ACUTE HEPATITIS E INFECTION PRESENTING AS FEVER AND MACULOPAPULAR RASH: A CASE REPORT

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Abstract. Extrahepatic manifestations of hepatitis E infection rarely include rash. We report a case of acute hepatitis E infection with rash. A 28-year-old Thai man presented with fever for 6 days and generalized maculopapular rash for 1 day. The laboratory results showed transaminitis with the peak alanine aminotransferase level of 2,850 U/l. Common etiologies of fever with rash such as other tropical diseases, systemic viral infections and drug induced hepatitis were investigated and excluded by absence history of drug usage and negative PCR and serology for dengue, scrub typhus, murine typhus or leptospirosis. A diagnosis of acute hepatitis E infection was made with a positive serum hepatitis E RNA. Rash is an uncommon extrahepatic manifestation of hepatitis E infection. Hepatitis E infection should be considered in the differential diagnosis of acute hepatitis with a maculopapular rash.

Keywords: acute hepatitis E, extrahepatic manifestation, maculopapular rash

INTRODUCTION

Hepatitis E virus (HEV) infection can occur in outbreaks or sporadically (Kamar *et al*, 2014). HEV infections are usually acute but may become chronic in immunocompromised hosts, such as solid organ transplant recipients and HIV-infected patients (Kamar *et al*, 2014). The extrahepatic manifestations of HEV infection include acute pancreatitis (Deniel *et al*, 2011; Raj *et al*, 2015), neurological complications, such as Guillain-Barre syndrome and neuralgic amyotrophy (Rianthavorn *et al*, 2010; Woolson *et al*, 2014; Lhomme *et al*, 2016), kidney impairment associated with cryoglobulinemia (Pischke *et al*, 2014; Kamar *et al*, 2014; Lhomme *et al*, 2016) and hematological disorders, such as aplastic anemia and thrombocytopenia (Colson *et al*, 2008; Au *et al*, 2011; Woolson *et al*, 2014). However, HEV infection with rash is rare (Al-Shukri *et al*, 2013). This is the first reported case of acute symptomatic HEV infection with rash in Thailand. This report can increase awareness of this uncommon presentation of HEV infection. HEV infection should be considered in

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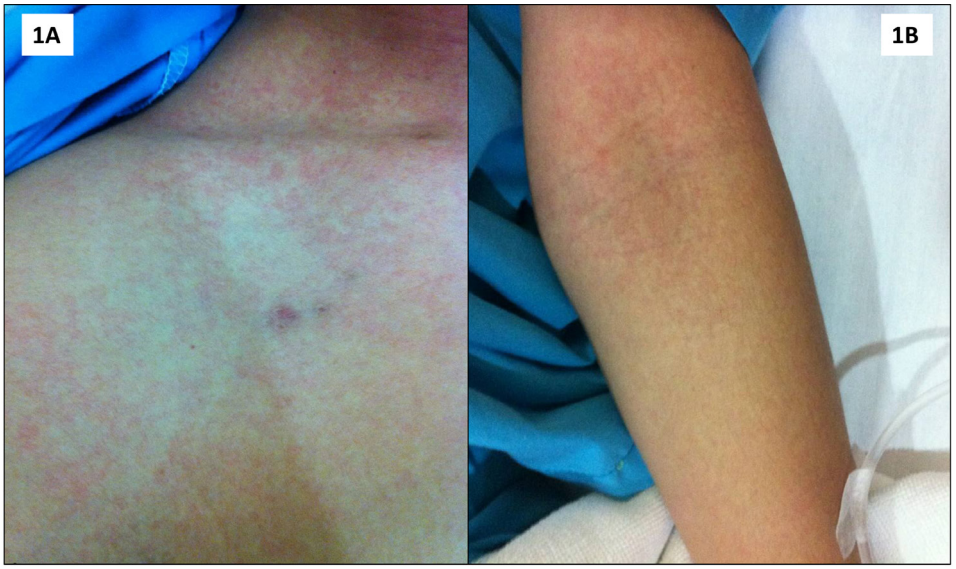

Fig 1–Ill-defined erythematous maculopapular rash at chest wall (1A) and upper extremities (1B).

differential diagnosis of a hepatitis patient with rash.

