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Letter to the Editor

Eosinophilic cholangitis with eosinophilic granulomatosis with polyangiitis: A case report and review of the literature

Dear Editor,

Eosinophilic cholangitis (EC) is a rare disorder characterized by sclerosing cholangitis, extrahepatic biliary strictures, obstructive jaundice, and a dense transmural eosinophilic infiltrate.¹ Only one case report of EC and recurrent eosinophilic granulomatosis with polyangiitis (EGPA) has been reported.² Here, we report the first case of new onset EGPA with EC. The patient had a good response to steroids and mepolizumab. The patient gave written informed consent and patient anonymity was preserved using methods approved by the Ethics Committee (11592).

A 50-year-old man with the recent onset of bronchial asthma and chronic sinusitis sought evaluation at an emergency room for abdominal pain, vomiting, and diarrhea. A diagnosis of biliary colic was made based on physical examination and CT scan, and he was discharged to home with a prescription for non-steroidal anti-inflammatory drugs (NSAIDs). Nevertheless, the symptoms persisted and progressed. In addition, neuropathic pain and purpura emerged in his lower extremities and the blood tests revealed eosinophilia, inflammation, and liver enzyme elevation. Gastrointestinal endoscopy detected duodenitis and multiple colon ulcers, that were diagnosed as eosinophilic enteritis based on colon biopsy. The patient was transferred to our hospital for further investigation. On physical examination there was abdominal tenderness in the left lower quadrant, nasal polyps, resolving purpura, and loss of sensation of the lateral aspects of both thighs. The total white blood cell count was 22,100/ μ L (normal range [NR]: 3300–9000/ μ L), with 51.5% eosinophils (NR: 0–8.5%). The laboratory data on admission indicated elevated serum levels of CRP (5.07 mg/dL, [NR: 0–0.3 mg/dL]), IgE (1379 IU/mL, [NR: 0–170 IU/mL]), IgG4 (771 mg/dL, [NR: 4.5–117 mg/dL]), IL-5 (11 pg/mL, [NR: <4 pg/mL]), and thymus and activation-regulated chemokine (TARC; 2446 pg/mL, [NR: 0–449 pg/mL]). Perinuclear, cytoplasmic, myeloperoxidase, and proteinase 3 anti-neutrophil cytoplasmic antibody (ANCA) titers were negative based on indirect immunofluorescence and enzyme-linked immunosorbent assays. A bone marrow biopsy revealed a hyperplastic bone marrow with increased eosinophils, but no malignant cells. Neurologic conduction testing was normal. Abdominal ultrasonography showed mild thickness of the gallbladder wall, gallstones, sludge, and echoic lesions of the intrahe-

patic bile duct walls. One week after admission, he had a sudden onset of right hypochondralgia with elevation of inflammatory markers and liver enzymes. Abdominal ultrasonography and a CT scan confirmed dilatation of the distal common bile duct and biliary sludge. Magnetic resonance imaging (MRI) revealed a high signal around the intrahepatic portal veins on T2-weighted images (Fig. 1A). Because cholangitis was suspected clinically, endoscopic retrograde cholangiopancreatography (ERCP), a bile duct biopsy, and drainage were performed. ERCP showed thickened walls in the upper and middle bile ducts and cystic duct with debris in the lower bile duct, which confirmed the diagnosis of cholangitis. The histologic evaluation demonstrated eosinophilic infiltration and degranulation in the bile duct mucosa, without IgG4-positive plasma cells, which was consistent with EC. Eosinophilic infiltration was more pronounced in the common hepatic duct than the distal common bile duct (Fig. 1C–E). The location of the bile duct eosinophilic infiltrate was consistent with EC because the common hepatic, proximal common bile, and cystic ducts are most commonly involved.¹ The patient was diagnosed clinically with vasculitis based on purpura, peripheral neuropathy, and exclusion of a malignancy and infection, and a diagnosis of EGPA was made according to the American College of Rheumatology (ACR) criteria.³ There were four of the six ACR criteria were met, as follows: presence of asthma; eosinophilia >10% on differential white blood cell count; paranasal sinus abnormality; and bile duct biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas. Treatment was started with prednisolone (60 mg per day [1 mg/kg]) and mepolizumab (300 mg per month). Abdominal pain, weight loss, purpura, hepatobiliary enzyme elevation, and eosinophilia improved rapidly within a few weeks (Fig. 1F). The high signal around the portal vein on T2-weighted images also disappeared in 1 month (Fig. 1B). The paranasal involvement and peripheral neuropathy resolved gradually within several months. After the patient was discharged to home, the glucocorticoid dose was tapered to 8 mg/day over 10 months. The patient has not relapsed during the follow-up period in our outpatient clinic and the blood eosinophil count has not exceeded 100/ μ L.

