A Possible Case of Hepatitis due to Hypereosinophilic Syndrome

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Abstract

A 63-year-old Japanese man whose white blood cell count and total-bilirubin and aminotransferase levels were elevated was referred to our hospital. Computed tomography did not reveal any abnormalities, and there was no evidence of gastritis or colitis on esophagogastroduodenoscopy. Although the patient had no history of drug use or allergies, a high concentration of eosinophils (80%) was noted. A liver biopsy revealed hepatitis with eosinophilic infiltration. The patient’s alanine aminotransferase and eosinophil levels improved with the administration of steroids. A second biopsy, performed 6 months later, showed the improvement of the eosinophilic infiltration. The patient was diagnosed with eosinophilic hepatitis due to the presence of hypereosinophilic syndrome without the dysfunction of other organs.

Key words: acute hepatitis, eosinophilia, eosinophilic hepatitis, hypereosinophilic syndrome

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Introduction

Eosinophilia can be classified into 3 categories: reactive eosinophilia, which may occur due to allergies or parasitic infections; clonal disorders of the bone marrow, such as eosinophilic leukemia; and hypereosinophilic syndrome (HES), which is persistent eosinophilia with an unknown etiology (1). HES is also characterized by the eosinophilic infiltration of several organs (1, 2). Although cardiovascular and neuron system diseases are often complications of hypereosinophilia, cases of hepatitis associated with idiopathic HES are rare (3-8). We herein report a case of hepatitis associated with eosinophilia which may have been due to HES.

Case Report

A 63-year-old man was referred to our hospital and admitted with a low fever, general fatigue, epigastralgia, and an itching sensation in February 2012. The patient had a history of cholecystectomy due to gall bladder stones (at 59 years of age) and treatment for a colon polyp (at 60 years of age), but no allergic episodes. Three years prior to his admission, an examination revealed a normal level of eosinophils. He had not recently taken any medication and had no family history of liver or hematological disease. The laboratory data on admission are shown in Table 1. His white blood cell count and eosinophil and aminotransferase levels were observed to be elevated. No viral markers, antinuclear or anti-mitochondrial antibodies, parasite eggs, or anti-parasitic antibodies were detected. The results of a bone marrow puncture examination ruled out eosinophilia caused...
Abdominal ultrasonography, abdominal dynamic computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) examinations revealed no obstruction of the bile ducts, hepatomegaly, or periportal edema. Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT showed a slightly diffuse uptake of FDG in the liver (mean SUV max 3.0) (Fig. 1). The results of esophagogastroduodenoscopy and total colonoscopy, were normal; neither eosinophilic gastritis nor colitis was observed in the mucosa specimens. A liver biopsy, which was performed on the day after admission revealed marked eosinophilic infiltration in the portal area and the liver parenchyma. Furthermore, the degeneration of hepatocytes and the activation of Kupffer cells were observed in both the central and periportal areas (Fig. 2), and the degeneration and ballooning of hepatocytes and cholestasis were observed in the liver specimen.

After the patient’s liver function test results showed no improvement in response to conservative supportive care, steroid pulse therapy (methylprednisolone, 1,000 mg/day) was initiated on day 7 after admission and continued for 3 days. Thereafter prednisolone (PSL) was administered with

