症 例 報 告

ACUTE HEPATITIS A IN A JAPANESE TRAVELER AFTER OCCURRENCE OF DENGUE FEVER DURING STAY IN INDIA

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Medical Student Clerkship Program of Nara Medical University For 4th Grade

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Received May 15, 2012

Abstract : We report a case of acute hepatitis A that developed following an occurrence of dengue fever during a stay in India. The patient was a 52-year-old Japanese man who visited Delhi, India, from September 29 to October 20, 2010. During that stay, he developed a high fever and rash, with thrombocytopenia and slight liver dysfunction (platelet count $7.0 \times 10^4/\mu l$, AST 94 IU/ml, ALT 63 IU/ml), then was diagnosed with dengue fever on October 14. Soon after returning to Japan, the patient was well, with anti-HA IgM, hepatitis B surface antigen, and anti-hepatitis C all negative, though liver dysfunction transiently worsened. The DENV genome-sequence was not amplified, while IgM and IgG antibodies were detected. In mid-December 2010, one month after returning from India, he noted fatigue and appetite loss. When the patient came to us on January 12, 2011, jaundice was apparent. A laboratory examination revealed highly elevated aminotransferase levels (AST 4002 IU/ml, ALT 4715 IU/ml) and positivity for anti-HA IgM, and we made a diagnosis of acute hepatitis A. The clinical course of acute hepatitis A showed smooth improvement without adverse symptoms. By the end of March 2012, the total bilirubin and aminotransferase levels were completely normalized. We recommend that non-immune individuals be pre-immunized with HA-vaccine and be fully aware of potential health risks at their intended destinations before traveling to endemic countries.

Key words : dengue fever, acute hepatitis A, Japanese traveler

INTRODUCTION

With increasing numbers of international travelers to various destinations, including countries with widespread infectious diseases, the risk for acquiring endemic infections is increased. Hepatitis A virus (HAV) and dengue virus (DENV) are two such pathogens, both of which pose significant health risks for international travelers, particularly those going to Africa, India, and Southeast Asia[1-3]. Here, we report a case of acute hepatitis A in a Japanese traveler following

an occurrence of dengue fever during a stay in India.

CASE REPORT

A 52-year-old Japanese man visited India on business. He arrived on September 29, 2010 and stayed in a hotel located in the heart of the national capital, Delhi. On October 9, generalized rashes appeared, along with a rapidly rising temperature (<39℃) and headache. Although the rashes disappeared soon within 1 day, the fever remained high for a few days.

He visited a hospital on October 11 and was given an anti-pyretic, and the fever was alleviated by October 13. However, thrombocytopenia ($7.0x10^4/\mu l$) was found on October 14 along with a positive result in a test for the non-structural antigen 1 for DENV (DENV-NS1). The patient was hospitalized under the diagnosis of DF with thrombocytopenia and carefully observed, though his general condition was quite good without fever or hemorrhagic signs. Aminotransferase levels were mildly elevated, with AST (94 IU/ml) higher than ALT (63 IU/ml).

After reaching a minimum value of $4.9x10^4/\mu l$ on October 16, platelet count in peripheral blood began to increase and was $13.0x10^4/\mu l$ on October 18. He was discharged and returned to Japan on October 20.

The patient visited us on October 21 with his medical records from India. Laboratory data upon admission in Delhi (Table 1)included positive results for DENV-NS1 antigen, thrombocytopenia, and mild liver derangement. Malaria and typhoid fever seemed to be denied by the findings of a commercially available malaria-diagnosis kit and Widal test, though there were no blood smear, blood test, or urine culture findings, and no description about leptospirosis.