CASE REPORT

A 28-year-old Thai male soldier presented to the Hospital for Tropical Diseases, Thailand with a 6-day history of fever, myalgia and dry cough, a 2-day history of nausea and vomiting and a 1-day history of pruritic maculopapular rash beginning on the chest and back and spreading centrifugally. The patient had no complaints of arthralgia, abdominal pain, diarrhea, bleeding or abnormal urination. He denied a history of travel abroad or eating mushrooms, improperly cooked meat or seafood. He denied any history of contact with people with the same symptoms. He did have a history of hospital admission for dengue fever 6 months previously, and denied any other illnesses. He denied a history of chronic medical problems, drug use or allergies. He denied a history of tobacco use and alcohol use. He had never received a hepatitis A or B vaccination.

Physical examination revealed a temperature of 38.3°C, a pulse rate of 85/min, a respiratory rate of 20/min and a blood pressure of 107/67 mmHg. His general appearance was alert, had a sthenic body build; there was no pallor, he had mildly icteric sclerae and mild jaundice. He had no other signs of chronic liver disease. His abdomen was non-tender on palpation and he had no hepato- or spleno-megaly. On skin examination he had an ill-defined erythematous maculopapular rash on his chest, back and upper extremities (Fig 1).

On admission (day seven of fever), his total bilirubin level was 5.57 mg/dl and direct bilirubin was 4.97 mg/dl, aspartate aminotransferase level was 2,863 U/l, alanine aminotransferase level was 2,850 U/l and alkaline phosphatase level was 170 U/l. He had a prolonged prothrombin time of 13.8 (normal range: 10.5-13.5) seconds. His complete blood count was

normal. An upper abdominal ultrasound showed neither biliary tract obstruction nor an abscess.

The differential diagnosis included acute viral hepatitis, exanthematous viral infection, common tropical diseases such as leptospirosis, typhoid, and rickettsiosis as well as drug induced hepatitis.

Further investigations for definite diagnosis were done. His hemoculture showed no bacterial growth. Hepatitis A virus (HAV) IgM, IgG and hepatitis C virus antibody were negative. HBsAg and anti-HBc IgG were negative but anti-HBs was positive, therefore he had immunity to HBV from vaccination. Indirect immunofluorescence assay (IFA) for scrub typhus and murine typhus and microscopic agglutination test (MAT) for leptospirosis were negative for acute or convalescent serum. Dengue NS1 antigen and dengue polymerase chain reaction (PCR) were negative. The dengue IgM was positive in an acute serum and declined to negative level in a convalescent serum while there was no rising of IgG response, this finding was compatible with the history of 6 months previously dengue infection. Drug induced liver injury with rash was excluded by history. Epstein-Barr (EBV) virus IgM was negative and IgG was positive. Anti-HEV IgM was positive and reverse transcription PCR for HEV-RNA was positive. HEV genotype classification was performed at the ORF3 region by semi-nested PCR using an outer primer pair with F3-HE364 (nucleotide 5021-5044 and 5432-5451) and an inner primer pair with F3-HE363 (nucleotide 5021-5044 and 5428-5447). The PCR product from this patient was similar to that found in a study by Vina-Rodriguez *et al* (2015). Phylogenetic analysis of this isolate (Th-Hu-2014-TM, accession number KP886949) revealed it belonged to HEV genotype 3

Table 1
Summary reported cases of rash in acute hepatitis E.

Reference	Number of cases	Age (years), Sex	Country	Character of rash	Other extrahepatic manifestations	Genotype	Outcome	Underlying diseases
McCrudden *et al*, 2000	1	51, Female	United Kingdom	Macular	Arthralgia	No data	No data	No data
Peron *et al*, 2006	2	No data	France	Not specified	N/A	3	No data	No data
Al-Shukri *et al*, 2013	1	52, Female	United Kingdom	Generalized maculopapular	Arthritis	3	Recovery	None
Pischke *et al*, 2014	1	35, Male	Germany	Erythematous, mainly affected lower limbs	Cryoglobulinemia, thrombocytopenia, and kidney impairment	No data	Death from severe intestinal mucositis	Liver transplantation

N/A, not available.

