Concurrent Primary Sclerosing Cholangitis and Eosinophilic Colitis

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Abstract

A 39-year-old man presented with diarrhea and abdominal pain. At 26 years of age, he was found to have eosinophilia and abnormal liver function parameters, for which prednisolone therapy was started. He subsequently underwent a liver biopsy and endoscopic retrograde cholangiopancreatography, and received a diagnosis of primary sclerosing cholangitis (PSC). On presentation to our hospital, he was further diagnosed with eosinophilic colitis based on aggravation of diarrhea and severe eosinophilic infiltration in the colonic mucosa. We herein report a rare case of concurrent PSC and eosinophilic colitis.

Key words: primary sclerosing cholangitis, eosinophilic colitis

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Introduction

Primary sclerosing cholangitis (PSC) is a relatively uncommon disease in Japan. This condition is characterized by chronic cholestasis of unknown etiology (1), and is accompanied by eosinophilia and inflammatory bowel disease, at a frequency of 39% and 37%, among Japanese patients, respectively (2). In comparison, eosinophilic gastroenteritis (EG) is characterized by eosinophilic infiltration of the gastrointestinal wall with peripheral eosinophilia and produces lesions most commonly in the stomach, duodenum and small intestine and less commonly in the esophagus and large intestine (3-5). EG is known to occur concurrently with PSC and eosinophilic cholangitis, although only a few such cases have been reported. We herein report the case of a patient initially found to have abnormal liver function parameters with eosinophilia that was histologically diagnosed as PSC who subsequently developed eosinophilic colitis during the course of treatment.

Case Report

A 39-year-old man with no history of smoking or alcohol consumption presented at our hospital with abdominal pain

and diarrhea. His family history included pancreatic cancer in his father and Klippel-Feil syndrome in his brother. He had no other contributory medical or allergic history.

In 1997 (at 26 years of age), he experienced an unusual sensation in his pharynx and consulted a physician at a nearby clinic, where he was found to have eosinophilia (WBC: 24,400/ μ L, eosinophils: 79%) and abnormal liver function parameters and subsequently underwent more specific examinations. His laboratory data included an aspartate aminotransferase (AST) level of 380 IU/L, alanine aminotransferase (ALT) level of 270 IU/L, alkaline phosphatase (ALP) level of 1,099 IU/L, gamma-glutamyl-transpeptidase (GGT) level of 130 IU/L, antinuclear antibody (ANA) titer of 1:2,560 (Ho), anti-smooth muscle antibody (ASMA) titer of 1:160 and IgG level of 2,772 mg/dL, with negative findings for anti-liver kidney microsome (aLKM)-1 antibodies, anti-mitochondrial antibodies (AMA) and hepatitis virus markers. Based on these results, a diagnosis of autoimmune hepatitis (AIH) was suspected. The human leukocyte antigen (HLA)-DR was determined to be DR4 and DR9. Although an adequate sample from the portal region was available, a liver biopsy showed only eosinophilic infiltration in the sinusoid and lobular necrotic areas, without typical findings of AIH (Fig. 1a). With respect to the eosinophilia, the IgE level was normal at 71 U/mL and

Figure 1. Pathological findings of the liver biopsy specimens. (a) On the initial liver biopsy performed in 1997, although an adequate sample from the portal region was available, only eosinophilic infiltration in the sinusoid and lobular necrotic portions was observed [Hematoxylin and Eosin (H&E) staining, $\times 400$]. (b) The second liver biopsy, performed in 1998, revealed onion skin-like fibrosis around the intrahepatic bile ducts (H&E staining, $\times 200$).

an allergen test was positive for cedar pollen only, ruling the possibility of parasitic disease. In addition, a bone marrow examination showed an increased eosinophil count, although no atypical cells were detected. Prednisolone (PSL) therapy (30 mg/day) was subsequently initiated for the patient's eosinophilia and suspected AIH.

The therapy resulted in improvements in the IgG level, transaminase level and eosinophil count; however, the biliary enzyme levels remained slightly elevated. The PSL therapy was continued at a reduced dose, and, six months later, a follow-up liver biopsy revealed onion skin-like fibrosis around the intrahepatic bile ducts (Fig. 1b), leading to a diagnosis of PSC. In 2001 (at 30 years of age), the patient presented with right hypochondrial pain and fever and was admitted for a closer examination. Under suspicion of cholangitis, endoscopic retrograde cholangiopancreatography (ERCP) was performed, the results of which revealed irregular narrowing of the intra- and extra-hepatic bile ducts, thus supporting the diagnosis of PSC (Fig. 2a). The administration of ursodeoxycholic acid (UDCA) at a dose of 150 mg/day, in addition to PSL at an increased dose of 25 mg/day, was then started. The dose of PSL was gradually tapered, although abnormal biliary enzyme levels continued to be observed (ALP: 425 IU/L, and GGT: 338 IU/L). After two years, the patient developed diarrhea and abdominal pain and consequently underwent colonoscopy at a nearby clinic, which demonstrated edema and erosion of the intestinal mucosa. Furthermore, a colon biopsy performed prior to treatment had shown severe infiltration of eosinophils with no evidence of UC, such as cryptitis, crypt abscesses or basal plasmacytosis, leading to a diagnosis of UC at the clinic. Additional treatment with 5-aminosalicylic acid (5-ASA) was then administered. Although the patient's symptoms gradually improved, he was referred to our hospital in May 2008, and has since been followed up on an outpatient basis at our hospital. Following discontinuation of the therapy

