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Recent Trend of Hepatitis E Virus Infection in Chiba Area, Japan: 3 of 5 Cases with Rheumatoid Arthritis

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Key Words
Autoimmune hepatitis · Hepatitis E virus · Rheumatoid arthritis · IgA anti-hepatitis E virus antibody

Abstract
Hepatitis E virus (HEV) infection is an emerging health concern in developing and developed countries, such as Japan. Five cases have recently been diagnosed as hepatitis E. Of interest, 3 of them had rheumatoid arthritis (RA), although a previous study demonstrated a lack of association between HEV and RA. One of the other patients developed autoimmune hepatitis and was successfully treated with corticosteroids approximately 150 days after the diagnosis of hepatitis E. In RA patients with liver dysfunction, the presence of HEV infection should be evaluated immediately because these patients are often relatively old. Further investigation of the association between HEV and autoimmune hepatitis is needed.

Introduction

Hepatitis E virus (HEV) is a non-enveloped, single-stranded positive-sense RNA virus of approximately 7.2 kb [1]. HEV infection is transmitted primarily through the fecal-oral route [1, 2]. HEV infection may lead to acute hepatitis, including acute liver failure [3], and chronic

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hepatitis in organ transplant recipients [4]. HEV infection is recognized as a serious health problem in developing and in developed countries [1–6].

In Japan, 3.4% of qualified blood donors were positive for immunoglobulin (Ig)G anti-HEV antibodies [7]. Our previous study showed that 23% of the indigenous Japanese population, including individuals over 50 years of age [8], were positive for IgG anti-HEV antibodies. This suggests that Japanese subjects are susceptible to HEV infection and demonstrates the importance of controlling and investigating HEV infection due to the lack of availability of an HEV vaccine in Japan. In 2011, IgA anti-HEV antibody tests were available for the diagnosis of HEV by the Japanese national health insurance system [9].

In patients with rheumatoid arthritis (RA), acute liver injury associated with autoimmune hepatitis and drug-induced liver injury (DILI), reactivation of hepatitis B virus (HBV), and liver dysfunction caused by other reasons are occasionally observed [10, 11]. Here, we report 5 patients who were recently identified to have HEV infection, 3 of whom were also diagnosed with RA.

Case Report

Five cases of HEV infection were observed in our hospital between January 2014 and April 2015. HEV infection was diagnosed by positivity for IgA anti-HEV antibody [9]. The clinical features of the 5 patients in the present study are briefly described in table 1. Case 5 visited our hospital approximately 150 days after onset. All patients were over 50 years old, and 4 of them were female patients. Three cases visited a hospital for their RA, and they took several types of medicine to treat the RA. Cases 2 and 4 drank alcohol (40 and 20 g daily, respectively). Autoantibodies were positive in 3 cases (cases 1, 2, and 5). The clinical courses and laboratory data from the first visit are shown in figure 1 and table 2, respectively.

Case 1

A 64-year-old female who was diagnosed with RA 9 years ago and who received treatment in another hospital was referred to our hospital with general fatigue and liver dysfunction (table 1; fig. 1a). Laboratory data on the first visit to our hospital showed an improved liver function test (table 2a). Her height and body weight were 147 cm and 44 kg, respectively. She was positive for HEV genotype 3 RNA and IgA anti-HEV antibody (fig. 1a). She was also positive for anti-mitochondrial antibody, and a liver biopsy showed Scheuer stage I of primary biliary cirrhosis (PBC) (fig. 2a, b). We ultimately diagnosed her as having HEV infection and PBC, although we initially doubted DILI.

Case 2

A 59-year-old male with a diagnosis of alcoholic liver disease was referred to our hospital with general fatigue and marked liver dysfunction (tables 1, 2b; fig. 1b). His height and body weight were 176 cm and 69 kg, respectively. He was positive for HEV genotype 3 RNA and IgA anti-HEV antibody (fig. 1b). We diagnosed him as having HEV infection. After admission to our hospital, he was given bed rest and peripheral parenteral nutrition, and his condition improved. This patient had consumed deer meat approximately 1 month before admission.

