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Case Report

A Male Patient with Acute Hepatitis E Showing Asymptomatic and Transient Hyperthyroidism Due To Autoimmune Thyroiditis

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1. Abstract

Although numerous extrahepatic manifestations associated with hepatitis E virus (HEV) infection have been reported, thyroid disorder is extremely rare. Here, we present a male patient with acute hepatitis E (AHE) showing asymptomatic and transient hyperthyroidism due to autoimmune thyroiditis. Immunoglobulin A class antibody against HEV and HEV-RNA (subgenotype; 3a) were positive. On admission, free T3 and T4 thyroid hormones were elevated, while thyroid stimulating hormone was decreased. Moreover, anti-thyroglobulin antibody and anti-thyroid peroxidase antibody were positive, suggesting autoimmune thyroiditis-associated hyperthyroidism. However, the characteristic symptoms or signs of hyperthyroidism were absent. AHE was self-limiting and thyroid hormone levels and thyroid-related antibodies became normal without specific treatment for hyperthyroidism. This rare case suggests that the screening test of thyroid function may be important in AHE to clarify the prevalence of thyroid disorder associated with AHE, even if thyroid-related symptoms or signs are absent.

2. Keywords: Acute hepatitis E; Extrahepatic manifestation; Autoimmune thyroiditis; Hyperthyroidism

3. Introduction

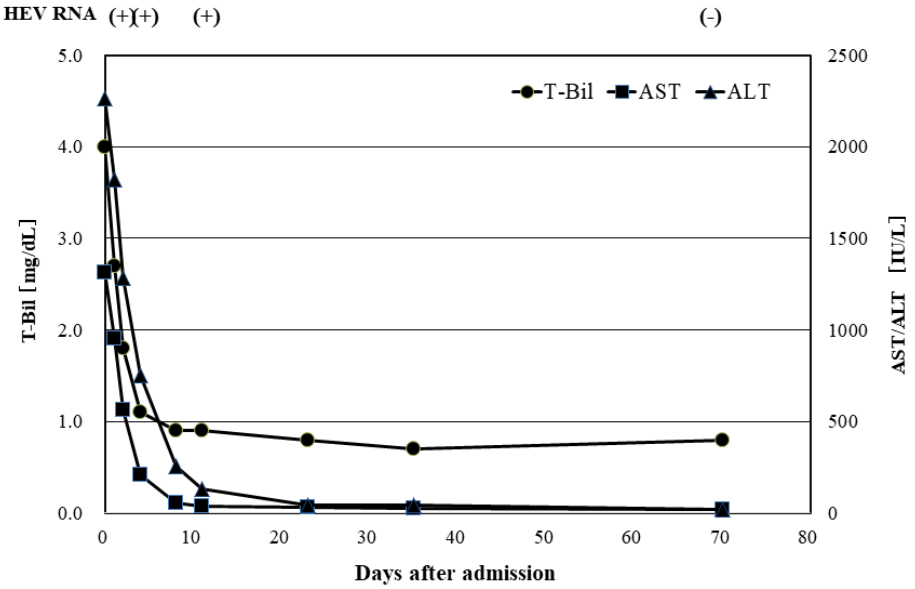
Hepatitis E virus (HEV) is one of the major causes of acute sporadic viral hepatitis worldwide [1-5]. In general, HEV is enterically transmitted, and blood-borne infection of HEV is extremely rare [6-8]. Four major pathogenic genotypes of HEV (GT1-4) have been identified with a specific geographical distribution [1-4]. HEV genotypes 3 and 4 are known as zoonotic and autochthonous viruses [1-6, 9]. In Japan, HEV genotypes 3 and 4 are the major genotypes (5, 10, 11). Although acute hepatitis E (AHE) is usually a self-limiting disease with complete recovery, immunocompromised patients could develop chronic hepatitis, eventually leading to liver cirrhosis [3, 12-16]. Extrahepatic manifestations associated with HEV infection have been reported, including neurological disorders such as Guillain-Barré syndrome, renal failure, hematological disorders, and acute pancreatitis [17-20]. However, alterations in thyroid functions have been rarely reported in AHE [21-26]. The case of a male AHE patient with asymptomatic and transient hyperthyroidism due to autoimmune thyroiditis is presented.

