

A Possible Case of Hepatitis due to Hypereosinophilic Syndrome

Tomoe Kawamura¹, Atsushi Hiraoka¹, Akiko Toshimori¹, Hidetaro Ueki¹, Miho Kaneto¹,
Toshihiko Aibiki¹, Tomonari Okudaira¹, Hiroka Yamago¹, Hiromasa Nakahara¹,
Hideomi Tomida¹, Yoshifumi Suga¹, Nobuaki Azemoto¹, Kenichiro Mori¹, Hideki Miyata¹,
Tomoyuki Ninomiya¹, Masashi Hirooka², Masanori Abe², Bunzo Matsuura², Yoichi Hiasa²,
Katsumi Kito³ and Kojiro Michitaka¹

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

(Intern Med 55: 1453-1458, 2016)

(DOI: 10.2169/internalmedicine.55.5982)

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

¹Gastroenterology Center, Ehime Prefectural Central Hospital, Japan, ²Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Japan and ³Department of Pathology, Ehime Prefectural Central Hospital, Japan

Received for publication June 16, 2015; Accepted for publication August 23, 2015

Correspondence to Dr. Atsushi Hiraoka, hirage@m.ehime-u.ac.jp

Table 1. Laboratory Data.

Peripheral blood		Biochemistry		Immunological markers		Parasite eggs (-)	
WBC	33,200 / μ L	TP	7.9 g/dL	ANA	<40	Anti-parasitic antibodies (-)	
Seg	9.0 %	ALB	4.4 g/dL	AMA-M2	<5.0	Dirofilaria immitis	
Eo	80.0 %	T-Bil	0.5 mg/dL	IgG	1,343 mg/dL	Toxocara canis	
	(26,568 / μ L)	AST	101 IU/L	IgG4	295 mg/dL	Ascaris suum	
Ba	1.0 %	ALT	158 IU/L	IgM	270 mg/dL	Anisakis	
Lym	8.5 %	ChE	479 IU/L	IgE	547 IU/mL	Gnathostomiasis	
Mon	1.5 %	LDH	389 IU/L	TSH	1.19 μ IU/mL	Strongyloides stercoralis	
RBC	4.12 $\times 10^6$ / μ L	ALP	1,649 IU/L	FT3	2.27 pg/mL	Paragonimus westermani	
Hb	13.3 g/dL	γ -GTP	824 IU/L	FT4	1.87 ng/dL	Paragonimus miyazaki	
Ht	39.3 %	BUN	10.8 mg/dL	Viral markers		Fasciola hepatica	
Plt	29.5 $\times 10^4$ / μ L	Cr	0.65 mg/dL	HBsAg	(-)	Clonorchis sinensis	
		Na	140 mEq/L	anti-HCV	(-)	Diphyllobothrium mansonii	
		K	4.5 mEq/L	Tumor markers		Cysticercus cellulosae	
PT	71.7 %	Cl	106 mEq/L	AFP	1.7 ng/mL		
PT-INR	1.21	HbA1c	5.4 %	PIVKA-II	18 mAU/mL		
		FBS	116 mg/dL				