### Table 1. Laboratory Data.

| Peripheral blood | Biochemistry | Immunological markers |
|------------------|--------------|-----------------------|
| WBC 33,200 /μL   | TP 7.9 g/dL    | ANA <40               |
| Seg 9.0 %        | ALB 4.4 g/dL   | AMA-M2 <5.0           |
| Eo 80.0 %       | T-Bil 0.5 mg/dL| IgG 1,343 mg/dL       |
| (26,568 /μL)    | AST 101 IU/L   | IgG4 295 mg/dL        |
| Ba 1.0 %         | ALT 158 IU/L   | IgM 270 mg/dL         |
| Lym 8.5 %       | ChE 479 IU/L   | IgE 547 IU/mL         |
| Mon 1.5 %       | LDH 389 IU/L   | TSH 1.19 μIU/mL       |
| RBC 4.12×10^12 /μL | ALP 1,649 IU/L | PTH 2.27 pg/mL        |
| Hb 13.3 g/dL    | γ-GTP 824 IU/L | FT3 1.87 ng/dL        |
| Ht 39.3 %       | BUN 10.8 mg/dL | Viral markers         |
| Plt 29.5×10^11 /μL | Cr 0.65 mg/dL | HbsAg (-)             |
| PT 71.7 %       | Na 140 mEq/L   | anti-HCV (-)          |
| PT-INR 1.21     | K 4.5 mEq/L    | Tumor markers         |
|                  | HbA1c 5.4 %    | AFP 1.7 ng/mL         |
|                  | FBS 116 mg/dL  | PIVKA-II 18 mAU/mL    |

**Figure 1.** (a) The abdominal contrast enhanced computed tomography (CT) and (b) magnetic resonance cholangiopancreatography (MRCP) findings showed no obstruction of the bile ducts, hepatomegaly, or periportal edema. (c) Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT showed the slightly diffuse uptake of FDG in the liver (mean SUV max 3.0).
Discussion

A diagnosis of HES can be made if all of the following criteria are met: persistent eosinophilia (>1,500 eosinophils/μL) for at least 6 months, or death before 6 months with signs and symptoms of HES; the lack of evidence of parasitic, allergic or other recognized causes of eosinophilia; and signs and symptoms of organ system involvement or dysfunction either directly related to eosinophilia or unexplained in the given clinical setting (1, 2). However, Simon et al. recently reported that the original criteria used to define the disorder should be refined, due to advances in both the understanding of HES and the therapeutic agents that are used in its treatment (9).

The present case did not meet the criterion of persistent eosinophilia (>1,500 eosinophils/μL) for at least 6 months. However, we suspect that the liver function test abnormality that was seen in our patient was a clinical feature of HES, because of lack of other causes of eosinophilia. Furthermore, the lack of persistent eosinophilia was thought to have been caused by the initiation of steroid therapy at the onset of acute hepatitis in a relatively early phase of HES. Simon et al. noted that persistent eosinophilia, as shown by >1,500 eosinophils/μL for at least 6 months, is not necessary for a diagnosis of HES (9). This seems to be reasonable, given that some HES cases are resolved in less than 6 months. Additional investigations of this issue are needed.

The frequency of liver involvement in HES has been reported to range from 30-32% (1, 3). The reports describing liver injury associated with hypereosinophilia are summarized in Table 2. Budd-Chiari syndrome, which can be associated with HES (10), is thought to be important in the different cases.
Steroid pulse therapy (methylprednisolone, 1,000 mg/day) was given for 3 days. Thereafter prednisolone (PSL) was administered with a tapering protocol, which improved the elevated levels of aminotransferase and eosinophils. No re-elevation of eosinophils or aminotransferases was observed. Starting from 9 weeks after beginning steroid therapy, the dosage of PSL was increased back to 40 mg/day due to the onset of erythema multiforme. WBC: white blood cells, Eo: eosinophils, ALT: alanine transaminase, γ-GTP: γ-glutamyltransferase

Microphotograph images from the second liver biopsy. a: Enlarged portal area with fibrosis mainly around the sites of bile duct proliferation (Azan staining). b: The proliferation of bile ducts in the portal area. The eosinophilic infiltration was improved in both the parenchyma and the portal area (Hematoxylin and Eosin staining).
The various types of hepatitis associated with HES have been termed chronic active hepatitis (8, 11, 12, 14), eosinophilic hepatitis (15), and hepatitis associated with HES (7). Croffy et al. described patients with HES whose initial biopsy findings showed acute hepatitis, who were diagnosed with chronic hepatitis based on additional biopsy findings after undergoing steroid therapy (11). In addition, Minola and Sonozogni reported a case of acute hepatitis in a patient with eosinophilic infiltration in the lung which was finally proven to be chronic hepatitis (8). Thus, HES causes chronic liver injury in some cases.