3. Case Report

A 43-year-old man had been treated for type 2 diabetes mellitus (DM) and dyslipidemia elsewhere for 12 years. He had been prescribed pioglitazone hydrochloride (30 mg/day), a sodium glucose cotransporter 2 inhibitor (empagliflozin: 10 mg/day), metformin hydrochloride (1500 mg/day), and a glucagon-like peptide receptor agonist (subcutaneous injection: dulaglutide 0.75 mg, once a week) with periodic follow-up (once a month) at an outpatient clinic before the onset of symptoms. However, because his glycemic control was poor, an α-glucosidase inhibitor (miglitol) was started. Twelve days after starting miglitol, he developed anorexia, fatigue, myalgia, and arthritis without pyrexia. Blood chemistry data were as follows: aspartate aminotransferase (AST) 1,313 IU/L; alanine aminotransferase (ALT) 2,266 IU/L; and total bilirubin (T-Bil) 4.0 mg/dL. The patient was referred and admitted to Morioka Municipal Hospital. He had a history of alcohol intake (estimated consumption of ethanol of about 36 g/day) twice a week for 23 years. He had no family history of DM. He was obese with a body mass index of 28.4 kg/m^2, and he had mild hypertension. On physical examination, although slight jaundice was observed, skin eruption, lymphadenopathy, and hepatosplenomegaly were absent.

Table 1 shows the laboratory data on admission. The platelet count showed a slight decrease (the platelet count was 11.2 x 10^4/μL 3 months before the onset of hepatitis). Serum liver enzymes (AST, ALT, alkaline phosphatase, and γ-glutamyl transferase) were significantly elevated. The T-Bil level was slightly elevated, and prothrombin time activity was normal. Serum immunoglobulin G, A, and M concentrations were normal. The serum antinuclear antibody titer was slightly positive at 1:80, but anti-mitochondria antibody-M2 was negative. Of the viral hepatitis markers (hepatitis A, B, C, and E), only immunoglobulin A-class HEV antibody (IgA-HEV Ab) was positive. Thus, informed consent was obtained from the patient to measure HEV-RNA and its genotype. HEV-RNA was positive on admission, and its subgenotype was determined to be 3a according to the previously described method [10]. The nucleotide sequence of the HEV genome has been deposited to DDBJ/EMBL/Gen Bank databases under accession no. LC554176. The patient had no history of drinking unsterilized water or of consuming raw fish or shellfish. He also denied the intake of raw or undercooked meat/offal from livestock or wild animals such as deer or boar. He also had no history of travelling to an HEV endemic area such as Southeast Asia. The markers for Epstein-Barr virus and cytomegalovirus infection were not examined, because typical signs of infection with these viruses, such as fever, pharyngitis and tonsillitis, were not observed throughout the course. Abdominal sonography and computed tomography showed only diffuse fatty deposition in the liver and slight splenomegaly. A drug-lymphocyte stimulation test with miglitol was not performed, because IgA-HEV Ab was positive the day after admission, establishing the diagnosis of acute hepatitis with HEV infection (AHE). After admission, serum AST and ALT levels decreased rapidly and became normal on day 70 of admission. The elevated serum T-Bil level also normalized in 10 days. The platelet count increased gradually and returned to normal (data not shown). Serum HEV-RNA was negative 9 weeks after the onset of hepatitis (Figure).

Figure



Surprisingly, on admission, the patient's thyroid-stimulating hormone (TSH) level was low, whereas free thyroid hormone 3 (FT3) and free thyroid hormone 4 (FT4) levels were considerably elevated. In addition, the titers of anti-thyroglobulin antibody (TgAb) and anti-thyroid peroxidase antibody (anti-TPOAb) were both clearly high (Table 1). These data met the diagnostic criteria of hyperthyroidism due to autoimmune thyroiditis. However, because there were no characteristic signs and/or symptoms such as goiter, sweating, tachycardia, tremor, or weight loss due to hyperthyroidism before and after the onset of acute liver injury, it was decided to carefully observe the course without treatment for hyperthyroidism. As shown in Table 2, the TSH level increased gradually, and the FT3 and FT4 levels decreased gradually; these thyroid hormones eventually normalized following the improvement of liver function. Both serum TgAb and anti-TPOAb became undetectable 168 days after admission.

Table 1. Laboratory findings on admission.