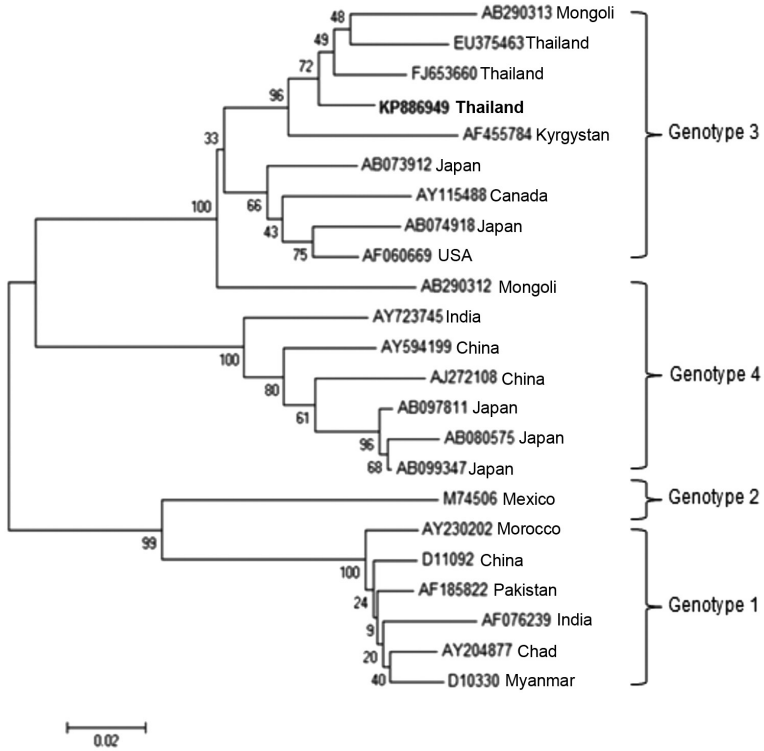

Fig 2–Phylogenetic analysis of HEV sequence at ORF3 region of our acute isolate (Th-Hu-2014-TM with accession No. KP886949) using neighbor-joining method. The reliability of the phylogenetic tree was accessed by bootstrap re-sampling (1,000 replicates).

(Fig 2), similar to a Thai swine HEV strain (EU375463) and a Thai human HEV strain (FJ653660) previously described (Siripanyaphinyo *et al,* 2009; Rianthavorn *et al,* 2010).

Management included intravenous fluids, low dose paracetamol for fever and empiric ceftriaxone to cover leptospirosis and typhoid until the result of blood cultures and paired sera were negative. The rash and fever disappeared on the second day of hospitalization; the total hospital stay was eight days.

After hospitalization, the patient was followed up every two weeks twice and then monthly. His bilirubin level turned to normal by the second month and his liver enzymes returned to normal by three months.

DISCUSSION

HEV infection with rash is rare. Only five cases have been reported in the literature (Table 1) (McCrudden *et al*, 2000; Peron *et al*, 2006; Al-Shukri *et al*, 2013; Pischke *et al*, 2014). Three cases were reported as single case reports while Peron *et al* (2006) reported two cases. In two cases the rashes were described as macular or maculopapular as in the present case (McCrudden *et al*, 2000; Al-Shukri *et al*, 2013). Fever with rash and hepatitis is usually due to other viral infections, such as flavivirus, herpes group virus, rickettsial

infections or non-infectious causes, such as a drug hypersensitivity reaction (Chalasani *et al*, 2014). Other causes of fever and rash were excluded in our case and the other reported cases.

The mechanism for rash with acute HEV infection is unclear but may be related to the immune response to HEV infection (Lhomme *et al*, 2016). There may be a link between extrahepatic manifestation and the HEV genotype; neurological disorders and some neurotrophic variants mostly in HEV genotype 3, acute pancreatitis and HEV genotype 1, kidney injury and HEV genotypes 1 and 3 (Kamar *et al*, 2014). All the HEV cases with rash reported in the literature were autochthonous (occurred sporadically) and in three cases with available genotype data, all were genotype 3, similar to our patient. HEV genotype 3 typically causes sporadic infections in developed and developing countries through food-borne transmission (Kamar *et al*, 2014). All reported cases of acute HEV infection in Thailand are genotype 3 and are closely related to swine source (Siripanyaphinyo *et al*, 2014). In our case, the source of infection was not identified.

In conclusion, rash is an uncommon extrahepatic manifestation of hepatitis E infection. However, physicians should be aware of this uncommon presentation. Hepatitis E infection should be in the differential diagnosis of patients with fever, rash and elevated liver enzymes.

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