Eosinophilic Cholangitis with Initial Clinical Features Indistinguishable from IgG4-Related Cholangitis

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Abstract

A 66-year-old woman presented with jaundice, elevated liver enzymes, peripheral eosinophilia and increased levels of immunoglobulin (Ig) G4. The image findings of the biliary tree revealed multifocal strictures mimicking primary sclerosing cholangitis. A biopsy specimen of the liver demonstrated an infiltration of inflammatory cells consisting of several eosinophils and IgG4-positive plasma cells. The liver enzymes and eosinophil count were normalized immediately after the administration of an oral steroid. Finally, the patient was diagnosed with eosinophilic cholangitis based on the clinical manifestations, although she had features of both eosinophilic cholangitis and IgG4-related cholangitis. This case indicates that the two entities may show similar manifestations and thus they should be discriminated carefully.

Key words: eosinophilic cholangitis, IgG4-related cholangitis, sclerosing cholangitis, eosinophilia, autoimmune pancreatitis

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Introduction

Eosinophilic cholangitis is a rare cholangitis characterized by peripheral blood eosinophilia and eosinophilic infiltration into the bile duct and/or the gallbladder. This entity was first reported by Butler et al in 1985, in a case that showed gallbladder wall thickening and stenosis of the intrahepatic bile duct (1). Eosinophilic infiltration of the cystic duct, gallbladder, lymph nodes and bone marrow was also demonstrated in that case. Improvement of biliary strictures and liver enzyme levels with steroid therapy is a distinctive feature differentiating this entity from primary sclerosing cholangitis. Thereafter, several case reports describing eosinophilic cholangitis were published. On the other hand, immunoglobulin (Ig) G4-related cholangitis, which is the biliary manifestation of IgG4-related systemic disease (2, 3), is another entity that is characterized by steroid-responsive biliary strictures.

Due to the infrequency of eosinophilic cholangitis, the diagnostic criteria for this disease have not yet been established; furthermore, the clinicopathological difference between IgG4-related cholangitis and eosinophilic cholangitis is rarely discussed. We report herein a case of eosinophilic cholangitis with multifocal biliary strictures which responded to steroid therapy. However, the diagnosis was problematic, because the patient had features of both eosinophilic cholangitis and IgG4-related cholangitis, i.e., marked peripheral blood eosinophilia and increased levels of serum IgG4, and an infiltration of both eosinophils and IgG4-positive plasma cells in the liver biopsy specimen. This case indicates that the two entities may show similar manifestations in some cases, and thus they should be discriminated carefully. The pathogenesis of these two entities is discussed.

Case Report

A 66-year-old Japanese woman had been treated for elevation of transaminase levels of unknown etiology for two years at another clinic. Her aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels had in-
Interendothelial cholangiography showed an irregularly shaped biliary tree with multifocal strictures and dilatations, which are similar to the cholangiographic findings of primary sclerosing cholangitis.

Figure 1. A computed tomography scan with drip infusion cholangiography also revealed mixed features of narrowing and dilatation of both the intrahepatic and extrahepatic bile ducts. The main pancreatic duct was smooth and expressed no abnormality on ERCP. On intraductal ultrasonography, irregular thickening of the wall of the extrahepatic bile duct was found (Fig. 3). These image findings were consistent with primary sclerosing cholangitis. A biopsy specimen of the upper extrahepatic bile duct obtained during ERCP via the papilla of Vater revealed an infiltration of inflammatory cells in the biliary mucosa, mainly composed of lymphocytes and several eosinophils (Fig. 4). Cellular atypia of the biliary epithelium were not observed in the biopsy specimen. The ultrasound-guided liver biopsy specimen showed inflammatory infiltration with abundant lymphocytes and plasma cells. Several eosinophils were also observed (Fig. 5A). The inflammatory cells were mainly observed around the portal region, and were rather sparse around the bile ducts. Periductal fibrosis with an onion-skin appearance, which is usually observed in primary sclerosing cholangitis, was absent. Immunohistochemical staining of the liver biopsy specimen revealed nine IgG4-positive plasma cells per high power field (HPF) (Fig. 5B). There were more IgG4-positive plasma cells than IgG1-positive plasma cells.
cells (Fig. 5C). Obliterative phlebitis was not confirmed in any of the biopsied specimens. A diagnosis of eosinophilic cholangitis was made based on the image findings, peripheral eosinophilia, and histological examination. A dose of 40 mg of oral prednisone and 600 mg of ursodeoxycholic acid were administered. Thereafter, AST, ALT, total bilirubin, eosinophils, and eosinophil cationic protein were all normalized within the following three weeks. Diffuse thickening of the extrahepatic bile duct wall and the gallbladder wall were also resolved, whereas the mixed features of narrowing and dilatation of the biliary tree had not improved. Although the levels of AST, ALT, and total bilirubin flared up again when the dose of oral prednisone was tapered, the liver enzyme levels were improved by the readministration of 40 mg of oral prednisone. The patient was kept under observation, since the stenosis of the bile duct had not changed.

