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Early Detection of a Case of Dengue Fever in Yamagata University Hospital

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ABSTRACT

Dengue fever (DF) is an acute febrile disease caused by dengue virus, which was re-emerged in tropical regions in the past 20 years. The numbers of imported DF were 6 to 44 per year in the recent Japan. We report a Japanese member of non-governmental organization (NGO) with dengue fever (DF). The patient developed sudden onset of high fever after returning to Japan, followed by rash and thrombocytopenia. DF was confirmed by isolation of dengue virus from serum, a positive reverse-transcriptase polymerase chain reaction (RT-PCR) test, and a high titer of IgM antibody to dengue virus. Dengue virus infection should be included in the differential diagnosis of the patients, developing high fever, skin rash, and thrombocytopenia after returning from endemic area.

Key words : dengue, fever, thrombocytopenia, lymphocyte

CASE REPORT

A 25-year-old Japanese woman, as a member of non-governmental organization (NGO),

stayed in the East Timor (ET) for 10 days in February 2002. The patient developed an acute fever (temperature; 40 °C) without cough, dyspnea, sore throat, or diarrhea, just returning from ET. She was treated with anti-

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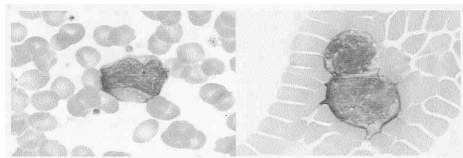


Fig. 1.
Atypical lymphocytes in peripheral blood on Day 7.

inflammatory drugs and anti-biotics in a local hospital. She continued to present with fever, and furthermore had diarrhea and vomiting for 2 days, despite of these treatments. On the 6 day after the onset of fever, the patient showed an erythematous rash with itching, and was admitted to Yamagata University Hospital for further evaluation.

Physical examination revealed multiple erythema with itching on extremities without edema, purpura, hepatosplenomegaly, or swelling of lymph nodes. She had anorexia and mild fever (temperature; 37.3 °C). The laboratory findings at that time included: hemoglobin 14.5 g/dl, hematocrit 43%, white blood cell (WBC) count 2,450/mm³ with 9% atypical lymphocytes, platelet count 60,000/mm³, total serum protein 6.6 g/dl, total serum albumin 3.8 g/dl, alanine aminotransferase (ALT) 37 IU/liter, aspartate aminotransferase (AST) 59 IU/liter, lactate dehydrogenase (LDH) 654 IU/liter, alkaline phosphatase 51 IU/liter, total serum bilirubin 0.4 mg/dl, serum creatinin 0.6 mg/dl, serum blood urea nitrogen 3 mg/dl, and c-reactive protein 0.1 mg/dl. Examination of both influenza A and B antigens from nasal mucosa was negative. Urinary analysis was normal. Prothrombin time, activated partial thrombin time, fibrinogen, and fibrin/fibrinogen degradation products, were all within normal limits. Extensive examination of peripheral blood films showed no evidence of

Table 1. Anti-IgM antibody to dengue virus

Test	Day 7	Day 8
Rapid Kit	+	Not done
IgM-capture ELISA test	10.7(+)	13.9(+)

any forms of malaria, but atypical lymphocytes (Fig. 1). Therefore, in the admission day, we considered the patient as having the possibility of dengue fever (DF), since she was bitten several times by the mosquitoes in the ET, a dengue epidemic area, and presented with leukocytopenia, thrombocytopenia, rash, and biphasic fever, considered to be the most characteristic features of classic dengue fever¹⁾. The serum samples on disease days 7 and 8 were quickly sent to the Department of Virology 1, National Institute of Infectious Disease, Japan (NIID) for the laboratory diagnosis of dengue virus infection. At the next day, the NIID reported that the patient had an anti-flavivirus IgM antibody by the IgM-capture enzyme-linked immunosorbent assay (ELISA) and immunochromatographic test (Rapid Kit)²⁾ (Table 1). Further laboratory investigations by reverse transcriptase-polymerase chain reaction (RT-PCR), hemagglutination inhibition (HI) test, and virus isolation, demonstrated that the patient was infected with type 2 dengue virus^{2),3)}. Within hospital day 3, the patient had a complete clinical recovery, and a platelet count of 155,000/mm³ and WBC count 6,440/mm³ with 12% atypical lymphocytes without therapy. Repeated blood and stool culture examination showed no evidence of bacterial infection, including *Salmonella typhi*. The patient was discharged on hospital day 4. A typical lymphocytes disappeared within 25 days of the onset of DF.

DISCUSSION

We diagnosed a patient with imported DF on the first hospital day, and the patient recovered from DF without specific therapy.

Dengue virus infection, which one of the most important infectious disease in tropical areas of the world, are subclinical or manifest as DF or dengue hemorrhagic fever (DHF)^{1,4}. Dengue infections are most prevalent in Southeast Asia, where all four serotypes 1 to 4 are continuously present⁵. Dengue viruses are transmitted by infected mosquitoes, *Aedes aegypti*. In most cases, DF is a self-limited syndrome of biphasic fever, headache, myalgia, lymphadenopathy, and rash accompanied by leukocytopenia and thrombocytopenia. Symptoms resolve after 2-7 days. Some patients have a risk of progressive development into DHF, a life-threatening syndrome, characterized by abnormalities in hemostasis and increased vascular permeability^{1,6,7,8,9}. In this case, clinical symptoms, such as rash and biphasic fever are typical of DF, but nausea and vomiting are uncommon to it. The present patient also showed typical laboratory findings in DF, including leukopenia, thrombocytopenia, and liver dysfunction¹. With these typical symptoms, findings, and history of bitten by the mosquitoes in dengue epidemic area, we could consider this patient to have DF. In the present study, atypical lymphocytosis and monocytosis on peripheral smear reached its peak on day 10 after fever onset, and disappeared gradually. A recent study has shown that the leukocyte profiles of DF reveals the CD4/CD8 ratio inversion, monocytosis, and atypical lymphocytosis^{1,10,11}. Thus, repeated examinations of peripheral smear may be

useful and essential, not only to exclude malaria infections, but also to make a correct diagnosis of DF.

Dengue virus infection is confirmed by the laboratory tests³. In the present case, a diagnosis of DF was confirmed by the positive results of an IgM antibody, and later by virus isolation from serum sample of disease day 7 that yielded a dengue 2 strain genome. The previous studies revealed that viruses are isolated from serum samples collected before fever subsides^{5,12}. In this case, her fever resolved within disease day 9. Thus, for isolation of virus and confirmation of dengue strain, it is important to preserve serum samples from febrile patients who have just returned from dengue epidemic areas.

The treatment and management of DF, whose pathogenesis is not clearly understood, are essentially supportive and symptomatic^{1,4,13}. For control of fever, anti-inflammatory drugs, especially including salicylic acid, should be avoided to prevent hemorrhagic tendency and acidosis¹. The present patient already had been treated with anti-inflammatory drugs and anti-biotics in a local hospital before making a definite diagnosis. Therefore, the recognition of DF in unknown febrile illness in a patient returning from an endemic area to Japan is important for clinicians to avoid an inappropriate therapy and examination. DF is a febrile imported disease worthy of more attention from the medical community in a distinct Japan^{12,14}. This is the first case of DF in Yamagata prefecture.

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