Case 3

A 74-year-old female who was diagnosed as having RA 20 years ago and was treated in a different hospital was referred to our hospital with general fatigue and liver dysfunction

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(tables 1, 2c; fig. 1c). Her height and body weight were 154 cm and 54 kg, respectively. Because she was treated with tofacitinib only 2 months previously, we initially doubted that DILI was caused by this drug. However, she was positive for HEV genotype 3 RNA and IgA anti-HEV antibody (fig. 1c). We diagnosed her as having HEV infection.

Case 4

A 52-year-old female who was diagnosed with RA 4 years ago and whose RA was treated in another hospital was referred to our hospital with general fatigue and liver dysfunction (tables 1, 2d; fig. 1d). Her height and body weight were 152 cm and 50 kg, respectively. She was positive for HEV genotype 3 RNA and IgA anti-HEV antibody (fig. 1d). We diagnosed her as having HEV infection. After admission to our hospital, she was given bed rest and peripheral parenteral nutrition, and her condition improved. A liver biopsy confirmed acute hepatitis (fig. 2c, d).

Case 5

A 77-year-old female who was diagnosed with HEV infection based on positivity for IgA anti-HEV antibody approximately 150 days before admission to our hospital was referred to our hospital with general fatigue and liver dysfunction (tables 1, 2e; fig. 1e). Her height and body weight were 144 cm and 50 kg, respectively. She was positive for antinuclear antibody, and her IgG was elevated. A liver biopsy showed typical characteristics of autoimmune hepatitis (fig. 2e–g). We began corticosteroid therapy, and her liver tests improved; however, her positivity for IgA anti-HEV persisted 9 months after onset. Upon admission to our hospital, although HEV RNA was negative, we diagnosed her as having HEV infection according to the changes of titers of anti-HEV antibodies (fig. 1e). An updated (1999) scoring system for the diagnosis of autoimmune hepatitis [12] indicated probable autoimmune hepatitis (score: 16) because viral hepatitis by HEV was not completely ruled out on this score system.

Discussion

In the current study, we presented 5 cases with HEV infection. The mean age of these patients was 65 ± 11 years, 4 patients were female, and 3 had RA. Two patients were over 65 years of age, and 1 of these 2 patients was over 65 years old and had RA. Only 1 male patient without RA reported consumption of deer meet before onset. In the other 4 patients, the infectious sources of HEV were unknown.

Pischke et al. [13] reported that patients with autoimmune hepatitis, but not RA or HBV/HCV patients, are more likely to test positive for anti-HEV. They reported that only 4 of 114 (3.5%) RA patients were positive for HEV-specific antibodies, similar to healthy individuals [11 of 537 (2.0%)]. However, we found that 3 of 5 patients with HEV infection had RA. The present study suggests that it is important to rule out HEV infection in RA patients with liver dysfunction.

Although an initial diagnosis of HEV infection was made based on the positivity for IgA anti-HEV antibody in case 5, she was also diagnosed as having autoimmune hepatitis based on a subsequent liver biopsy (fig. 2e). Although a corticosteroid was administered and her liver dysfunction improved, positivity for IgA anti-HEV antibody persisted for 9 months after onset. It is well known that autoimmune hepatitis rarely follows acute viral hepatitis [14]. Inagaki et al. [15] reported that a 65-year-old female with HEV RNA was diagnosed as having probable autoimmune hepatitis and was successfully treated with prednisolone. Nagasaki et al. [16] also recommended that HEV infection should be ruled out in the cases with acute

cryptogenic hepatitis, including autoimmune hepatitis. Three of the cases described in the present study were positive for autoantibodies. Careful attention should be given to these features [17]. Together, HEV infection could trigger autoimmune hepatitis in some cases.

Recently, reports about HBV reactivation in RA patients treated with newer biological drugs like tocilizumab and abatacept have been increasing [18]. A remarkably high incidence of tuberculosis in RA patients treated with TNF-α antagonists has been reported [19]. In the present study, 3 patients with RA were well controlled and had stable activity of RA. Of interest, case 3 took tofacitinib. Further studies will be needed.