It is often difficult to differentiate EGPA from hypereosinophilic syndrome (HES), especially when ANCAs are negative and biopsy does not prove vasculitis because EGPA and HES share several clin-

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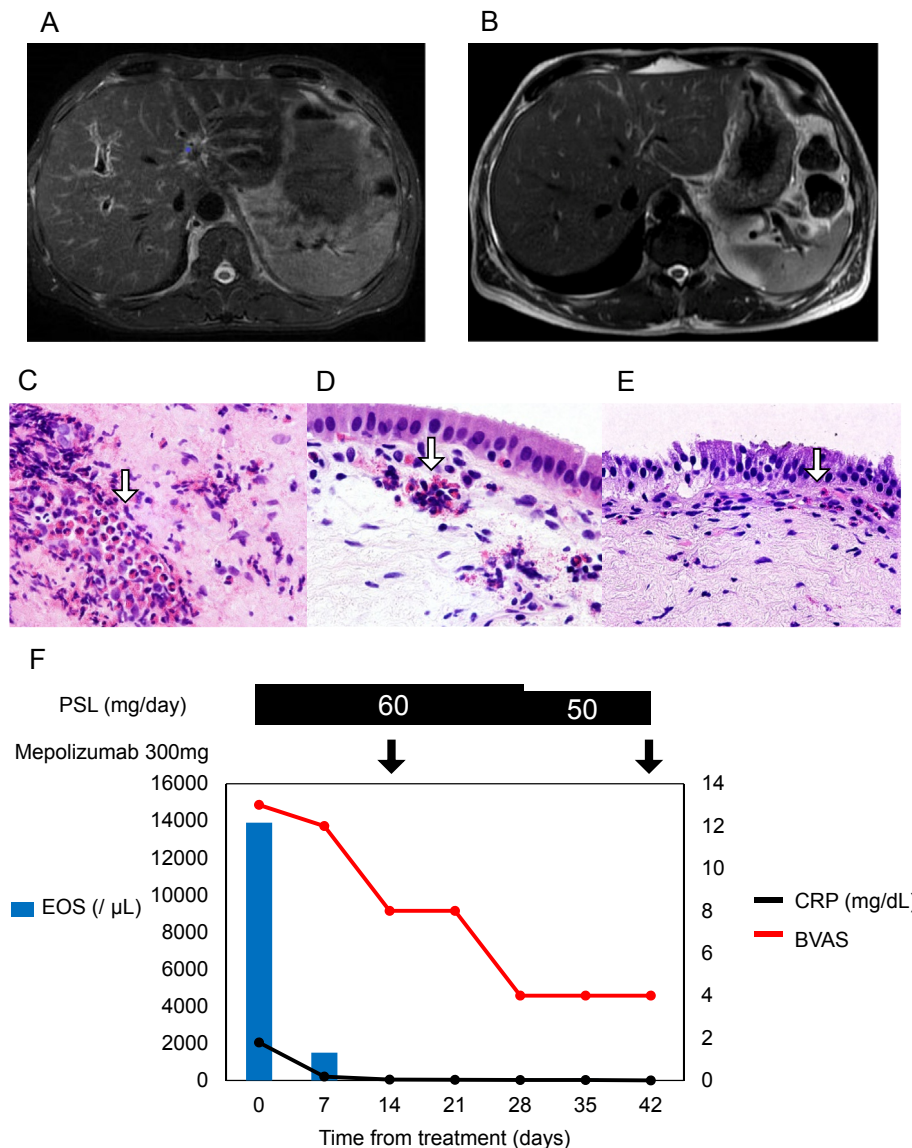


Fig. 1. Clinical characteristics of the patient. **A–B:** Magnetic resonance imaging (MRI) on T2-weighted images, before (**A**) and after treatment (**B**). **C–E:** Bile duct biopsy showing eosinophilic infiltration and degranulation (arrows) in the mucosa of common hepatic duct (**C**), middle common bile duct (**D**), and lower common bile duct (**E**); hematoxylin-eosin stain, at 600 $\times$. **F:** Eosinophil count (EOS), C-reactive protein (CRP), and Birmingham vasculitis score (BVAS) with prednisolone (PSL) dosage. Black arrows represent monthly subcutaneous injection of mepolizumab 300 mg.