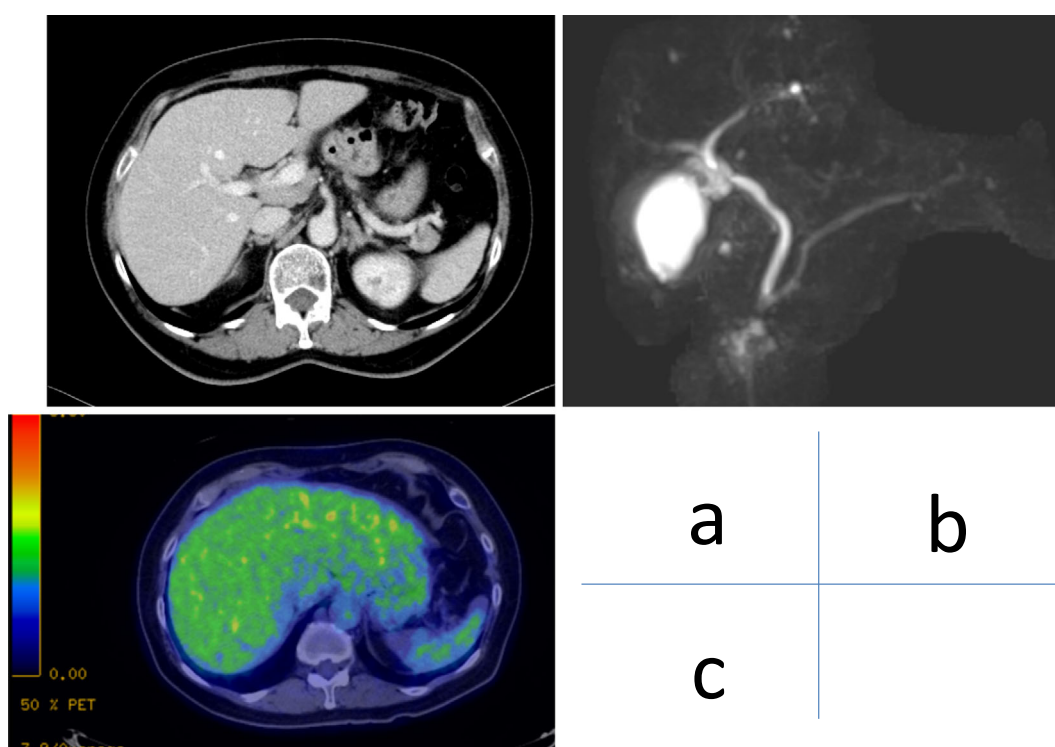


Figure 1. (a) The abdominal contrast enhanced computed tomography (CT) and (b) magnetic resonance cholangiopancreatography (MRCP) findings showed no obstruction of the bile ducts, hepatomegaly, or periportal edema. (c) Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT showed the slightly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

by myeloproliferative disease because the myeloblast findings were normal.

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 up-take 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