RA patients with liver dysfunction are treated with several medications, and DILI should also be ruled out (table 1), as well as viral hepatitis. In conclusion, due, in part, to the availability of the IgA anti-HEV antibody, we have recently diagnosed 5 cases as being positive for HEV. In RA patients with liver dysfunction, HEV infection should also be ruled out using the IgA anti-HEV antibody, because these patients include older patients. Further studies regarding the association between HEV and autoimmune hepatitis are needed. The present study also showed that HEV infection is an important emerging health concern.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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Table 1. Clinical features of 5 patients with HEV infection

	Case 1	Case 2	Case 3	Case 4	Case 5
Age, years/gender	64/female	59/male	74/female	52/female	77/female
Duration, days[1]	19	1	7	9	~150
Underlying diseases	RA	ALD	RA	RA	hypertension
Symptom(s)	fatigue	fever, fatigue	fatigue	epigastric discomfort	fatigue
Max. AST, IU/l	202	1,953	842	813	793
Max. ALT, IU/l	527	1,944	753	973	850
Max. total bilirubin, mg/dl	0.6	5.4	0.7	1.1	1.7
Min. PT, %	126	100	114	84	56
Source of infection	unknown	deer meat	unknown	unknown	unknown
ANA, -fold	80	160	80	40	320
ASMA, -fold/AMA M2	80/14.6	neg./neg.	neg./neg.	neg./neg.	neg./neg.
Medicine before onset	bucillamine, loxoprofen, methotrexate, folic acid, alendronate, eldecalcitol, rabeprazole sodium, magnesium oxide, UDCA	acetylsalicylic acid	tofacitinib, prednisolone, loxoprofen, salazosulfapyridine, eldecalcitol, tocopherol nicotinate, methylcobalamin, teprenone, limaprost alfadex	methotrexate, triamcinolone, folic acid, pregabalin, roxatidine acetate hydrochloride, neurotropin, amoxapine, sulpiride, etizolam	nifedipine, candesartan cilexetil, doxazosin, famotidine, rebamipide, UDCA

ALD = Alcoholic liver disease; AST = aspartate transaminase; ALT = alanine transaminase; Max. = maximum; Min. = minimum; PT = prothrombin time; ANA = anti-nuclear antibody; ASMA = anti-smooth muscle antibody; AMA = anti-mitochondrial antibody; neg. = negative; UDCA = ursodeoxycholic acid. [1] Duration between onset and visit to the hospital.