Hematology		CRP (mg/dL)	0.81	Hepatitis virus markers	
RBC (x 10^4/μL)	528	BUN (mg/dL)	10.4	IgM anti-HAV	(-)
Hb (g/dL)	15.1	CRNN (mg/dL)	0.83	IgA anti-HEV	(+)
Ht (%)	46			IgM anti-HBc	(-)
WBC (/μL)	3800	Blood coagulation		HBsAg/anti-HBs	(-)/(-)
Neutrophils (%)	44	PT-INR	0.88	Anti-HCV	(-)
Lymphocytes (%)	47.1			HEV-RNA	(+)
Monocytes (%)	6	Immunoglobulin		HEV subgenotype	3a
Basophils (%)	0.3	IgG (mg/dL)	1211		
Eosinophils (%)	2.8	IgA (mg/dL)	267	Autoantibodies	
Platelets (x 10^4/μL)	11.2	IgM (mg/dL)	182	ANA (x titers)	1:80
				AMA M2 (U/mL)	1.7 (-)
Blood chemistry		Thyroid hormones*			
T-Bil. (mg/dL)	2.7	TSH (μIU/mL)	0.086	Tumor markers	
AST (IU/L)	951	freeT3 (pg/mL)	9.16	AFP (ng/mL)	<2.0
ALT (IU/L)	1821	freeT4 (ng/mL)	4.49	PIVKA-II (mAU/mL)	58
LDH (IU/L)	573				
γGTP (IU/L)	271	Thyroid-related antibodies*			
ALP (IU/L)	629	TgAb (IU/mL)	2046		
T-Protein (g/dL)	7	anti-TPO Ab (IU/mL)	>600		
Albumin (g/dL)	2.4				

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; T-Bil., total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γGTP, γ-glutamyl transferase; ALP, alkaline phosphatase; T-Protein, total protein; CRP, C-reactive protein; BUN, blood urea nitrogen; CRNN, creatinine; PT-INR, prothrombin time-international ratio; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M, TSH, thyroid stimulating hormone; TgAb, thyroglobulin antibody; anti-TPOAb, anti-thyroid peroxidase antibody; HAV, hepatitis A virus; HEV, hepatitis E virus; HCV, hepatitis C virus; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; AFP, α-fetoprotein; PIVKA-II, protein-induced vitamin K absent-II.

*Baseline ranges shown in Table 2.

Table 2: Serial changes in serum thyroid hormone and thyroid-related antibody levels.

Days after admission	TSH μIU/mL (0.5-5.0)	FT3 pg/mL (2.3-4.0)	FT4 ng/mL (0.9-1.7)	TgAb IU/mL (<28.0)	Anti-TPOAb IU/mL (<16.0)
1	0.086	9.16	4.49		
4				2046.0	≧600
23	0.246	9.12	1.37		
70	0.576	5.30	1.37		
168	0.896	3.31	1.18	< 10.0	< 9.0
294	2.470	3.87	1.27		

TSH, thyroid stimulating honnone; FT3, free thyroid 3; FT4, free thyroid 4; TgAb, thyroglobulin antibody; anti-TPO Ab, anti-thyroid peroxidaseantibody.
( ); baseline ranges.

4. Discussion

Although the extrahepatic manifestations associated with HEV infection, neurological, hematological, renal, and pancreatic disorders, have often been discussed [17-21], thyroid dysfunction associated with HEV infection has been extremely rare [21-26]. In our Department of Internal Medicine in Morioka Municipal Hospital, serum thyroid hormones are routinely measured in patients with unknown acute liver injury, because patients with thyroid dysfunction often show abnormal liver function tests [27-30]. Therefore, a male AHE patient with hyperthyroidism due to autoimmune thyroiditis on admission was identified. Table 3 summarizes seven cases including the present case with thyroid disorders associated with AHE in previous reports: five cases had self-limiting acute hepatitis, one had a severe form of acute hepatitis, and one had acute fulminant hepatic failure. Furthermore, two were hepatitis B virus carriers. The present case had self-limiting acute hepatitis. Thyroid disorders reported in AHE patients include subclinical hyperthyroidisms, Graves' disease (GD), thyrotoxicosis, autoimmune thyroiditis, subacute thyroiditis, and thyroiditis. Of special interest, all had hyperthyroidism. The present case was considered to have had hyperthyroidism due to autoimmune thyroiditis, but the patient was asymptomatic, and the abnormal thyroid function was transient. Hyperthyroidism is generally classified into overt or subclinical hyperthyroidism, depending on the biochemical severity [31]. Overt hyperthyroidism is defined as subnormal, usually undetectable, serum TSH with elevated serum levels of FT3 and/or free FT4. Subclinical hyperthyroidism is defined as subnormal serum TSH with normal FT3 and FT4 levels. Both overt and subclinical disease may lead to characteristic signs and symptoms, although subclinical hyperthyroidism is usually considered milder. According to these findings, the present low TSH level with elevated FT3 and FT4 levels met the diagnostic criteria for hyperthyroidism. However,