Table 1. Laboratory Data (Oct 14, 2010)

Hematology		Chemistry		WIDAL TEST	
RBC	505 x 10^4 /μl	T. Bil	0.70 mg/dl	S. TYPHI "O" Antigen titier	< 1:80
Hb	16.5 g/dl	TP	6.4 g/dl	S. TYPHI "H" Antigen titier	1:160
Ht	47.5 %	ALB	3.8 g/dl	S. PARATYPHI "AH" Antigen titier	< 1:80
WBC	5400 /μl	AST	94 IU/l	S. PARATYPHI "BH" Antigen titier	< 1:80
Plt	7.0 x 10^4 μl	ALT	63 IU/l	**Malaria**	
Urinalysis		ALP	49 IU/l	*Pf* antigen	(−)
pH	7.0	γ-GTP	70 IU/l	*Pv* antigen	(−)
Sugar	(−)	BUN	22 IU/l	**DF**	
Protein	(+)	Cre	1.1 mg/dl	DENV-NS1	(+)

***S**: Salmonella* ***Pf**: Plasmodium falciparum,* ***Pv**: Plasmodium vivax*

Table 2 shows the laboratory results obtained at his first visit to us. Although platelet count was completely recovered, aminotransferase levels were moderately elevated, as AST was 219 IU/ml and ALT was 287 IU/ml. Anti-HA IgM, hepatitis B surface antigen, and anti-hepatitis C were all negative. Hepatitis E virus was not tested. An ultrasonography examination of the upper abdomen demonstrated no abnormal findings.

Table 2. Laboratory Data (Oct 21, 2010)

Hematology		Chemistry	
WBC	5690 /μl	T. Bil	0.5 mg/dl
RBC	493×10^4 /μl	TP	7.1 g/dl
Hb	15.5 g/dl	ALB	3.9 g/dl
Ht	44.7 %	AST	219 IU/l
Plt	30.9×10^4 μl	ALT	287 IU/l
Urinalysis		LDH	474 IU/l
pH	5.0	ALP	372 IU/l
Sugar	(−)	γ-GTP	126 IU/l
Occult blood	(−)	T-CHO	200 mg/dl
Protein	(−)	Glucose	115 mg/dl
Serology		CRP	0.4 mg/dl
HA-IgM	(−)	BUN	13.7 mg/dl
HBsAg	(−)	Cre	0.91 mg/dl
HCV-III	(−)		

We reevaluated liver function two weeks later on November 4, and noted that AST was decreased to 30 IU/ml and ALT to 48 IU/ml, nearly within normal ranges. We considered that the transient liver dysfunction was probably related to infection with DENV and subsequent host immune responses. Two serum samples obtained separately on October 21 and November 4 were tested by the Department of Virology, National Institute of Infectious Diseases (NIID) in Tokyo. The DENV genome-sequence was not amplified, while IgM and IgG antibodies were detected. These results confirmed that the patient was in the recovery period following a recent infection.After 1 month without symptoms, in mid-December 2010, the patient reported becoming easily fatigued and a decreased appetite, while his family members pointed out his jaundiced appearance at the beginning of January 2011. He came to us on January 12, at which time jaundice was recognizable. A laboratory examination revealed highly elevated aminotransferase levels and positivity for anti-HA IgM (Table 3), and we made a diagnosis of AHA. nfortunately, because there were no vacant beds for a new admission, we sent him to another nearby hospital. The clinical course of AHA showed smooth improvement, except for a

complication with intrahepatic cholestasis for a short limited period. By the end of March 2011, total bilirubin and aminotransferase levels were completely normalized.

Table 3. Laboratory data (Jan 21, 2011)

Hematology		Chemistry	
WBC	8920 /μl	T. Bil	5.1 mg/dl
RBC	599 × 10^4 /μl	D. Bil	3.6 mg/dl
Hb	17.4 g/dl	TP	7.2 g/dl
Ht	51.0 %	ALB	3.9 g/dl
Plt	16.3 × 10^4 μl	AST	4002 IU/l
		ALT	4715 IU/l
		LDH	1783 IU/l
Serology		ALP	1161 IU/l
HA-IgM	(+)	γ-GTP	672 IU/l
HBsAg	(−)	T-CHO	158 mg/dl
HCV-III	(−)	Glucose	98 mg/dl
		CRP	0.4 mg/dl

DISCUSSION

There are no known recent incidents of domestic DENV infection in Japan. In 2010, 244 cases of DENV infection in Japanese individuals were reported, of whom more than 90% had recently returned from Asian countries such as Indonesia and India[4]. On the other hand, 175 cases of AHA in Japan were reported in 2011[5]. The majority of those patients had no history of traveling abroad, though some had visited foreign countries, predominantly in Southeast Asia and the Indian sub-continent.