**Discussion**

Autoimmune pancreatitis was newly established as a category within the last decade, and is now recognized as a distinct entity with unique clinical, serological, and histological characteristics. In patients with autoimmune pancreatitis, increased levels of serum IgG4 are often observed, and such increases have been reported to be highly sensitive and specific biomarkers (4). The main histological features consist of pancreatic tissue fibrosis and abundant infiltration of lymphocytes and IgG4-positive plasma cells into pancreatic parenchyma. Autoimmune pancreatitis often involves extrapancreatic involvement, as seen in this case with eosinophilic cholangitis.

**Figure 4.** Histological findings of the bile duct. A biopsy specimen of the upper extrahepatic bile duct revealed the infiltration of inflammatory cells into the biliary mucosa, mainly composed of lymphocytes and several eosinophils. Hematoxylin and Eosin staining, original magnification ×100.

**Figure 5.** Histological findings of the liver. (A) A biopsy specimen of the liver demonstrated inflammatory infiltration with abundant lymphocytes and plasma cells. Several eosinophils were also observed. Hematoxylin and Eosin staining; original magnification ×100. (B) Some of the plasma cells stained positive for IgG4. Immunohistochemical staining of IgG4, original magnification ×400. (C) There were fewer IgG1-positive plasma cells than IgG4-positive cells. Immunohistochemical staining of IgG1, original magnification ×400.
creatic organs such as the bile duct, gallbladder, salivary glands, retroperitoneum, lymph nodes, kidneys, lungs, and prostate (5-8). Tissue infiltration of IgG4-positive plasma cells is also detected in these extrapancreatic lesions, and not only in the pancreas (5). Based on the histological findings, the term “IgG4-related systemic disease” has been proposed to describe this condition, and it has been suggested that autoimmune pancreatitis is a pancreatic manifestation of this systemic disease (5, 9).

The biliary tree is one of the most frequently affected extrapancreatic organs in autoimmune pancreatitis, and the term “IgG4-related cholangitis” was recently introduced to refer to the biliary manifestation of IgG4-related systemic disease (2, 3). IgG4-related cholangitis has sometimes been described as an isolated biliary tract lesion even in the absence of pancreatic involvement. The mixed features of narrowing and dilatation of the intrahepatic and/or extrahepatic bile duct are the most characteristic image findings. Long stenosis, segmental stricture, and long stricture with prestenotic dilatation of the biliary tree are characteristic findings in IgG4-related cholangitis, whereas band-like stricture, beaded appearance, pruned-tree appearance, or diverticulum-like formations generally are not found in IgG4-related cholangitis, but are found in primary sclerosing cholangitis (10). Ghazale et al reviewed 53 patients with IgG4-related cholangitis and described the patients’ characteristics as follows: man predominance, old-age onset (mean age, 62 years), presentation with obstructive jaundice, increased serum IgG4 levels, and moderate (11-30 cells/HPF) to severe (more than 31 cells/HPF) IgG4-positive cells in the bile duct (3). Forty-nine of the 53 patients presented with autoimmune pancreatitis, while only 4 patients lacked pancreatic involvement. Twenty-nine of the 30 patients responded to steroid therapy.