interestingly, the patient did not show any characteristic signs and/or symptoms associated with hyperthyroidism, suggesting the presence of asymptomatic hyperthyroidism. In addition, serum TgAb and anti-TPOAb were positive. Serum TgAb and anti-TPOAb may indicate autoimmune thyroid diseases including GD and Hashimoto's disease. Endogenous hyperthyroidism is most commonly due to GD or nodular thyroid disease. Toxic nodular goiter is less common than GD, and its prevalence may increase with age and in the presence of dietary iodine deficiency [32, 33]. Diffuse goiter was not observed throughout the course in the present case. Because thyroid sonography was performed 3 months after discharge, whether nodular goiter was present during the acute phase of hepatitis was not known.

Table 3. Cases of thyroid disorders associated with acute hepatitis E.

Case	Location	Sex/Age (y.o.)	Clinical types of HEV infection/ HEV genotype and subgenotype	Types of thyroid disorders	References
1	Hong Kong	M/38	Fulminant hepatic failure (with HBV carrier) n.t.	Thyrotoxicosis	Hui AY, et al. [22]
2	South Korea	F/34	Acute (with HBV carrier) n.t.	Subclinical hyperthyroidism	Kong SJ, et al. [23]
3		M/42	Acute n.t.	Graves' disease	
4	Germany	F/Middle	Acute n.t.	Autoimmune thyroiditis	Dumoulin FL, et al. [24]
5	Argentina	M/45	Acute 3a	Subacute thyroiditis	Martinez-Artola Y, et al. [25]
6	Japan	F/65	Acute (severe form) n.t.	Painless thyroiditis (serum thyroid hormone levels are not revealed)	Inagaki Y, et al. [26]
Present Care	Japan	M/43	Acute 3a	Asymptomatic hyperthyrodism (autoimmune thyroditis)	

n.t.; not tested

Mild and transient thrombocytopenia was also seen in the present patient. Idiopathic thrombocytopenia has been considered an extrahepatic manifestation of AHE [18, 34-37]. It is found that about 11.3% of HEV-infected patients had low platelet counts [36]. Because thrombocytopenia is occasionally observed in viral hepatitis other than AHE [38, 39], whether the mild thrombocytopenia was indeed an extrahepatic manifestation associated with HEV infection was not clear, although it is noteworthy that the decreased platelet count became normal in the convalescent phase of acute hepatitis in the present case.

The pathophysiological mechanism of the development of extrahepatic manifestations remains unclear. It may, however, involve either direct viral effects due to HEV replication in affected tissues or indirect immune-mediated mechanisms including cytokine reactions [19, 20, 40, 41]. The present case with transient and asymptomatic hyperthyroidism based on autoimmune thyroiditis suggests possible immune interactions between thyroid tissue and HEV. Associations between HEV genotype and/or subgenotype and extrahepatic manifestations have remained unclear, although the prevalence of HEV genotype 3 might be high in previous reports [17-20]. As indicated in Table 3, only two of seven AHE cases with thyroid dysfunction, one reported by Martinez-Artola et al. [25] and the present case, had their HEV genotype/subgenotype evaluated and showed 3a. Further study is needed to examine whether the HEV genotype affects the interaction between HEV and thyroid tissue.

The present case suggests the importance of assessing TSH and thyroid hormone levels in patients with acute viral hepatitis, even if there are no overt symptoms and signs of thyroid dysfunction. Although the prevalence of thyroid dysfunction in AHE may be low, the measurement of thyroid function and autoantibodies may lead to the early diagnosis of potential thyroid dysfunction.