with 5 mg/day of PSL and continued treatment with 5-ASA, the patient's symptoms were well controlled until a relapse of diarrhea with increased biliary enzyme levels was observed in July 2008. Magnetic resonance cholangiopancreatography (MRCP) showed no evidence of progressive dilatation or narrowing of the intra- and extra-hepatic bile ducts, with slight irregularity in the diameter of the intrahepatic bile ducts (Fig. 2b). Treatment with PSL at a dose of 5 mg/day was then resumed, and the patient's symptoms stabilized. In February 2010, he again developed abdominal pain and diarrhea (5-6 times/day). Despite increasing the dose of PSL to 20 mg/day, these symptoms did not improve, and the patient was admitted for further treatment.

The physical findings on admission included a body height of 182 cm, body weight of 60.3 kg, body temperature of 36.5°C, blood pressure of 120/60 mmHg and pulse rate of 72 beats/min. The patient's consciousness was clear, with no jaundice in the bulbar conjunctiva, anemia in the palpebral conjunctiva, rales or heart murmurs. The abdomen was flat and soft, with no tenderness. Neither the liver nor spleen were palpable.

The examination findings on admission are summarized in the Table. The WBC count was slightly increased with eosinophilia (12%). Biochemistry disclosed decreased albumin and increased biliary enzyme levels. A positive ANA test (1:320) and increased IgG level were also noted. On a stool culture test, only indigenous bacteria were detected, with no anti-*Entamoeba histolytica* antibodies.

Abdominal ultrasonography and CT revealed thickening of the common bile duct wall and mild dilatation of the intrahepatic bile ducts; however, no hepatomegaly/splenomegaly or intrahepatic tumorous lesions were observed. MRCP showed a mild irregularity in the diameter of the intrahepatic bile ducts, consistent with the findings obtained in July 2008. Colonoscopy demonstrated erosive lesions throughout the large intestine histologically character-

Figure 2. ERCP and MRCP images. Irregular narrowing of the intra- and extra-hepatic bile ducts progressively worsened. (a) ERCP performed in 2001. (b) MRCP performed in 2008. (c) MRCP performed in 2012.

Table. Laboratory Data on Admission

WBC	9,300 / μ L	TP	6.9 g/dL	IgG	2,107 mg/dL
Neut	45 %	Alb	3.5 g/dL	IgA	285 mg/dL
Lymph	32 %	AST	25 IU/L	IgM	108 mg/dL
Eosino	12 %	ALT	17 IU/L		
RBC	3.94×10^4 / μ L	LDH	175 IU/L	ANA	$\times 320$ (homogenous)
Hb	12.1 g/dL	ALP	387 IU/L	MPO-ANCA	(-)
Hct	36.2 %	γ -GTP	231 IU/L	PR3-ANCA	(-)
Plt	30.1×10^4 / μ L	T-Bil	0.5 mg/dL	CMV antigenemia	(-)
		D-Bil	0.1 mg/dL	Entamoeba histolytica Ab	(-)
PT	66.7 %	BUN	19 mg/dL		
APTT	25.1 sec	Cre	0.85 mg/dL		
		CRP	1.43 mg/dL	CD toxin	(-)

ized by severe eosinophilic infiltration (Fig. 3). Although we investigated the patient's upper gastrointestinal tract using endoscopy, we found no suspicious lesions of eosinophilic enteritis. Biopsies of the stomach and duodenum biopsy were not performed.

