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CLINICAL CASE REPORT

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Eosinophilic Cholangitis—A Challenging Diagnosis of Benign Biliary Stricture

A Case Report

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Abstract: When confronting a biliary stricture, both benign and malignant etiologies must be carefully considered as a variety of benign biliary strictures can masquerade as hilar cholangiocarcinoma (CCA). Therefore, patients could undergo a major surgery despite the possibility of a benign biliary disease. Approximately 15% to 24% of patients undergoing surgical resection for suspected biliary malignancy will have benign pathology. Eosinophilic cholangitis (EC) is a rare benign disorder of the biliary tract, which can cause obstructive jaundice and can pose a difficult diagnostic task.

We present a rare case of a young woman who was referred to our hospital with obstructive painless jaundice due to a biliary stricture at the confluence of the hepatic bile ducts, with a provisional diagnosis of cholangiocarcinoma.

Though, during her work up she was found to have EC, an extremely rare benign cause of biliary stricture, which is characterized by a dense eosinophilic infiltration of the biliary tree causing stricturing, fibrosis, and obstruction and which is reversible with short-term high-dose steroids.

Despite its rarity, EC should be taken into consideration when imaging modalities demonstrate a biliary stricture, especially if preoperative diagnosis of malignancy cannot be made, in the setting of peripheral eosinophilia and the absence of cardinal symptoms of malignancy.

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Abbreviations: ALT = alanine transaminase, AMA = antimitochondrial antibody, ANA = antinuclear antibody, ASMA = antismooth muscle antibody, CA 19–9 = Carbohydrate Antigen 19–9, CCA = cholangiocarcinoma, CEA = carcinoembryonic antigen, CEUS = contrast enhanced ultrasound, EC = eosinophilic cholangitis, ERCP = endoscopic retrograde cholangiopancreatogtaphy, GGT = gamma-glutamyl transferase, HES = hypereosinophilic syndrome, HIV = human immunodeficiency virus, IHD = intrahepatic duct, MRCP = magnetic resonance cholangiopancreatography, WBC = white blood cell count.

INTRODUCTION

A patient with obstructive jaundice owing to a proximal biliary tract and common hepatic duct stricture remains a stimulating diagnostic problem. In the absence of choledocholithiasis, clinicians are inclined to first consider this appearance as a cholangiocarcinoma (CCA), as the risk of misdiagnosis is associated with poor prognosis and few therapeutic options.[1–3] However besides malignant tumors, other unusual benign causes of biliary strictures have to be excluded as near 20% of these patients are found to have a benign disease postsurgery.

Thus although rare, this presentation may be the initial manifestation of several benign diseases difficult to be distinguished from a hilar malignancy such as primary sclerosing cholangitis, autoimmune pancreatitis and IgG4-related cholangitis, portal biliopathy, HIV-related cholangitis, parasitic infection, or an idiopathic benign focal stricture.[4]

In addition to the abovementioned benign conditions, eosinophilic cholangitis (EC) is a rare inflammatory condition of the biliary tract that can result in biliary obstruction and can mimic malignancy.[5] It is characterized by a dense eosinophilic infiltration of the biliary tree and/or the gallbladder causing fibrosis, stricturing, and obstruction. Therefore, it can present as both eosinophilic cholecystitis and eosinophilic cholangitis.[5,6] The etiology of the disease remains unclear and it has to be differentiated from other disorders with persistently eosinophilia with an identifiable cause.

We report herein a case of a young woman with eosinophilic cholangitis who presented with a dominant biliary stricture at the hepatic confluence mimicking CCA, which responded to steroid treatment.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal. The study obtained ethics committee approval from our institution.