ical features. It has been reported that ANCA are positive in 30–40% of EGPA patients.⁴ The pre-vasculitic phase of EGPA is characterized by an eosinophilic tissue infiltration without vasculitis. Even in the vasculitic phase, 63% of nerve biopsies and 67% of skin biopsies are positive for vasculitis.⁴ Although our patient was negative for ANCA and vasculitis by biopsy, he was diagnosed clinically with EGPA and fulfilled the ACR criteria. In addition, physical findings and serum biomarkers supported the diagnosis of EGPA. The patient had nasal polyps and purpura, which rarely occur in patients with HES.^{5,6} Serum chemokine eotaxin-3, a specific marker for active EGPA, but not HES, was markedly elevated (273 pg/mL) and much higher than the cut-off level of 80 pg/mL.⁷

The prognosis of EC with EGPA has not been elucidated. Only one case involving EC with EGPA and six cases of EC with HES have been reported (Table 1). Notably, two of the seven patients with EC relapsed and required additional immunosuppressants.^{2,8,9} All of the patients had eosinophilic gastroenteritis or eosinophilic

cholecystitis. Therefore, a bile duct biopsy is warranted in EGPA or HES patients with signs of sclerosing cholangitis and eosinophilic gastroenteritis or eosinophilic cholecystitis. Recently, mepolizumab, a monoclonal antibody that blocks interleukin-5, is available for treatment of EGPA. Wechsler *et al.*¹⁰ concluded that mepolizumab has a glucocorticoid-sparing effect and decreases EGPA relapses. Immunosuppressants are often toxic and associated with several adverse events, whereas mepolizumab is associated with safer profiles.¹⁰ Our patient is the first reported case of EC successfully treated with mepolizumab, which could be a new strategy for preventing relapse of EC with EGPA.

In summary, this is the first case report of EC with new onset EGPA. EC with EGPA was safely treated in combination with steroids and mepolizumab. Thus, in patients with EC, as a rare manifestation of EGPA, especially with eosinophilic gastroenteritis or eosinophilic cholecystitis, a bile duct biopsy should be considered to establish the diagnosis.

Table 1

Summary of case reports of eosinophilic cholangitis with HES or EGPA.

Patient age/Gender	Clinical diagnosis	Gastrointestinal involvement			Treatment	Outcome	Reference Number
		EC	ECC	EGE			
58/M	HES	+	–	–	Steroids	Remission	8
41/M	HES	+	+	–	Steroids, Cholecystectomy	Remission	8
28/M	HES	+	–	+	Steroids, HU	Relapsed with steroids and added HU	8
52/M	HES	+	–	+	Steroids, AZA	Relapsed with steroids and added AZA	8
20/M	HES	+	–	+	Steroids	Remission	8
42/F	HES	+	+	–	Steroids, Cholecystectomy	Remission	9
64/M	EGPA	+	–	+	Steroids, MTX	Died from heart disease	2
50/M	EGPA	+	–	+	Steroids, Mepolizumab	Remission	Present case

M, Male; F, Female; HES, Hypereosinophilic syndrome; EGPA, Eosinophilic granulomatosis with polyangiitis; EC, Eosinophilic cholangitis; ECC, Eosinophilic cholecystitis; EGE, Eosinophilic gastroenteritis; HU, Hydroxyurea; AZA, Azathioprine; MTX, Methotrexate.

Conflict of interest

TK receives grants from GlaxoSmithKline. YN receives financial support or fees from Bristol-Myers Squibb, Chugai, Kissei, and Pfizer. HS receives fees from Pfizer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Chugai, UCB, and Daiichi-Sankyo. KF has received grants, consulting fees, speaking fees, and/or honoraria from Takeda, Bristol-Myers Squibb, Mitsubishi Tanabe, Asahi Kasei, Sanofi, Eli Lilly, Daiichi-Sankyo, Ono, Janssen, AbbVie, Astellas, Eisai, Pfizer, Chugai, Novartis, UCB, Tsumura, Taisho Toyama, Nihon Kayaku and Ayumi. The rest of the authors have no conflict of interest.

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