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Letter to the Editor

A rare case of eosinophilic cholangiopathy

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Wenya Li[1], Feizhao Jiang[2], Xiaoxiao Li[2], Hong Li[2] and Zhihai Zheng[2]

Abstract

Eosinophilic cholangiopathy is termed as a rare, benign, and self-limiting disease. Moreover, the interference of malignant tumor to diagnosis and the changing process of disease make the accurate treatment proposal challenging. A significant number of patients require surgery for the definitive diagnosis and resolution of symptoms. We put forward a case of eosinophilic cholangiopathy infiltrating the gallbladder and bile duct with bone marrow involved, coupled with peripheral eosinophilia. The patient underwent a successful treatment using laparoscopic cholecystectomy and steroids, instead of extrahepatic bile duct excision with Roux-en-Y hepaticojejunostomy. The patient gets an accurate treatment in a minimally invasive manner. In conclusion, surgery refers to not only a diagnostic methodology but also a treatment. When the bile duct and gallbladder are involved at the same time, and cannot distinguish benign and malignant diseases, laparoscopic cholecystectomy is feasible, the effect is the same, and the symptoms of eosinophilic cholecystitis are relieved.

Keywords

Eosinophilic cholangiopathy, eosinophilic cholecystitis, hypereosinophilic syndrome, eosinophilia

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Introduction

Eosinophilic cholangiopathy (EC) refers to a rare condition, which is characterized by the eosinophilic infiltration of the biliary tract.[1] When eosinophilic infiltration is localized in the bile duct, it is termed as eosinophilic cholangitis. As it deals with the gallbladder, it is termed as eosinophilic cholecystitis. EC is the term put to use for describing the changes in either gallbladder or bile duct or both of them.[2–4] Eosinophilic cholecystitis has a clinical presentation, which shares similarity with that of typical cholecystitis.[5] EC typically results in diffuse thickening of biliary ducts. In the same similar manner as the mechanisms of other diseases, which involve bile ducts, EC has the potential to pose a tough diagnostic challenge owing to the fact that it is able to mimic cholangiocarcinoma.[6] Matsumoto et al.[4] put forward the diagnosis of EC: (1) the stenosis or wall thickening of the biliary system, (2) the histopathologic findings of eosinophilic in filtration, and (3) the reversibility of biliary abnormalities without treatment or following the steroid treatment. A significant number of patients require surgery for the definitive diagnosis and resolution of symptoms. We put forward a case of EC infiltrating the gallbladder and bile duct with bone marrow involved, coupled with peripheral eosinophilia. The patient underwent a successful treatment using laparoscopic cholecystectomy and steroids, instead of extrahepatic bile duct excision with Roux-en-Y hepaticojejunostomy. As for the etiology, we take into account idiopathic hypereosinophilic syndrome (HES).

[1]Wenzhou Medical University, Wenzhou, China
[2]Department of General Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Corresponding author:
Zhihai Zheng, Department of General Surgery, The First Affiliated Hospital of Wenzhou Medical University, No. 2 Fuxue Lane, Wenzhou 325000, Zhejiang, China.
Email: zheng_zhihai@163.com

Table 1. Records of regular blood laboratory tests before and after surgery.

Items	1 week before surgery	1 week after surgery	2 weeks after surgery	1 month after surgery
White blood cell count (L)	14.86×10^9	12.5×10^9	10.6×10^9	8.73×10^9
Eosinophil count (L)	7.22×10^9	4.23×10^9	0.77×10^9	0.34×10^9
Hemoglobin (g/L)	172	150	149	150
Platelet (L)	109	194	205	213
Albumin (g/L)	40.6	29.8	33.7	46
ALT (U/L)	434	103	55	43
AST (U/L)	106	40	28	18
Alkaline phosphatase (U/L)	426	112	115	74
GGT (U/L)	754	154	98	53
LDH (U/L)	783	–	278	–
PT (s)	13.9	–	13.7	–
APTT (s)	39	–	39.9	–
D-dimer (mg/L)	3.05	–	3.64	–

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; LDH: lactate dehydrogenase; PT: prothrombin time; APTT: activated partial thromboplastin time.