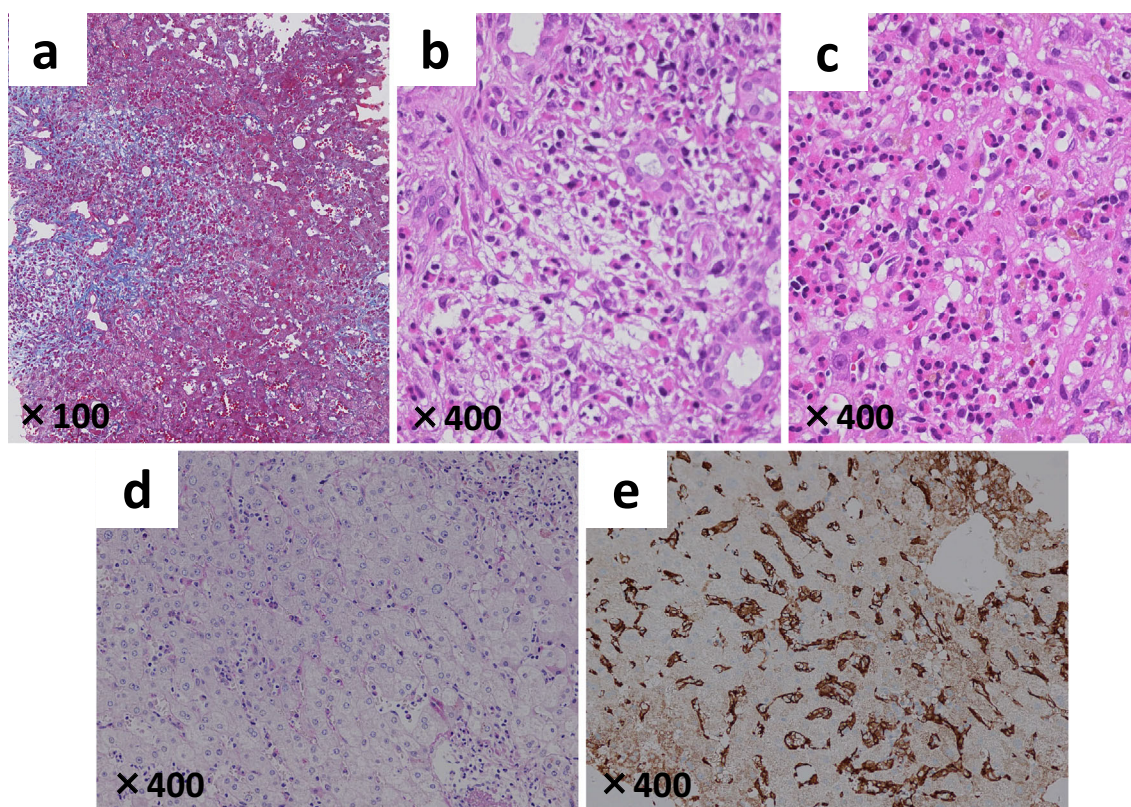


Figure 2. Microphotographs from the first liver biopsy. a: Enlarged portal area with an irregular border (Azan staining). b: Eosinophilic infiltration in the portal area [Hematoxylin and Eosin (H&E) staining]. c: Severe eosinophilic infiltration in the liver parenchyma with degeneration of the hepatocytes (H&E staining). d: Kupffer cells containing phagocytic debris (D-PAS staining). e: Activated Kupffer cells were strongly positive for CD163 (immunostaining with CD163).

a tapering protocol (Fig. 3). The elevated levels of aminotransferase and eosinophils slowly improved, and the patient was discharged 56 days after admission. No re-elevation of eosinophils or aminotransferase was observed with low doses of PSL (5 mg/day) and ursodeoxycholic acid (UDCA) (600 mg/day). It should be noted, however, that even though the levels of alkaline phosphatase (ALP) and γ -glutamyltransferase (γ -GTP) gradually decreased, they did not return to their normal ranges.

A second liver biopsy, which was performed on day 220 after the initial hospitalization, revealed that the eosinophilic infiltration had improved in both the portal area and the liver parenchyma; fibrosis and bile duct proliferation were also observed (Fig. 4). As a result of steroid therapy, the period of eosinophilic elevation was shorter than 6 months. Because we could not identify any apparent cause of the eosinophilic elevation or any other organ disorders, and based on the liver biopsy results, we suspected that the patient's hepatitis was associated with HES.

