as the only cure [7, 8].

3.3 Clinical presentation

Nash et al. conducted a study where they collected around 23 cases of EC revealing that this disease [9]:

- Slightly more prevalent in men than women (1,6:1).
- The most common presenting symptoms were abdominal pain followed by jaundice.
- Around 69.6% of patients demonstrated peripheral eosinophilia and 30.4% had normal eosinophilic count.

One of the challenges that accompanies eosinophilic cholangitis is the fact that it can present with a multitude of nonspecific signs and symptoms that makes it hard to differentiate from malignancy such as:

- Abdominal mass
- Abdominal pain
- Jaundice
- Generalized fatigue
- Nausea and vomiting
- Weight loss

At this point, it can be anything and a more in-depth investigation is required. So where do we go from there?

3.4 Investigations

The issue with eosinophilic cholangitis is that it mimics malignancy very closely so what are the options that we have that can help differentiate it from cancer?

Normal routine labs, taking into account the presenting symptoms should be done.

- CBC with differential to look at the eosinophilic count.
- A liver function test:
    - Bilirubin (total and direct) may be elevated.
    - ALT and AST may or may not be increased.

- ALP and GGT are usually increased like any other diseases involving the biliary tree.

- Amylase and lipase to rule out a pancreatic cause.

- Since eosinophilic cholangitis can mimic cholangiocarcinoma, tumors markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) can be ordered and surprisingly may be elevated making the diagnosis even more challenging.

Again, looking at the laboratory investigation, it is still hard to pinpoint the diagnosis, the next step would be to move on into imaging modalities.

3.5 Imaging modalities

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 (see **Figure 2**) and contrast enhanced CT and MRCP with or

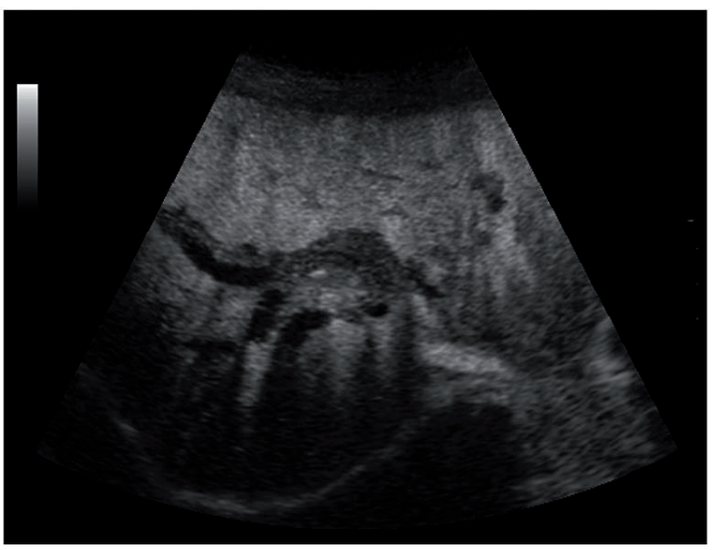

Figure 2.
This contrast enhanced ultrasound (CEUS) shows thickened wall of intrahepatic bile ducts (from hilar to peripheral) with dilation, and the lesion was well enhanced.

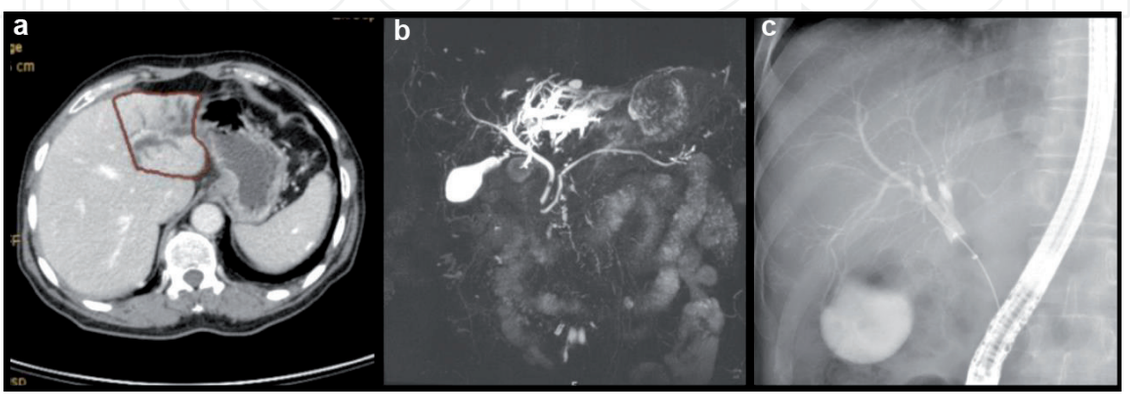

Figure 3.
(a) Computed tomography scan (CT scan) of abdomen and pelvis; (b) magnetic resonance cholangiopancreatography (MRCP); (c) endoscopic retrograde cholangiopancreatography showing a focal dilation of the biliary tree to the left lobe through the suggestion of subtle ill-defined enhancing mass lesion at the level of liver hilum.

without biliary dilation (see **Figure 3**). 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.

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.

ERCP with brush biopsy, PET-CT (see **Figure 4**) and an endoscopic guided fine needle aspiration (EUS guided FNA) are also used to try to differentiate a benign from a malignant cause of biliary tree dilation. As you can see, the CT scan shows an ill-defined enhancing mass lesion at the level of liver hilum suggesting cholangiocarcinoma.