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CASE PRESENTATION

A previously healthy 27-year-old Caucasian female patient was referred to our hospital due to fatigue, abdominal discomfort, and sudden onset of painless obstructive jaundice secondary to a dominant biliary stricture. On admission, physical examination disclosed no abnormalities except for scleral icterus. She was afebrile. Her past medical history was unremarkable, with no known allergies. She denied any previous episodes of jaundice or weight loss. Laboratory tests carried out upon admission showed a cholestatic jaundice with total bilirubin level of 6 mg/dL whereas alanine transaminase (ALT) and gamma-glutamyl transferase (GGT) were mildly increased normal serum tumor markers (CarcinoEmbryonic Antigen [CEA] and Carbohydrate Antigen 19–9, CA 19–9). A full blood count demonstrated an increased white blood cell count (WBC) of 14,650/μL with 17% eosinophils. Liver ultrasound showed a mild irregular intrahepatic duct dilatation, adenomyomatosis of the gallbladder, and mildly enlarged retroportal lymph nodes. MRI and MRCP confirmed a dominant biliary stricture at the hepatic confluence indicative of a Bismuth-Corlette type IV tumor and mild bilateral dilatation of the intrahepatic ducts (IHDs) (Figure 1A). The patient underwent an ERCP and a spyglass cholangioscopy with brush biopsy where no stones were identified in the biliary tree (Figure 1B). The main pancreatic duct was normal. In cytopathology of biliary brushing specimens typical eosinophils were noticed, whereas cellular atypia of the biliary epithelium was not observed (Figure 2). At that time, during her clinical course eosinophil count had risen up to 27% of WBC. Serum IgG4 levels were minimally elevated to 130 mg/dL (normal 4.8–105 mg/dL), whereas serum IgE was within normal range. Autoimmune antibodies, including anti mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), and antinuclear antibody (ANA), were within normal range and the patient also denied any relevant medical history involving autoimmune diseases. Serologic tests for HIV, hepatitis virus markers, and parasites were also negative. Stool specimens showed no ova or parasites and the patient also denied any recent journey abroad. Colonoscopic examination revealed no evidence of inflammatory bowel diseases.

Owing to clinical suspicion of the underlying disorder, our differential diagnosis was pointed toward EC based on the imaging findings, peripheral eosinophilia, and cytopathology examination. We offered a 3-week course of high-dose steroids with oral prednisone 60 mg o.p.d. On reassessment 2 weeks after initiation of steroids eosinophils and total bilirubin were all normalized. Yet, due to adenomyomatosis of the gallbladder and mildly enlarged retroportal lymph nodes diagnosed on US, she underwent a laparoscopic cholecystectomy and liver biopsy. The gallbladder and lymph node specimens did not reveal any eosinophilic infiltration, apart from the adenomyomatosis of the gallbladder. The liver biopsy was unremarkable. The patient continued on steroids for another 6 weeks tapered down by 10 mg every week and on follow-up after 6 months her MRCP findings were unremarkable (Figure 3). As of today, 18 months following the diagnosis, she remains asymptomatic and off steroid treatment.

DISCUSSION

Eosinophilic cholangitis is an extremely rare benign cause of biliary obstruction and it may affect the entire extrahepatic biliary tree mimicking malignancy. Albot et al first described this entity in 1949 in relation to eosinophilic cholecystitis.[7] Leegaard et al first reported eosinophilic cholangitis in 1980.[8] Butler et al reported in 1985 a case that showed gallbladder wall thickening and stenosis of the intrahepatic bile duct associated with eosinophilic infiltration of the cystic duct, gallbladder, lymph nodes, and bone marrow.[9] EC usually presents in the fourth to fifth decade although age at diagnosis varies significantly. It is characterized by dense transmural eosinophilic infiltration of the biliary tract, not necessarily associated with peripheral eosinophilia.[1] Although the disease may involve the whole or part of the biliary tree due to an unexplained eosinophilic proliferation, nonetheless the severity and the prognosis vary considerably. Localized bile duct involvement is rare and has been reported in only 4 cases in the literature.[10] The disease may rapidly progress, eventually causing hepatotoxicity and fibrosis and ultimately leading to the need for liver transplantation.[11]

The precise pathogenesis of the disease is poorly understood and there is no clear relationship between EC and hypereosinophilic syndrome (HES) in the literature. Indeed, most of the reported cases of EC do not appear to have

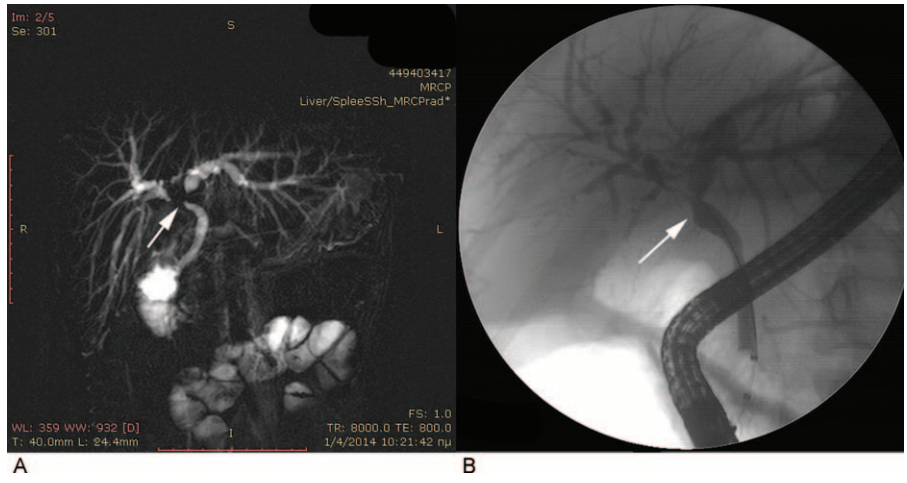

FIGURE 1. MRCP (A) and ERCP (B) findings showing a dominant stricture of the confluence of the right and left hepatic duct (arrow). MRCP = magnetic resonance cholangiopancreatography, ERCP = endoscopic retrograde cholangiopancreatogtaphy.