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 para-

sitic, 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 dif-

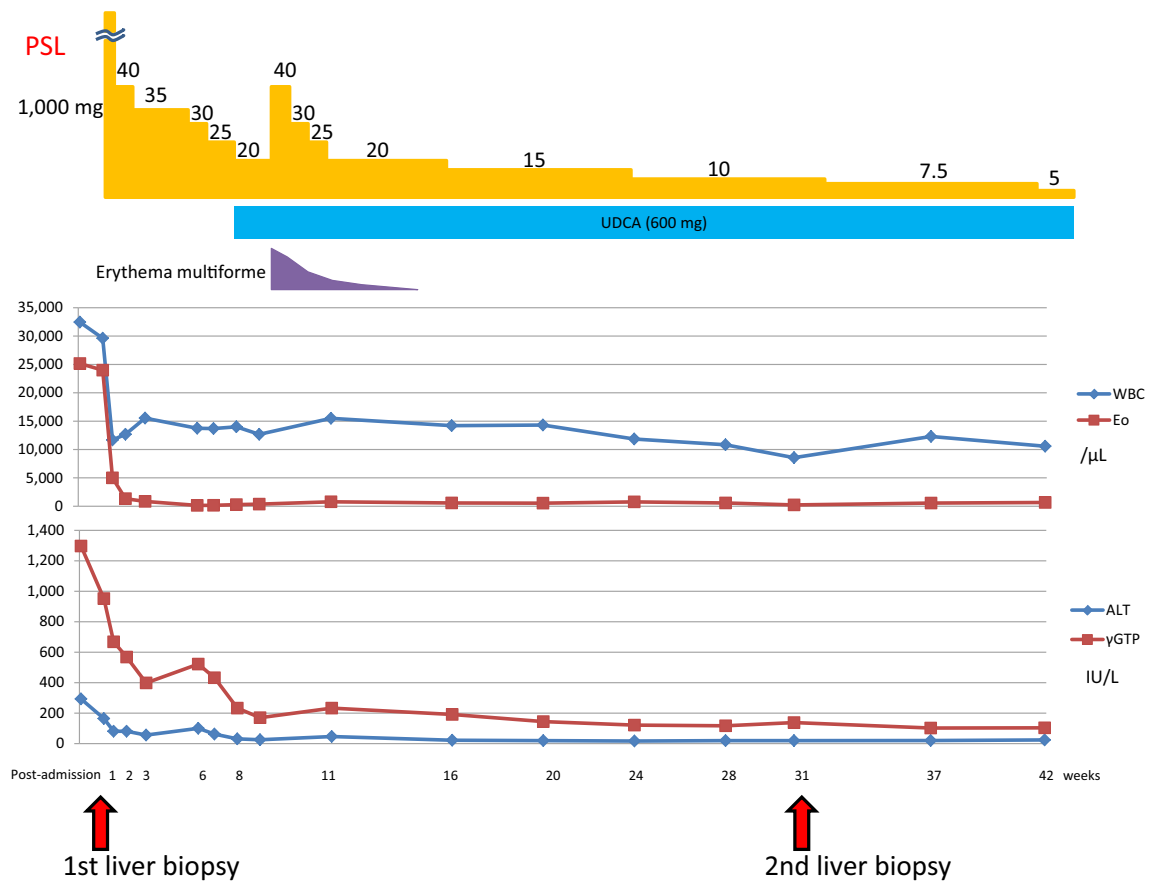


Figure 3. Steroid pulse therapy (methylprednisolone, 1,000 mg/day) was given for 3 days. Thereafter prednisolone (PSL) was administered with a tapering protocol, which improved the elevated levels of aminotransferase and eosinophils. No re-elevation of eosinophils or aminotransferases was observed. Starting 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

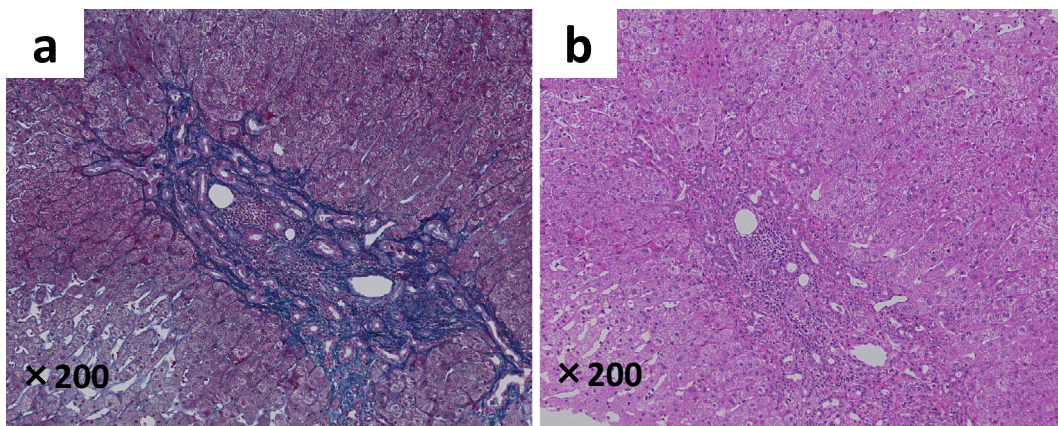


Figure 4. Microphotograph images from the second liver biopsy. a: Enlarged portal area with fibrosis mainly around the sites of bile duct proliferation (Azan staining). b: The proliferation of bile ducts in the portal area. The eosinophilic infiltration was improved in both the parenchyma and the portal area (Hematoxylin and Eosin staining).

ferential diagnosis of liver injury in HES. In the present case, Budd-Chiari syndrome was ruled out based on the abdominal ultrasonography and dynamic CT imaging findings.

Furthermore, the initial liver biopsy findings showed acute hepatitis with a high degree of eosinophilic infiltration in the portal area, which is in line with previous re-

Table 2. Published Reports of Liver Injury Associated with Hyper Eosinophilia.

Year	Reference No.	Age/sex	Symptoms	WBC/eosinophils	Liver biopsy findings	Treatment
1988	11	23/M	Weight loss, liver dysfunction	WBC 7,500 Eo 20%	Portal triad enlarged and infiltrated with mononuclear cells	PSL 30 mg/day →PSL 20 mg + AZA 100 mg
1988	11	20/M	Malaise, fatigue, diffuse myalgias	WBC 19,000 Eo 77%	Portal triad enlarged and infiltrated with mononuclear cells and large number of eosinophils	PSL 30 mg/day
1988	11	28/M	Fatigue, malaise, tea-colored urine	WBC 16,700 Eo 52%	Chronic active hepatitis with bridging fibrosis, portal inflammation, and nodule formation	PSL 40 mg/day →PSL 5 mg + AZA 100 mg
1988	11	34/M	Pruritic rash, nausea, dark urine	WBC 7,500 Eo 22%	Portal inflammation and large number of eosinophils in portal area	PSL 30 mg/day
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, liver dysfunction	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

ports (3, 11-13).