Case report

This case report obtained the informed consent of the patient. A man, aged 31 years, was admitted to a local hospital with complaint of abdominal colic pain and diarrhea for 3 days. Blood tests were carried out. In accordance with the results, the white blood cell (WBC) count was 4200/L, together with 21.1% of eosinophils. Serum total IgE was 275 IU/mL. Moreover, the levels of red blood cells (RBCs), platelet, coagulation tests, serum total protein and albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), cGTP, amylase, and CRP were normal (Table 1). Abdominal computed tomography (CT) without contrast medium revealed an insignificantly enlarged gallbladder. Upper gastrointestinal endoscopy indicated no abnormal findings except nonatrophic gastritis. Colonoscopy did not shed light on any abnormal findings from the terminal ileum to the rectum. The patient was treated with cephalosporins through the hospital stay. Following approximately 1 week of treatment, despite his symptoms gradually resolved, the levels of WBC and eosinophilic were not decreased as the complete blood count (CBC) was checked. Thereafter, he was discharged from the local hospital, followed by visiting the outpatient clinic of Shanghai Ruijin Hospital (Shanghai, China) for further examinations to confirm the diagnosis. Immunoglobulin G (IgG) quantitative levels, parasitic cytology, and stool cultures were negative. He was diagnosed as idiopathic HES. His eosinophilia persisted; nevertheless, his symptoms resolved spontaneously. Accordingly, he was discharged without systemically treating corticosteroids.

Nonetheless, abdominal pain showed appearance again after 3 months, and he underwent to receive treatment with cephalosporins again at the local hospital. However, the symptoms got even worse, and subsequently, he got transferred to our hospital. He denied making use of any illicit drugs, meanwhile admitting to social smoking coupled with daily alcohol consumption. There was no history of foreign travel or significant allergic or atopic reactions. Physical examination showed that there were right upper quadrant tenderness and a positive Murphy's sign. Liver function tests showed the following: total bilirubin 19 μmol/L, direct bilirubin 13 μmol/L, alkaline phosphatase 426 U/L, ALT 434 U/L, AST 106 U/L, gamma-glutamyl transferase 754 U/L, and LDH 783 U/L. In addition, the total WBC count was 14.86×10^9/L, and the eosinophil count was 7.22×10^9/L, with a differential cell count of 30.5% neutrophils, 14.5% lymphocytes, and 48.6% eosinophils. The patient's hemoglobin, hematocrit, and platelet counts were 172 g/L, 51.9%, and 109×10^9/L, respectively. D-dimer runs up to 3.05 mg/L. Hepatitis virus of B and C screening, HIV screening, tumor and immunological markers, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), were all falling in the normal range. Abdominal magnetic resonance imaging (MRI) indicated the diffuse thickening of the extra-intrahepatic bile

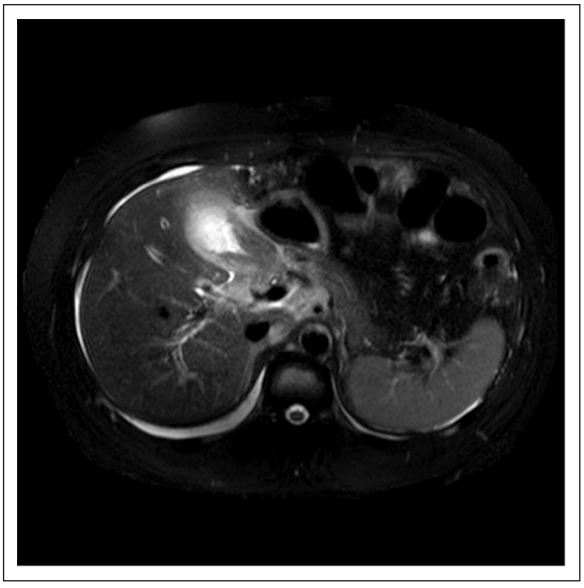

Figure 1. Diffuse thickening of the extra-intrahepatic bile ducts walls as well as the gallbladder wall.

ducts wall as well as the gallbladder wall (Figure 1). In addition to cirrhosis, splenomegaly and ascites, hilar, and retroperitoneal lymphadenopathy were also observed. All in all, the possibility of malignancy was quite difficult to exclude. Chest CT revealed a slight pleural effusion on both sides. That was reason why laparoscopic laparotomy was performed. We discovered the fact that the momentum was adherent to the gallbladder. Furthermore, the gallbladder and common bile duct were thickened with a small amount of brown ascites. On the basis of the operative and macroscopic findings, we just carried out laparoscopic cholecystectomy. The pathologic findings of the resected gallbladder indicated a number of eosinophils and lymphocytes infiltrations through all of the layers of the gallbladder wall without vasculitis (Figure 2). In accordance with these findings, the patient was diagnosed as eosinophilic cholangiopathy convincingly.