Table 2. Laboratory data for 5 patients with HEV infection on their first visit

Category	Units	Category	Units	Category	Units
a *Case 1*					
AST	22 IU/l	WBC	6,600 /mm^3	IgM HA	(–)
ALT	46 IU/l	RBC	419×10^4/mm^3	IgM HBc	(–)
G-GTP	35 IU/l	Hb	13.2 g/dl	HBsAg	(–)
ALP	185 IU/l	Hct	38.5%	HBsAb	(–)
LDH	172 IU/l	Platelets	301×10^3/mm^3	HBcAb	(–)
TP	7.5 g/dl	Eosinophils	1.5%	HBV DNA	(–)
ALB	3.9 g/dl	PT%	126%	HCV Ab	(–)
T. Bil	0.5 mg/dl	PT-INR	0.91	HCV RNA	(–)
D. Bil	0.1 mg/dl	ESR	25 mm/h	IgA HEV	(+)
T. CHO	187 mg/dl	HbA1C	5.0%	ANA	×80
UA	5.0 mg/dl	IgG	1,580 mg/dl	ASMA	×80
UN	13 mg/dl	IgM	337 mg/dl	AMA M2	14.6 (+)
Cre	0.46 mg/dl	IgA	299 mg/dl	aLKM1	(–)
CRP	0.1 mg/dl	TSH	1.086 μIU/ml	AFP	3.2 ng/ml
b *Case 2*					
AST	1,953 IU/l	WBC	3,900 /mm^3	IgM HA	(–)
ALT	1,944 IU/l	RBC	473×10^4/mm^3	IgM HBc	(–)
G-GTP	401 IU/l	Hb	14.6 g/dl	HBsAg	(–)
ALP	710 IU/l	Hct	43.4%	HBsAb	(–)
LDH	1,293 IU/l	Platelets	127×10^3/mm^3	HBcAb	(–)
TP	7.4 g/dl	PT%	111%	HBV DNA	(–)
ALB	3.9 g/dl	PT-INR	1.01	HCV Ab	(–)
T. Bil	4.5 mg/dl	ESR	35 mm/h	HCV RNA	(–)
D. Bil	3.2 mg/dl	HbA1C	5.4%	IgA HEV	(+)
T. CHO	197 mg/dl	IgG	1,928 mg/dl	ANA	×160
UA	5.6 mg/dl	IgM	259 mg/dl	ASMA	(–)
UN	20 mg/dl	IgA	259 mg/dl	AMA	(–)
Cre	0.79 mg/dl	TSH	3.604 μIU/ml	HIV	(–)
CRP	2.2 mg/dl	HA	71 ng/ml	AFP	26.5 ng/ml
c *Case 3*					
AST	262 IU/l	WBC	12,800 /mm^3	IgM HA	(–)
ALT	444 IU/l	RBC	386×10^4/mm^3	IgM HBc	(–)
G-GTP	68 IU/l	Hb	12.2 g/dl	HBsAg	(–)
ALP	229 IU/l	Hct	36.9%	HBV DNA	(–)
LDH	310 IU/l	Platelets	286×10^3/mm^3	HCV Ab	(–)
TP	7.4 g/dl	Eosinophils	0.2%	HCV RNA	(–)
ALB	4.1 g/dl	PT%	114%	IgA HEV	(+)
T. Bil	0.6 mg/dl	PT-INR	1.02	ANA	×80
D. Bil	0.1 mg/dl	ESR	27 mm/h	ASMA	(–)
T. CHO	200 mg/dl	HbA1C	5.4%	AMA	(–)
UA	6.4 mg/dl	IgG	1,551 mg/dl		
UN	19 mg/dl	IgM	187 mg/dl		
Cre	0.68 mg/dl	IgA	145 mg/dl		
CRP	3.4 mg/dl	TSH	1.017 μIU/ml		
d *Case 4*					
AST	565 IU/l	WBC	4,200 /mm^3	IgM HA	(–)
ALT	973 IU/l	RBC	411×10^4/mm^3	IgM HBc	(–)
G-GTP	506 IU/l	Hb	14.1 g/dl	HBsAg	(–)
ALP	1,214 IU/l	Hct	41.0%	HBV DNA	(–)

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LDH	374 IU/l	Platelets	327×10³/mm³	HCV Ab	(–)
TP	7.9 g/dl	Eosinophils	0.7%	HCV RNA	(–)
ALB	4.2 g/dl	PT%	108%	IgA HEV	(+)
T. Bil	4.3 mg/dl	PT-INR	1.00	ANA	×40 (–)
D. Bil	3.3 mg/dl	ESR	22 mm/h	ASMA	(–)
T. CHO	161 mg/dl	HbA1C	4.9%	AMA M2	1.6 (–)
UA	3.7 mg/dl	IgG	1,552 mg/dl		
UN	8 mg/dl	IgM	211 mg/dl		
Cre	0.53 mg/dl	IgA	178 mg/dl		
CRP	1.1 mg/dl	TSH	0.743 μIU/ml		
e *Case 5*					
AST	209 IU/l	WBC	9,200 /mm³	IgM HA	(–)
ALT	227 IU/l	RBC	381×10⁴/mm³	IgM HBc	(–)
G-GTP	56 IU/l	Hb	12.5 g/dl	HBsAg	(–)
ALP	723 IU/l	Hct	37.5%	HBV DNA	(–)
LDH	338 IU/l	Platelets	132×10³/mm³	HCV Ab	(–)
TP	7.1 g/dl	Eosinophils	0.5%	HCV RNA	(–)
ALB	2.5 g/dl	PT%	60%	IgA HEV	(+)
T. Bil	1.5 mg/dl	PT-INR	1.27	HEV RNA	(–)
D. Bil	0.4 mg/dl	ESR	20 mm/h	IgG HEV	(+)
T. CHO	146 mg/dl	HbA1C	4.9%	ANA	×320 (+)
UA	5.1 mg/dl	IgG	2,777 mg/dl	ASMA	(–)
UN	10 mg/dl	IgM	163 mg/dl	AMA	(–)
Cre	0.54 mg/dl	IgA	560 mg/dl	ACE	31.9
CRP	0.8 mg/dl	TSH	1.151 μIU/ml	NH3	82 μg/ml