In the present patient, although increased serum IgG4 levels and infiltration of IgG4-positive cells in the liver biopsy specimen were revealed, a diagnosis of IgG4-related cholangitis was not made based on the following findings: diffuse enlargement of the pancreas and irregular narrowing of the main pancreatic duct were absent, the cholangiographic findings lacked long stenosis and segmental stricture, and the biliary strictures did not improve after administration of steroids (10). In addition, upon analysis of the number of IgG4-positive plasma cells nine cells/HPF infiltrated into the liver, which was considered to be mild infiltration (11). Thus, the present patient was finally diagnosed with eosinophilic cholangitis. Nevertheless, the diagnosis of primary sclerosing cholangitis accompanied with eosinophilic cholangitis was not completely ruled out in this patient, because the cholangiographic images were compatible with those of typical primary sclerosing cholangitis and the multifocal stenosis was not improved after steroid therapy. The clinical course of this patient will be monitored with this differential diagnosis in mind.

Eosinophilic cholangitis is another entity that causes biliary strictures and responds to steroids. Due to the infrequency of occurrence, the diagnostic criteria for eosinophilic cholangitis have not been established. Peripheral blood eosinophilia, eosinophilic infiltration into the biliary tree, and normalization of liver enzymes or resolution of stricture by steroid therapy are the diagnostic clues for this entity. The present patient demonstrated these features, and was thus diagnosed with eosinophilic cholangitis. The pathogenesis of eosinophilic cholangitis is still unknown, but an allergic mechanism is thought to play a key role in its development. Direct cytotoxicity of the eosinophil granulocytes or antibody-dependent cellular toxicity may cause bile duct damage which resembles that in primary sclerosing cholangitis. In fact, most of the reported cases have shown increased levels of IgE, interleukin 5, or eosinophil cationic protein. IgE and interleukin 5 are produced by B lymphocytes in patients experiencing allergy and they induce the differentiation and maturation of eosinophilic granulocytes (12, 13). Eosinophil cationic protein is one of the major cationic granule proteins released by activated eosinophils, and is presently the most widely used clinical biomarker of eosinophil activity in atopic diseases. Increased levels of these biomarkers indicate the presence of an allergic mechanism against unknown allergens in eosinophilic cholangitis.

The immunologic functions of IgG4 in allergic responses have also been demonstrated by several investigators. In allergic individuals, exposure to high doses of allergens leads to a high concentration of specific IgG4, detectable IgE and T regulatory immune responses. IgG4 has a unique functional ability to inhibit the formation of allergen-IgE complexes and thus might play an anti-inflammatory role in immunity (14). In fact, non-allergic beekeepers have an over 1,000 times higher ratio of specific IgG4 versus IgE than allergic individuals (15). Therefore, IgG4 is considered to act as a blocking antibody in the context of allergen-specific IgE-induced immune responses, and may protect individuals from harmful allergic reactions. Thus, in the present patient, the increased serum IgG4 levels and infiltration of IgG4-positive cells in the liver biopsy specimen may have been caused by allergic mechanisms.

In recent years, it has been reported that an allergic mechanism may also play a key role in the pathogenesis of IgG4-related cholangitis (6), though an autoimmune mechanism is considered to be the main cause of inflammation, because of the high prevalence of several autoantibodies in patients with IgG4-related systemic disease (16, 17). It is well known that mild to moderate peripheral hypereosinophilia and eosinophilic infiltration into the affected organs is often observed in IgG4-related systemic disease (3, 18). Zen et al reported that the expression of T helper 2 cytokines, including interleukin 5, and regulatory immune reactions are up-regulated in the affected tissues in patients with IgG4-related systemic disease (19). They have suggested that the predominance of T helper 2 cells might reflect an allergic mechanism in its pathogenesis.

In conclusion, IgG4-related cholangitis and eosinophilic
cholangitis may share the same pathogenesis related to an allergic reaction, and some cases may have manifestations of both entities. Consequently, IgG4-related cholangitis and eosinophilic cholangitis should be discriminated carefully in such cases.

References