Thereafter, the patient was transferred to the hematology department in order to search for the cause of the disease. We discovered that antinuclear (ANA), antimitochondrial (AMA), anti-smooth muscle (ASM) antibodies, stool ova, and parasite examinations were negative. Immunoglobulin G (IgG) quantitative levels had a normal range, but the serum total IgE was >3000 IU/mL. A bone marrow biopsy sheds light on a significant increase in eosinophilic cells (25% of all granulocytes) with active hematopoietic proliferation within the normal range. The genes of *JAK2* and *FGFR1* were not

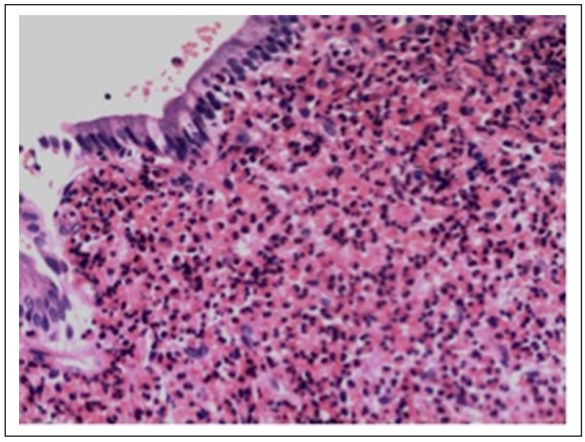

Figure 2. Pathology of the resected gallbladder.

detected to undergo mutation. In addition, *FGFR1* gene and *PDGFR*β gene were not detected to rearranged, and *FIP1LI* and *PDGFRa* genes were not detected to have fusion. As these findings suggested, the patient was diagnosed with eosinophilic and cholangiopathy with the idiopathic eosinophilic syndrome. Then, the patient began to take steroids (prednisolone 30 mg/day) in time. The clinical symptoms of abdominal pain and epigastric tenderness were enhanced in 2 days. Furthermore, eosinophils in peripheral blood dropped to approximately the normal range within 4 days of the treatment of methylprednisolone needle, and the liver function showed enhancement. Following the surgery, coupled with approximately 2-month treatment of steroids (methylprednisolone 40 mg ivgtt qd and imatinib 200 mg qd for 4 days, followed by continuous methylprednisolone 8 mg po qd), the patient did contrast-enhanced CT (CECT) scan of the chest and abdomen. Accordingly, we discovered a mild dilatation of the left intrahepatic bile duct without pleural fluid and ascitic fluid. During 15-month follow-up subsequent to the surgery, the patient took methylprednisolone tablet (8 mg) daily, remaining asymptomatic with normal liver function. Nevertheless, the peripheral eosinophils were recurrent rise and fall. Records of regular blood laboratory tests before and after surgery were shown in Table 1.

Discussion

Eosinophilic pneumonia and eosinophilic gastroenteritis (EC) are well known as disorders linked to eosinophilic infiltration. Nevertheless, EC is an uncommon, benign, inflammatory condition of the

biliary tree. Taking a look back, it was TK Rosengart et al.[7] who made use of the term eosinophilic cholangitis for the bile duct changes that occurred these patients in 1990. Subsequently, in 1997, Tenner et al.[2] first put forward the broader term "eosinophilic cholangiopathy," aimed at describing the changes in the gallbladder as well as bile ducts. We searched 24 literature studies on the PubMed and Web of Science core with the use of the keyword "eosinophilic cholangitis" between 1949 and 1997, besides searching "eosinophilic cholangiopathy" from 1997 to the present. Accordingly, five cases of them reported that eosinophils just infiltrated both the gallbladder and bile duct among the digestive tract organs.[2,6–9]

EC is termed as a rare, benign, and self-limiting disease. Moreover, the difficulty involved with the exclusion of malignancy and the variable course of the disease make the accurate treatment recommendations quite challenging.[9–11] Laboratory values are of great use to distinguish between benign and malignant biliary obstruction, meanwhile being typically incapable of determining the exact cause of a biliary stricture. A variety of modalities are available for the evaluation of the biliary system nowadays. In addition to ultrasound, MRI, and magnetic resonance cholangiopancreatography (MRCP), noninvasive radiology, including CECT, may provide meaningful information about the extent of obstruction, the extent of bile duct dilatation, and the presence of masses or distant metastases.[12,13] The results presented that hereunder were of significance to carry out the diagnosis of EC. Nonetheless, the diagnosis of EC is termed as a tough thing, besides being solely based on the histological findings.[6]