5. Conflict of Interest: The authors declare that they have no conflicts of interest.

6. Human/Animal Rights

All procedures followed were in accordance with the ethical standards of the Iwate Medical University on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki.

7. Informed Consent: Informed consent was obtained from the patients that was included in this study.

8. Author Contribution

Suzuki K. conducted and wrote this article. Kumagai I. summarized the clinical data as a chief physician and partially wrote this article. Kitada K., Kondo K., and Kato A. actually participated with the examinations and treatments for this patient. Yoshida Y. and Miyasaka A. prepared serum samples of this patient and sent those to Jichi Medical University. Takikawa Y. kindly advised for the preparation of this article. Takahashi M. and Okamoto H. measured the serum markers of hepatitis E virus (HEV) including HEV-RNA and its genotype. All the authors carefully read this article and appropriately advised to Suzuki K. before submission of this article.

References

1. Okamoto H, Takahashi M, Nishizawa T. Features of hepatitis E virus infection in Japan. Intern Med. 2003; 42: 1065-1071.

2. Purcell RH, Emerson SU. Hepatitis E: an emerging awareness of an old disease. J Hepatol. 2008; 48: 494-503.

3. Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. N Engl J Med. 2012; 367: 1237-1244.

4. Wedemeyer H, Pischke S, Manns MP. Pathogenesis and treatment of hepatitis E virus infection. Gastroenterology. 2012; 142: 1388-1397.

5. Takahashi M, Okamoto H. Features of hepatitis E virus infection in humans and animals in Japan. Hepatol Res. 2014; 44: 43-58.

6. Matsubayashi K, Nagaoka Y, Sakata H, et al. Transfusion-transmitted hepatitis E caused by apparently indigenous hepatitis E virus strain in Hokkaido, Japan. Transfusion. 2004; 44: 934-940.

7. Hewitt PE, Ijaz S, Brailsford SR, et al. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet. 2014; 384: 1766-1773.

8. Matsui T, Kang JH, Matsubayashi K, et al. Rare case of transfu- sion-transmitted hepatitis E from the blood of a donor infected with the hepatitis E virus genotype 3 indigenous to Japan: viral dynamics from onset to recovery. Hepatol Res. 2015; 45: 698-704.

9. Ruggeri FM, Bartolo ID, Ponterio E, et al. Zoonotic transmission of hepatitis E in industrialized countries. New Microbiol. 2013; 36: 331-344.

10. Mizuo H, Suzuki K, Takikawa Y, et al. Polyphyletic strains of hepatitis E virus are responsible for sporadic cases of acute hepatitis in Japan. J Clin Microbiol. 2002; 40: 3209-3218.

11. Suzuki K, Kataoka K, Miyamoto Y, et al. Clinical and molecular analysis of sporadic acute hepatitis A and E and the specific viral genotypes isolated in Iwate and three neighboring prefectures in the northern part of Honshu, Japan, between. 2004 and 2013. Hepatol Res. 2015; 45: 714-727.

12. Suzuki K, Aikawa T, Okamoto H. Fulminant hepatitis E in Japan. N Engl J Med. 2002; 347: 1456.

13. Kamar N, Bendall R, Legrand-Abravanel F. et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. N Engl J Med. 2008; 358: 811-817.

14. Dalton HR, Bendall RP, Kaene FE, et al. Persistent carriage of hepatitis E virus in patients with HIV infection. N Engl J Med. 2009; 361: 1025-1027.

15. Inagaki Y, Oshiro Y, Tanaka T, et al. A nationwide survey of hepatitis E virus infection and chronic hepatitis E in liver transplant recipients in Japan. E Bio Medicine. 2015; 2: 1607-1612.

16. Riveiro-Barceiela M, Rodríguez-Frías F, Buti M. Hepatitis E virus: new faces of an old infection. Ann Hepatol. 2013; 12: 861-870.

17. Kamar N, Dalton HR, Abravanel F, Izopet J. Hepatitis E virus infection. Clin Microbiol Rev. 2014; 27: 116-138.

18. Kamar N, Marion O, Abravanel F, Izopet J, Dalton HR. Extrahepatic manifestations of hepatitis E virus. Liver Int. 2016; 36: 467-472.

19. Bazerbachi F, Haffar S, Garg SK, Lake JR. Extra-hepatic manifestations associated with hepatitis E virus infection: a comprehensive review of the literature. Gastroenterol Report. 2015; 4: 1-15.