The patient was initially suspected to have an impaired liver function due to AIH; however, he was later diagnosed with PSC based on the findings of narrowing and dilatation of bile ducts and liver histology. Moreover, the clinical symptoms of abdominal pain and diarrhea and the colonoscopic findings of severe eosinophilic infiltration suggested

that he had developed eosinophilic colitis concurrently with PSC, resulting in the aggravation of the symptoms of enteritis. The patient was therefore treated with methylprednisolone at a dose of 250 mg/day for three days, followed by oral PSL at a dose of 40 mg. Blood test results showed reduced inflammation, and the patient's diarrhea improved. The abdominal symptoms remained well controlled, even after tapering the dose of PSL. The patient was then followed up on an outpatient basis. However, the abnormal biliary enzyme levels persisted, and in September 2012 MRCP revealed progressive dilatation and narrowing of the intrahe-

Figure 3. Colonoscopic images and histological findings of a biopsy specimen of the large intestine. Colonoscopy revealed erosive lesions throughout the large intestine, and the histological examination of the colon biopsy specimen revealed severe eosinophilic infiltration. No findings suggestive of ulcerative colitis, such as crypt abscesses, crypt distortion or basal plasmacytosis, were observed. (a) Transverse colon. (b) Ascending colon. (c) Biopsy of the transverse colon [Hematoxylin and Eosin (H&E) staining, $\times 40$]. (d) Biopsy of the ascending colon (H&E staining, $\times 400$).

patic bile ducts (Fig. 2c). The above clinical course is summarized in Fig. 4.

Discussion

In the present case, a diagnosis of AIH was initially suspected based on the examination findings obtained in 1997, including a positive ANA titer, abnormal liver function parameters and an increased IgG level. Nevertheless, the initial liver histology was characterized primarily by eosinophilic infiltration, and no typical findings of AIH, such as interface hepatitis, plasma cell infiltration or rosette formation, were observed. Although a possible effect of PSL therapy was also considered, onion skin-like periductal fibrosis was observed around the bile ducts on the second liver biopsy, which, combined with the MRCP findings, supported the diagnosis of PSC. It has been previously reported that approximately 36% of Japanese patients with PSC are positive for ANA, some of whom also have increased IgG levels (2).

Regarding eosinophilic colitis, the present patient initially exhibited findings of non-specific chronic inflammation that responded to steroid therapy. In addition, the histological examination performed at symptom relapse revealed eosino-

philic infiltration, which satisfied the diagnostic criteria for eosinophilic colitis (6). Furthermore, although prednisolone (PSL) therapy was started for eosinophilia and suspected AIH, the patient developed eosinophilic colitis, resulting in the aggravation of the symptoms of enteritis. According to this clinical course, we judged this case as involving steroid-dependent eosinophilic colitis. In fact, steroid dependence has been reported in some patients with eosinophilic colitis (7). In contrast, concurrent PSC and eosinophilic colitis, as noted in the present report, has only been reported in two previous cases (8, 9). However, considering that PSC is often associated with eosinophilia (10-12) and that some cases may be reported as unclassifiable enteritis or ulcerative colitis with an increased eosinophil count (2, 13), additional similar cases may have been overlooked and consequently not reported. The mechanism underlying the development of concurrent PSC and eosinophilic enteritis has not been elucidated to date. However, possible mechanisms include the involvement of factors that promote the proliferation of eosinophils in the bone marrow and their migration to inflammatory tissue, as well as the expression of eosinophilic granular proteins at affected sites, including eosinophil peroxidase (EPO) (14, 15). These factors were not assessed in

Figure 4. Clinical course of the patient. CS: colonoscopy, UDCA: ursodeoxycholic acid, PSL: prednisolone, ALT: alanine aminotransferase, ALP: alkaline phosphatase

relationship to eosinophilia in the present case.

In the current case, eosinophilic cholangitis is another differential diagnosis of PSC. Eosinophilic cholangitis is a relatively rare disease histologically characterized by inflammatory cell infiltration into the bile ducts, primarily by eosinophils. This condition is not easily distinguished from PSC, which is also associated with an increased eosinophil count and similar imaging findings (16). A diagnosis of eosinophilic cholangitis cannot be ruled out in this case because a bile duct biopsy was not performed; however, this possibility is unlikely based on the liver biopsy findings and the fact that the abnormal biliary enzyme levels persisted, even after treatment with PSL. Miura et al. reported a case of eosinophilic cholangitis associated with periductal fibrosis on histology (17). Since periductal fibrosis does not present with an onion skin-like pattern, a typical finding of PSC, the case reported by Miura et al. is not comparable to the present case. However, in some cases involving patients with eosinophilic cholangitis without peripheral eosinophilia, making the differential diagnosis of PSC is difficult without performing a bile duct biopsy. Eosinophilic cholangiopathy may also be confused with PSC with eosinophilia. IgG4-related sclerosing cholangitis is another potential differential diagnosis, although it was unlikely in this case, as the serum IgG4 level remained within the normal range during the course of treatment and no positive results were obtained on the liver biopsy with IgG4 immunostaining. Concurrent eosinophilic cholangitis and eosinophilic gastroenteritis has been reported in six other cases (18-23). Although the imaging findings of the bile duct lesions in these cases are similar to those of PSC, all of the patients responded well to treatment with corticosteroids, which is not consistent with

the present case.

We herein presented a rare case of concurrent PSC and eosinophilic colitis. Further accumulation of similar cases is warranted.

The authors state that they have no Conflict of Interest (COI).

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