Recently, the cause leading to EC is unknown. Nonetheless, it has been previously reported to be associated with not only cholelithiasis[14] but also idiopathic HES,[15] parasitic infection,[16,17] and allergy. High eosinophil syndrome (HES) is characterized by an eosinophil count of 1.5×10^9/L or higher, lasting for at least 6 months, unknown cause, and related to signs of organ involvement and dysfunction.[18] The guideline published in 2017 segregated the causes of eosinophilia into three key categories, including secondary (reactive), primary, and idiopathic.[19] The causes of secondary eosinophilia, which include not only allergic disorders but also drugs, parasitic and fungal, vasculitides, gastrointestinal disorders, nonhematological neoplasms, rheumatological disease, and so on. The primary cause indicated hematological neoplasms with clonal eosinophilia. In this manner, in a case where there are no observed detectable primary or secondary causes for eosinophilia, it is placed into the so-called idiopathic eosinophilia. The most severe pathology in this spectrum of diseases is idiopathic hypereosinophilic syndrome (IHES), involving the eosinophilic infiltration of the bone marrow as well as other organs. IHES is characterized by the persistent eosinophilia of 1.5×10^9/L for a minimum of 6 months or any eosinophilia resulting in death within 6 months; the lack of an identified cause for the eosinophilia, which includes parasitic infections, collagen vascular diseases, and allergies; the organ system involvement or dysfunction owing to eosinophilic infiltration or eosinophilia-associated damage.[20,21]

The association that exists between EC and HES is not certain. It is obscure of the particular pathogenesis, together with why eosinophil granulocyte selectively infiltrates one or more organs with or without peripheral blood eosinophilia. There are neither sufficient cases nor pathological tissues supporting further investigation.

We implied that our patient had EC considering the peripheral blood eosinophilia as well as the histopathological examination of the gallbladder. The peripheral blood eosinophil count of the patient was up to 7.22×10^9/L, reaching the quantitative needs of eosinophil for HES diagnosis. Besides that, the bone marrow biopsy is capable of demonstrating eosinophilic infiltration as well.[22] Despite the fact that the bile duct is not examined histologically, there are three points that extend support to the case of eosinophilic cholangiopathy. First, treating corticosteroids following the cholecystectomy responded quite efficiently. Second, MRI indicated a diffuse thickening of the extra-intrahepatic bile ducts wall as well as the gallbladder. Third, the intraoperative macroscopic results were presented above. Comprehensively inquiring about the history, laboratory tests, bone marrow biopsy, and other examinations significantly helped us to eliminate the causes like allergy, parasitic infection, vasculitides, gastrointestinal disorders, rheumatological disease, hematological neoplasms, and cholelithiasis.

In a case when we do not avail the support of the histopathological examination, the presence of peripheral eosinophilia most likely constitutes a sign to the diagnosis of EC. Nevertheless, it is neither

sensitive nor specific of the dense eosinophilic infiltration of the bile duct.[14] Moreover, the bone marrow biopsy has the potential to illustrate eosinophilic infiltration.[22] The manifestation from liver MRI prompted that malignant tumors were not possible to be excluded. Accordingly, merely the conservative treatment was worrying, as scaring as waling on thin ice. Currently, in retrospect, it is considered as quite wise and precise for us to select cholecystectomy rather than Roux-en-Y hepaticojejunostomy with the occurrence of abdominal pain. Laparoscopic cholecystectomy reduces the problem of bile drainage in the next few days, while the surgical trauma is relatively small. The most pivotal thing was that the histological examination provided us with a robust proof for diagnosing EC linked to IHES.

Conclusion

In conclusion, surgery refers to not just a diagnostic methodology but also a treatment. When both the bile duct and gallbladder involve at the same time, and benign and malignant diseases are unable to be identified, cholecystectomy can be carried out laparoscopically, which has uniformly good results coupled with the symptomatic relief for eosinophilic cholecystitis. Patients receiving treatment need long-term follow-up to ensure no recurrence of the disease or manifestations in other organs.

Declaration of conflicting interests

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Ethical approval

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Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

ORCID iD

Zhihai Zheng https://orcid.org/0000-0002-3519-3776

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