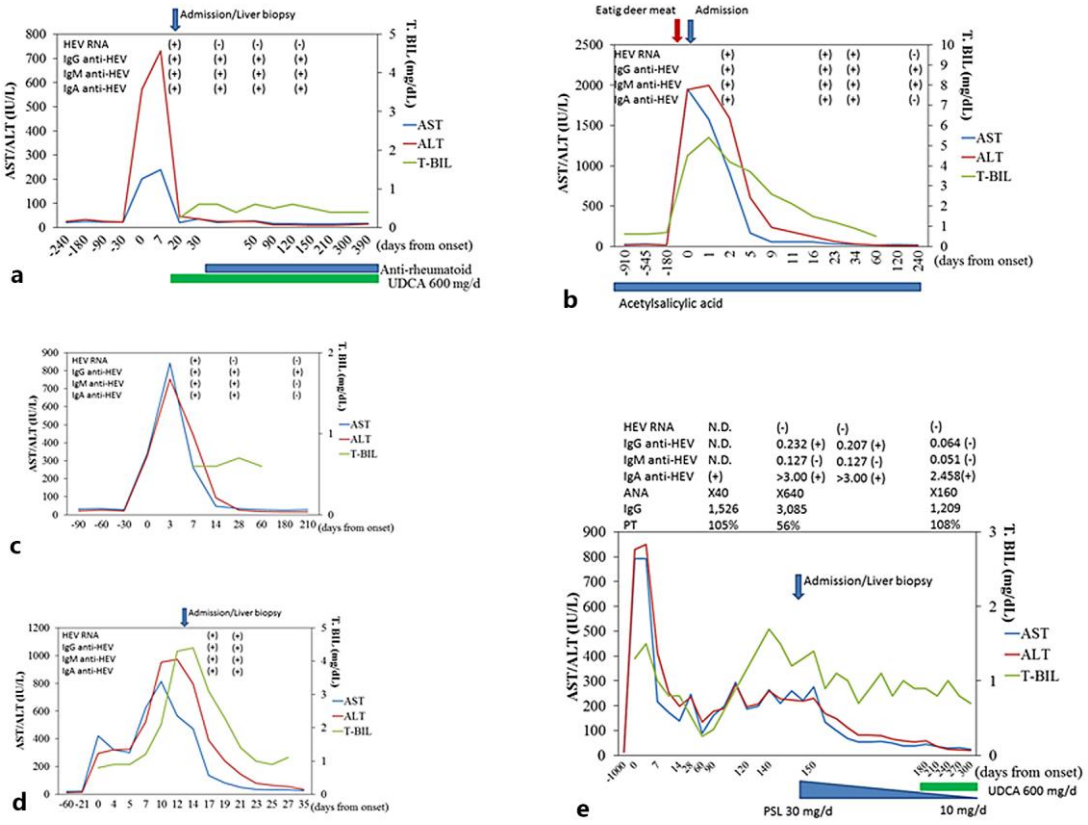

Fig. 1. Clinical course of 5 patients with HEV infection in the present study. **a** Case 1. **b** Case 2. **c** Case 3. **d** Case 4. **e** Case 5. Cases 1, 3, and 4 visited a hospital for their RA. Cases 1–4 were positive for HEV RNA at least at one time point. Samples from cases 2–4 contain HEV genotype 3b determined based on an analysis of the 412-nt ORF2 sequence [20]. As the HEV RNA level was low titer in case 1, the sample from case 1 contains HEV genotype 3 determined based on an analysis of the 97-nt ORF2/3 sequence [20]. In case 5, we did not detect HEV RNA, but we diagnosed this case as HEV infection according to changes in titers of anti-HEV antibodies. AST = Aspartate transaminase; ALT = alanine transaminase; T-BIL = total bilirubin; UDCA = ursodeoxycholic acid; ANA = anti-nuclear antibody; PT = prothrombin time; PSL = prednisolone.