In the present case, longer periods were needed for the normalization of ALP and γ-GTP than were required for the normalization of ALT. The proliferation of bile ducts and fibrosis in the portal area were observed in the findings from the second liver biopsy, and were thought to play important roles in the clinical course of ALP and γ-GTP. A previous case report described a patient who was diagnosed with primary sclerosing cholangitis (PSC) after 11 years of marked eosinophilic infiltration in the liver (16). On the other hand, eosinophilia has been reported in 27% of PSC cases complicated with ulcerative colitis (17). Although the pathogenesis of this phenomenon has yet to be clarified, eosinophilic infiltration in the portal area may result in fibrosis both in the portal area and around the bile duct. Although the IgG4 level was elevated, there were no findings of PSC on MRCP in our patient. Nevertheless, PSC should be kept in mind and a long follow-up period is necessary in cases in which marked eosinophilic infiltration is noted in the liver.

In other reports, a therapeutic outcome was obtained in 4 of 9 patients who were treated with PSL (Table 2), while relapse was noted in 2 (50%) of those 4 cases. It was noted that the combination of PSL and UDCA could prevent the relapse of hepatitis in autoimmune hepatitis cases (19). However, there is no established treatment strategy for hepatitis caused by HES; thus we treated our patient with PSL and UDCA to prevent relapse (we intend to stop the administration of PSL after confirming remission). It should be noted, however, that there are no definite criteria for stopping PSL in patients with hepatitis caused by HES. The accumulation of cases with liver injury caused by HES will be

| Year | Reference No. | Age/sex | Symptoms | WBC/eosinophils | Liver biopsy findings | Treatment |
|------|---------------|---------|----------|-----------------|----------------------|-----------|
| 1991 | 12 | 19/M | Abnormal liver function, icterus | WBC 16,500/ Eo 60% | Inflammatory infiltrate containing large numbers of eosinophils in portal zone and surrounding periportal parenchyma | PSL 60 mg/day |
| 1994 | 18 | 70/F | Fever, general malaise | WBC 9,140/ Eo 60% | Multi-nucleation and degeneration of hepatocytes with occasional ballooning and massive infiltration of eosinophils | SNMC |
| 2005 | 8 | 28/F | Acute hepatitis | WBC 8,800/ Eo 24% | Lymphocytic infiltrate with interface hepatitis and spotty necrosis; eosinophils rare with inflammatory cells | PSL 20 mg/day |
| 2007 | 10 | 27/M | Abdominal fullness | WBC 8,000/ Eo 65% | Nodule was obstructive thrombophlebitis with a dense infiltration of eosinophils | PSL 60 mg/day |
| 2009 | 14 | 49/F | Jaundice | WBC 5,300/ Eo 22% | Eosinophilic infiltration in portal and central vein area with focal necrosis around central vein | PSL 30 mg/day → PSL 5 mg + AZA 100 mg |
| 2010 | 13 | 38/M | Pruritic rash | WBC 12,800/ Eo 52.5% | Marked infiltration of eosinophils in portal tract and lobular parenchyma | PSL 60 mg/day |
| Present case | 63/M | Epigastralgia, dysfuction liver | WBC 33,200/ Eo 80.0% | Moderate infiltration of eosinophils at Glisson’s capsule, liver parenchyma, and sinusoid | PSL 40 mg after PSL pulse therapy |

WBC: white blood cells, Eo: eosinophils, PSL: prednisolone, AZA: azathioprine, SNMC: stronger neo-minophagen-C

Table 2. Published Reports of Liver Injury Associated with Hyper Eosinophilia.
needed to clarify the clinical features and prognosis of this disease, and establish an effective treatment protocol to prevent relapse.

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

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