20. Pischke S, Hartl J, Pas SD, et al. Hepatitis E virus: Infection beyond the liver?. J Hepatol 2016; 66: 1082-1095.

21. Fousekis F, Mitselos IV, Christodoulou DK. Extrahepatic manifestation of hepatitis E virus: An overview. Clin and Mole Hepatol. 2020; 26: 16-23.

22. Hui AY, Chan HL, Chan FK, Leung NW, Sung JJ. Fulminant hepatic failure in a patient with inactive HBsAg carrier state, acute hepatitis E and thyrotoxicosis. Hepatol Res. 2003; 27: 248-251.

23. Kong SJ, Min SK, Kim IK. Two cases of acute hepatitis E in patients with hyperthyroidism. Korean J Gastroenterol. 2005; 47: 65-71.

24. Dumoulin FL, Liese H. Acute hepatitis E virus infection and autoimmune thyroiditis: yet another trigger. BMJ Case Reports. 2012; 2012: bcr1220115441.

25. Martínez-Artola Y, Poncino D, García ML. Acute hepatitis E virus infection and association with a subacute thyroiditis. Ann Hepatol. 2012; 27: 248-251.

26. Inagaki Y, Oshiro Y, Hasegawa N, et al. Clinical feature of hepatitis E virus infection in Ibaragi, Japan: Autochthonous hepatitis E and acute-on-chronic liver failure. Tohoku J Exp Med. 2015; 235(4): 275-282.

27. Ferrari SM, Fallahi P, Antonelli A, Benvenga S. Environmental issues in thyroid diseases. Front Endocrinol. 2017; 8: 50.

28. Babb RR. Associations between diseases of the thyroid and the liver. Am J Gastroenterol. 1984; 79: 421-423.

29. Huang MJ, Liaw YF. Clinical association between thyroid and liver diseases. J Gastroenterol and Hepatol. 1995; 10: 344-350.

30. Lin TY, Shekar AO, Li N, et al. Incidence of abnormal liver biochemical tests in hyperthyroidism. Clin Endocrinol. 2017; 86: 755-759.

31. Ross DS, Burch HB, Cooper DS, et al. 2016 American thyroid association guideline for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016; 26: 1343-1421.

32. Laurberg P, Pedersen KM, Vestergaard H, Sigurdsson G. High incidence of multinodular toxic goiter in the elderly population in a low iodine intake area vs. high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. J Intern Med. 1991; 229: 415–420.

33. Abraham-Nordling M, Bystrom K, Torring O, et al. Incidence of hyperthyroidism in Sweden. Eur J Endocrinol. 2011; 165: 899-905.

34. Colson P, Payraudeau E, Leonnet C, et al. Severe thrombocytopenia associated with acute hepatitis E virus infection. J Clin Microbiol. 2008; 46: 2450-2452.

35. Fourquet E, Mansuy JM, Bureau C, et al. Severe thrombocytopenia associated with acute autochthonous hepatitis E. J Clin Viol. 2010; 48: 73-74.

36. Woolson KL, Forbes A, Vine L, et al. Extra hepatic manifestations of autochthonous hepatitis E infection. Aliment Pharmacol Ther. 2014; 40: 1282-1291.

37. Cines DB, Liebman H, Stasi R, et al. Pathobiology of secondary immune thrombocytopenia. Semin Hematol. 2009; 46(1 Supple 2): S2-S14.

38. Kim HS, Kim HS, Lee JY, et al. Initial thrombocytopenia as a simple,

valuable predictor for clinical manifestation in acute hepatitis A. Scand J Gastroenterol. 2008; 43: 81-88.

39. Joo EJ, Chang Y, Yeom JS, Lee YG, Ryu S. Hepatitis B infection is associated with an increased incidence of thrombocytopenia in healthy adults without cirrhosis. J Viral Hepatol. 2017; 24: 253-258.

40. Wedemeyer H, Rybczynska J, Pischke S, Krawczynski K. Immunopathogenesis of hepatitis E virus infection. Semin liver Dis. 2013; 33: 71-78.

41. Ramos-Levi AM, Marazuela M. Pathogenesis of thyroid autoimmune disease: the role of cellular mechanisms. Endocrinol Nutr. 2016; 63: 421-429.