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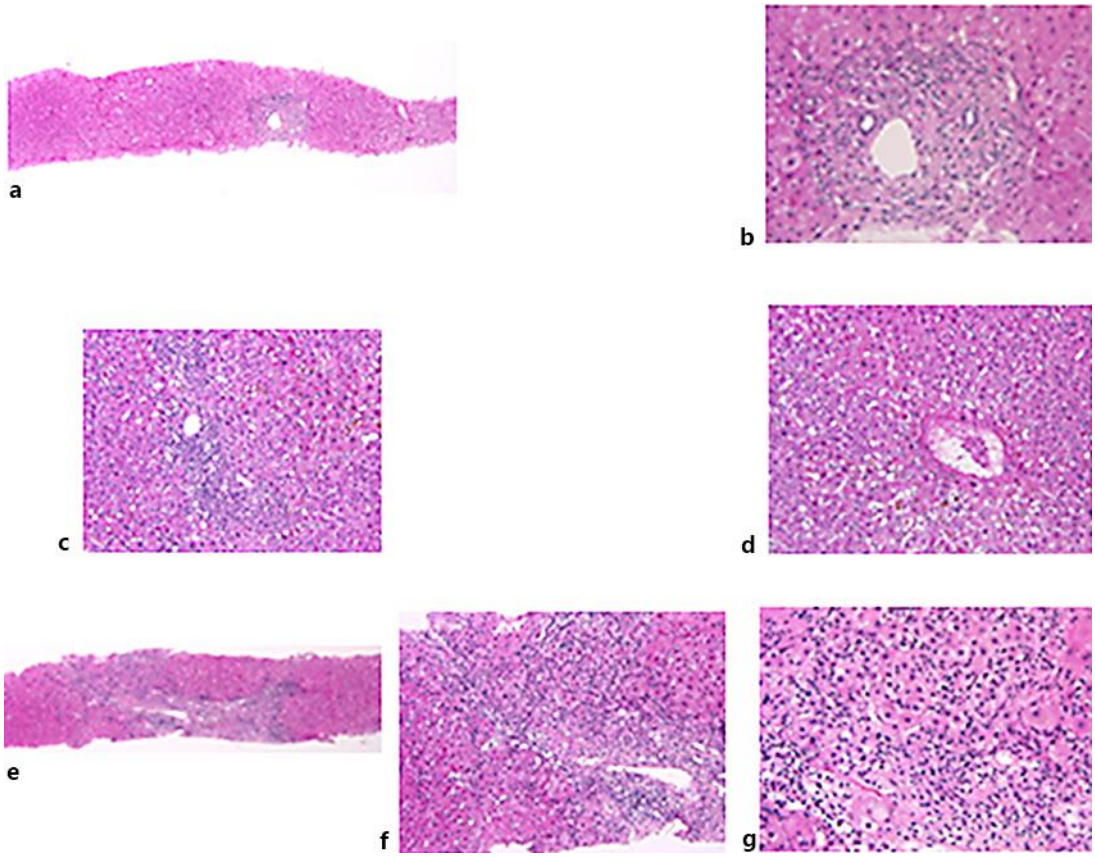

Fig. 2. Liver biopsy findings in cases 1, 4, and 5. In case 1, the hepatic architecture was preserved (**a** HE, ×40), and findings were compatible to Scheuer stage I of PBC (**b** HE, ×100). In case 4, the hepatic architecture was preserved, and marked inflammation in periportal areas (**c** HE, ×100) and centrilobular necrosis (**d** HE, ×100) were observed, indicating acute hepatitis. In case 5, a liver biopsy showed a partly preserved hepatic architecture but no cirrhosis (**e** HE, ×40). Marked inflammation including rosette formation in the periportal area (**f** HE, ×100) and plasma cell infiltration (**g** HE, ×100) were observed, suggesting autoimmune hepatitis.