ERCP with brush biopsy may not show malignant cells.

EUS-guided FNA may show a background of mixed inflammation including many eosinophils.

Sometimes the diagnosis can be made, and targeted treatment can be started but most of the time, the index of suspicion for malignancy remains high.

3.6 Proposed diagnostic criteria

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

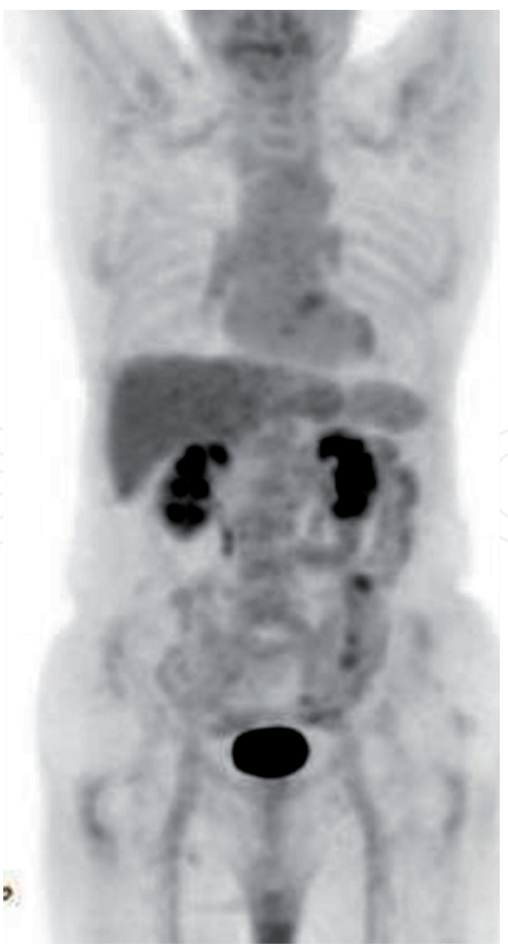

Figure 4.
This positron emission tomography-computed tomography (PET-CT) reveals a soft tissue lesion within the main left biliary duct but does not show any fluorodeoxyglucose (FDG) activity. This still does not exclude cholangiocarcinoma.

contrast-enhanced ultrasound (CEUS). However, they suggested the following requirements to accurately diagnose EC [6]:

1. Thickening of the biliary wall or narrowing of the biliary tree;

2. Eosinophilic infiltration on histopathology;

3. Regression of the stricture or resolution of other biliary abnormalities in the absence of treatment or subsequent steroid therapy.

3.7 Treatment

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 3 weeks, but most of the published cases of EC were treated surgically and received a retrograde diagnosis (see **Figure 5**) [10].

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 [11].

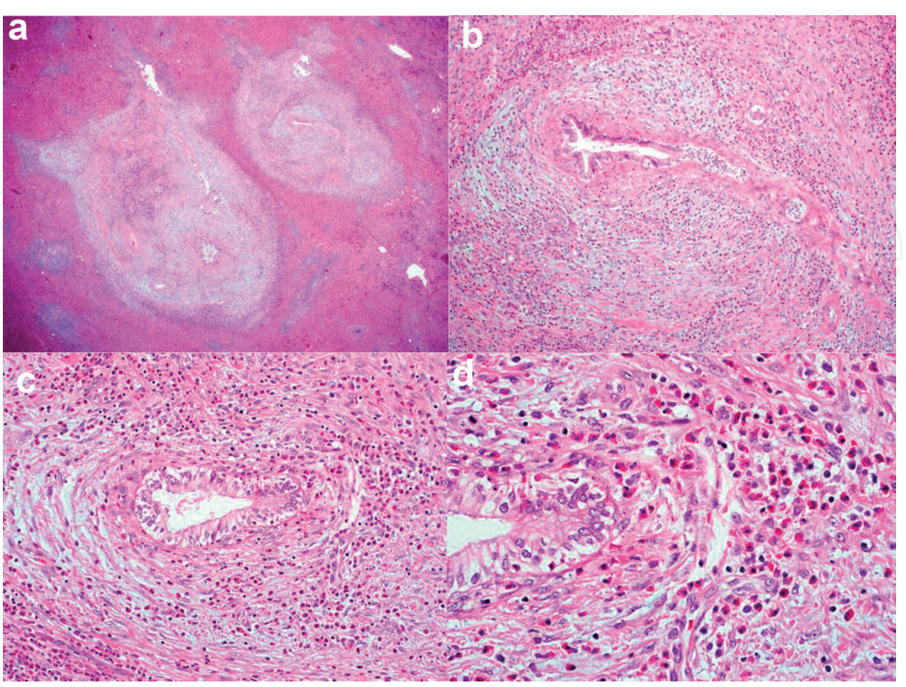

Figure 5.
(a) Severe degree of periductal onion skin fibrosis (hematoxylin and eosin stain displaying 2× magnification). (b and c) The inflammatory infiltrates around the partially damaged bile duct are mostly eosinophilic cells (hematoxylin and eosin stain displaying 10× magnification). (d) The eosinophilic count exceeds 40 cells per HPF (hematoxylin and eosin stain displaying 40× magnification).

A diagnostic trial of oral corticosteroid can be tried to see if any resolution occurs, however the dose and duration of treatment are yet to be determined due to the poor understanding of the diseased natural course.

4. Conclusion

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.

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