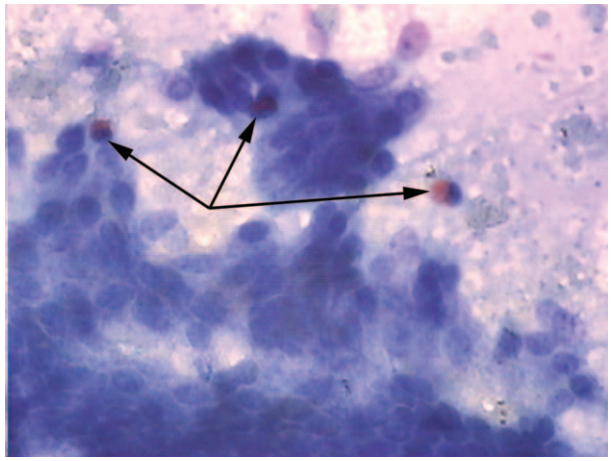

FIGURE 2. Smear from brushing cytology obtained during ERCP. Typical eosinophils can be seen without any evidence of malignancy (black arrows). Giemsa stain, magnification ×400. ERCP = endoscopic retrograde cholangiopancreatogtaphy.

completely met the criteria for HES.[12] HES have been classified as the heterogeneous group of uncommon disorders characterized by persistent eosinophilia (defined as >1500/μL for 6 months) in the peripheral blood, exclusion of both clonal and secondary eosinophilia and organ dysfunction as Chusid et al proposed in 1975.[13] Because HES has required organ dysfunction associated with high-grade eosinophilia, it is important to distinguish those conditions with overlapping clinical presentations such as known disorders of specific organ systems accompanied by eosinophilia. There are several settings defined as hypereosinophilia with organ-restricted involvement confused with HES.[12] Hence, although that blood eosinophilia can develop with a number of gastrointestinal and hepatobiliary

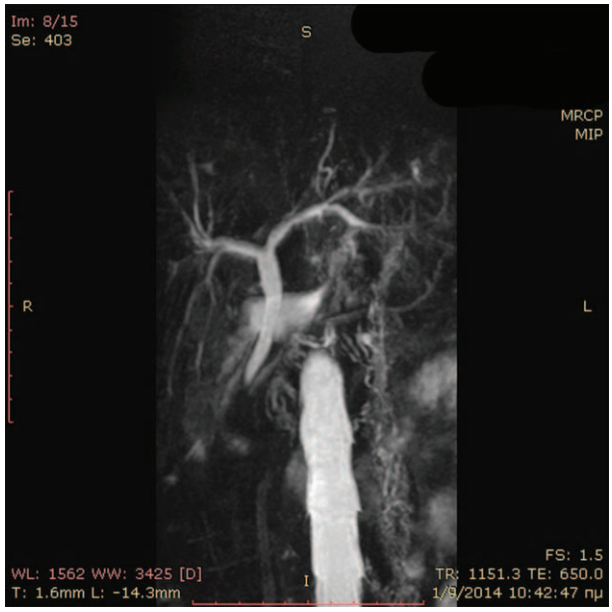

FIGURE 3. Corresponding image (MRCP) 6 months after initial presentation showing the resolution of the biliary stricture. MRCP = magnetic resonance cholangiopancreatography.

disorders, tissue eosinophilia is more characteristic presenting eosinophil mediated-pathology by means of organ-restricted involvement, which may be associated with marked peripheral eosinophilia. Yet, marked peripheral eosinophilia has been seen in primary biliary cirrhosis, sclerosing cholangitis, EC, eosinophilic esophagitis, and eosinophilic gastroenteritis.

Terms such as eosinophilic cholangitis, eosinophilic cholangiopathy, hypereosinophilic syndrome, and eosinophilic gastroenteritis have been used interchangeably in the literature to describe the occurrence of obstructive biliary tree pathology in association with eosinophilia and /or involvement of other organs of the gastrointestinal tract. However when referring to eosinophilic cholangiopathy, one refers to an eosinophil mediated-pathology, which may be associated with peripheral eosinophilia. Moreover, due to the characteristic inflammatory process, eosinophilic cholangitis and/or eosinophilic cholecystitis could be the most appropriate term rather than eosinophilic cholangiopathy. The disease could further be described as localized, when it involves only a specific portion of the extrahepatic biliary tree or diffused, when it affects the extrahepatic biliary tree including the gallbladder.