We encountered a case of AHA in a Japanese patient after returning to Japan from India, where DF was contracted. In endemic countries, most DENV and HAV infections are acquired in early childhood[1-3]. A DENV infection may be symptomless, particularly in children, or can present an acute fever that is self-limiting in most cases. Hepatitis A infections are also often subclinical, with 70% of infections in children under six years of age remaining asymptomatic. However, travelers to such endemic countries from non-endemic countries must be careful, because these diseases are also symptomatic and occasionally cause severe illness. The incubation period for a dengue infection is generally four to seven days (range 3-14), while that for HAV infection is 15 to 50 days, with a mean period of 30 days. Considering that India has high rates of hepatitis A and dengue infections, it is likely that our patient was infected during his 3-week stay there. However, because of the differences between incubation periods, the

patient developed DF during the stay in Delhi and then AHA late after returning to Japan.

Dengue is classified as DF, DHF, or dengue shock syndrome (DSS), depending on the severity and features[2,3]. DF is an acute febrile illness characterized by frontal headache, retroocular pain, muscle and joint pain, nausea, vomiting, and rash. The febrile painful period of DF lasts five to seven days and DENV disappears from the blood after an average of five days, which is closely correlated with the disappearance of fever. The clinical features of the present case were quite typical for DF and the febrile period was five days (started October 9, ended October 13). Warning signals, such as spontaneous bleeding, vomiting, intense abdominal pain, painful hepatomegaly, breathing discomfort, lethargy, pleural effusion, and ascites, often appear when fever subsides[6]. Although there were no warning symptoms in our patient, thrombocytopenia was noted on day 6 after onset, which is also one of the manifestations of DHF and DSS. Therefore, we think that this patient should have been hospitalized to watch carefully for signs of aggravation to the more severe forms DHF and DSS.

As for liver dysfunction in DF, hepatic involvement is commonly seen, though severe hepatic derangement is rare[7-11]. It was also observed that AST increased more quickly and then returned to normal as compared to ALT. In the present case, AST and ALT were 94 and 63 IU/ml, respectively, on October 14 (day 6 from onset of DF), 219 and 287 IU/ml, respectively, on October 21 (day 13 from onset) and 30 and 48 IU/ml on November 2 (day 25 from onset), seemingly following a common clinical course of DF from the viewpoint of liver function. Since fever was alleviated by day 5 from the onset, it is conceivable that DENV was eliminated within the first week of illness. Therefore, we consider that hepatocyte injury was probably caused by a direct effect of DENV and subsequently mediated by host immune responses, though the precise mechanisms by which the hepatocytes became injured in this case are unknown.

DENV belongs to the family Flaviviridae, genus Flavivirus, and is transmitted to humans by Aedes mosquitoes, mainly Aedes aegypti. Based on neutralization assay data, four serotypes (DENV-1, DENV-2, DENV-3, DENV-4) can be distinguished. It is noteworthy that subsequent infection of pre-immune individuals with a different DENV serotype can exacerbate rather than mitigate disease. This phenomenon is considered to be caused by antibodies and termedantibody-dependent enhancement (ADE) of the disease[2,3]. In addition, four human genotypes have been identified in HAV[12], all of which belong to a single serotype. Therefore, AHA is the most common vaccine-preventable infection encountered in travelers visiting regions with high endemicity. It has also been reported that vaccination resulted in a significant reduction in the incidence of hepatitis A infection in travelers. The present patient did not receive any vaccinations. We strongly recommend that non-immune individuals be pre-immunized with HA-vaccine before traveling to endemic countries. Furthermore, there is a need for specialized travel health services in Japan and Japanese travelers should be given important information regarding health risks at their intended destinations[13].

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