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

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).

References

1. Fauci AS, Harley JB, Roberts WC, et al. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. *Ann Intern Med* **97**: 78-92, 1982.
2. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome. Analysis of fourteen cases with review of the literature. *Medicine* **54**: 1-27, 1975.
3. Weller PF, Budley GJ. The idiopathic hypereosinophilic syndrome. *Blood* **83**: 2759-2779, 1994.
4. Scooley RT, Flaum MA, Gralnick HR, Fauci AS. A clinicopathologic correlation of the idiopathic hypereosinophilic syndrome. II. Clinical manifestations. *Blood* **58**: 1021-1026, 1981.
5. Parillo JE, Borer JS, Henry WL, et al. The cardiovascular manifestations of the hypereosinophilic syndrome. Prospective study of 26 patients, with review of the literature. *Am J Med* **67**: 572-582, 1979.
6. Aoyama T, Matsumoto T, Uchiyama A, et al. Recurrent severe acute hepatitis caused by hypereosinophilic syndrome associated with elevated serum immunoglobulin G4 levels. *Clin J Gastroenterol* **7**: 516-522, 2014.
7. Nagamura N, Ueno S, Fujishiro H, Oonuma H. Hepatitis associated with hypereosinophilia suspected to be caused by HES that also presented with the pathological features of IgG4-related disease. *Intern Med* **53**: 145-149, 2014.
8. Minola E, Sonozogni A. Chronic hepatitis in hypereosinophilic syndrome: report of an usual case. *Infez Med* **13**: 182-186, 2005.
9. Simon HU, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol* **126**: 45-49, 2010.
10. Inoue A, Michitaka K, Shigematsu S, et al. Budd-Chiari Syndrome associated with hypereosinophilic syndrome; a case report. *Intern Med* **46**: 1095-1100, 2007.
11. Croffy B, Kopelman R, Kaplan M. Hypereosinophilic syndrome association with chronic active cepatitis. *Dig Dis Sci* **33**: 233-239, 1988.
12. Foong A, Scholes JV, Gleich GJ, Kephart GM, Holt PR. Eosinophil-induced chronic active hepatitis in the idiopathic hypereosinophilic syndrome. *Hepatology* **13**: 1090-1094, 1991.
13. Nakazawa A, Tamai H, Hayashi A, et al. Active hepatitis with marked eosinophilic infiltration in the hypereosinophilic syndrome patient. *Nihon Naika Gakkai Zasshi (Journal of the Japanese Society of Internal Medicine)* **4**: 822-824, 2010 (in Japanese).
14. Omata F, Shibata M, Nakano M, et al. Chronic hepatitis with eosinophilic infiltration associated with asthma. *Intern Med* **48**: 1945-1949, 2009.
15. Hood B, Nowicki MJ. Eosinophilic hepatitis in an adolescent during lisdexamfetamine dimesylate treatment for ADHD. *Pediatrics* **125**: e1510-e1513, 2010.
16. Watanabe H, Ohira H, Kuroda M, et al. Primary sclerosing cholangitis with marked eosinophilic infiltration in the liver. *J Gastroenterol* **30**: 524-528, 1995.
17. Horiuchi K, Kakizaki S, Kosone T, et al. Marked eosinophilia as the first manifestation of sclerosing cholangitis. *Intern Med* **48**: 1377-1382, 2009.
18. Muramatsu H, Nojiri S, Nagamachi Y, et al. Postinfantile giant cell hepatitis accompanied by hypereosinophilia. *Kanzo (Acta Hepatologica Japonica)* **35**: 864-869, 1994 (in Japanese, Abstract in English).
19. Miyake Y, Iwasaki Y, Kobashi H, et al. Efficacy of ursodeoxycholic acid for Japanese patients with autoimmune hepatitis. *Hepatol Int* **3**: 556-562, 2009.