An allergic mechanism is thought to play a key role in the development of EC. In most of the reported cases there were increased levels of IgE, interleukin 5, or eosinophil cationic protein. IgE and interleukin 5 are produced by B-lymphocytes in allergic conditions and they induce the differentiation and maturation of eosinophilic granulocytes.[14] Disease progression is even more confusing; it is more likely that eosinophil granulocytes are directly cytotoxic as they may release free radicals or tissue-damaging proteins capable of inducing tissue remodeling and fibrosis. Eosinophil cationic protein is one of the major cationic granule proteins released by activated eosinophils. It is presently the most widely used clinical biomarker of eosinophil activity in atopic diseases.[15] Furthermore, it has been demonstrated by Wong et al that eosinophils produce transforming growth factor-β, a cytokine known for its ability to stimulate fibrosis.[16] Accordingly, eosinophil-associated tissue remodeling plays an important role in the fibrotic conditions of different etiopathology, including endomyocardial fibrosis, scleroderma and scleroderma like-conditions, idiopathic pulmonary and retroperitoneal fibrosis, asbestos-induced lung fibrosis, and wound repair. Eosinophil-associated tissue remodeling has been added recently to the list of eosinophil-associated atopic disorders, in which remodeling plays an important role in both symptoms and disease complications.[17]

In our case, the diagnosis of EC was based on the presence of eosinophilia, cytopathology findings of eosinophilic infiltration in the biliary epithelium, and reversibility of the biliary stenosis with steroid treatment. Yet, although peripheral eosinophilia may be a trace to the diagnosis it is not always present, and it is neither sensitive nor specific for EC. Eosinophilia on peripheral blood smear associated with a biliary stricture is usually associated with parasitic infections such as Ascaris spp, known to cause biliary tract infections in endemic areas, which could be easily excluded by stool cultures for parasites. Elevated serum tumor markers are useful in supporting only the diagnosis of a malignant process as elevated CA 19–9 levels are noted similarly in benign cases of obstructive jaundice, as normal biliary epithelial cells in bile ducts and gallbladder epithelium express CA19–9 and CEA.[18] Imaging modalities can provide information regarding the level of obstruction, extent of biliary dilatation, and the presence of other causes of biliary obstruction. EC is characterized by a dense transmural eosinophilic infiltration of the biliary tract, generating segmental or diffuse thickening of the bile duct wall, which is a

characteristic but nonspecific finding on cross-sectional imaging and MRCP.[10,14] However, irregular narrowing of the bile duct on MRCP can also be seen in malignancy that comprises a different treatment. Therefore, invasive imaging modalities such as ERCP and/or cholangioscopy (SpyGlass system) are imperative in order to obtain tissue for diagnosis by means of brush cytology and biopsy in order to attempt to confirm the presence of malignancy. In a previously published case of EC, despite a notable diagnostic work up including Contrast Enhanced UltraSound (CEUS), the authors conclusion was that histopathological findings is one of the principal making the diagnosis. The authors described that the staining of a parenchymal echo in the bile duct wall on CEUS was considered to be a characteristic finding of EC in this case excluding malignancy. However, their final diagnosis was based mainly on histology, the presence of eosinophilia, and the reversibility of the biliary stenosis after steroid treatment.[6] Based on previous reports in the literature, a reasonable interval to resolution of biliary stenosis would be within 3 to 5 weeks, after initiation of steroid treatment.[5,6]

Although there are various modalities to evaluate the biliary tract, precise diagnosis of EC is not always possible and surgery is usually necessary to exclude CCA. EC may be a self-limiting disease, which makes treatment recommendation difficult forward facing a misdiagnosed malignancy.[3] Instead, surgical treatment of a biliary stricture remains the definitive treatment in case where there is a high suspicion of malignancy. Most of the cases of EC reported in the literature underwent surgery and received a retrograde diagnosis. Some authors suggested that a diagnostic trial of oral corticosteroids might be considered before surgical intervention, as EC is highly responsive to oral steroids as in the present case.[6] The present case is one of few cases of EC to be diagnosed without surgery, which allowed us to consider other therapeutic management. Nevertheless, there are several cases of EC in the literature with spontaneous regression of a biliary stricture without any specific treatment.

Eosinophilic cholangitis is a rare cause of a biliary stricture; however, it should be considered as malignant masquerade especially in the setting of peripheral eosinophilia and the absence of cardinal symptoms of malignancy. Up to now, the only definite diagnostic evidence of the disease is the cytopathology and the regression of the disease after steroid treatment, which may reflect a surgeon's sigh of relief. However, the dose and duration of treatment are yet to be defined, as the natural course of this disease is poorly understood.

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