A False Positive Dengue Fever Rapid Diagnostic Test Result in a Case of Acute Parvovirus B19 Infection

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Abstract

An outbreak of dengue fever occurred in Japan in August 2014. We herein report the case of a 63-year-old man who presented with a persistent fever in September 2014. Acute parvovirus B19 infection led to a false positive finding of dengue fever on a rapid diagnostic test (Panbio Dengue Duo Cassette™). To the best of our knowledge, there are no previous reports of a false positive result for dengue IgM with the dengue rapid diagnostic test. We believe that epidemiological information on the prevalence of parvovirus B19 is useful for guiding the interpretation of a positive result with the dengue rapid diagnostic test.

Key words: dengue fever, parvovirus B19, rapid diagnostic test, false positive

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Introduction

An outbreak of dengue fever occurred in Japan in August 2014. Since the disease has no pathognomonic features that reliably distinguish it from other febrile illnesses, both the patient’s history and laboratory diagnostic tests are important for confirmation (1). The rapid diagnostic test is useful because it is quick and easy to perform. The literature shows that a few false positive results have been obtained from the sera of patients with Japanese encephalitis, St. Louis encephalitis, yellow fever, malaria, leptospirosis, and past dengue infection (2).

To the best of our knowledge, there have been no previous reports of the dengue rapid diagnostic test giving a false positive result in a case of acute parvovirus B19 infection.

Case Report

A 63-year-old man who had recently undergone mitral valve plasty was referred to our hospital in mid-September with a fever and fatigue. The patient had been well until 5 days before the referral, when he developed a fever with a peak temperature of 39.1°C, together with fatigue, and came to the medical walk-in clinic at our hospital. Approximately 10 days before the onset of his fever, he had returned from a 3-day trip to Tokyo and Hokkaido. He stated that during his trip he had not been bitten by a mosquito, but had had contact with an ill child. On examination, his temperature was 37.5°C; blood pressure, 109/67 mmHg; heart rate, 95 bpm; and oxygen saturation, 98% while breathing ambient air. The conjunctivae were not pale. His abdomen was soft without hepatomegaly and with a palpable spleen. He had a diffuse petechial rash on his legs and feet (Fig. 1). A CBC showed pancytopenia; WBC was 3,600/mm³; hemoglobin, 11.7 g/dL; and platelet count, 75,000/mm³. Liver and kidney function tests were normal. C-reactive protein (CRP), C3, C4, and CH50 complement levels were 2.99 mg/dL, 57 mg/dL, 12 mg/dL, and 22.1 U/mL, respectively. Testing for dengue IgM (rapid diagnostic test, Panbio Dengue Duo Cassette™) was positive (Fig. 2), and tests for Epstein-Barr virus, cytomegalovirus, rubella, and measles suggested a previous infection. Parvovirus B19-specific IgM antibody was 10.9 (positive cutoff: 0.80 or higher) and IgG antibody was 7.21 (positive cutoff: 0.80 or higher). A few days later, PCR testing for parvovirus B19 nucleic acid was positive, which
is not the diagnostic method of choice during this period. However, detection of dengue-specific IgM and IgG antibody for dengue IgM and IgG. The sensitivity of each approach is influenced by the duration of the patient’s illness. Because dengue viremia can be detected for 4-5 days after onset of the illness, virus detection using methods such as RT-PCR can be used to diagnose the infection during that period. However, detection of dengue-specific IgM and IgG is not the diagnostic method of choice during this period. Dengue-specific IgM antibody may be detected as early as 4-5 days after the onset of a fever, and IgM levels can continue to increase for approximately 2 weeks and persist for as long as 5-6 months (2, 3, 9). Indeed, the detection of dengue-specific IgM antibody for dengue fever using the Panbio Dengue Duo Cassette™ test is confirmed by DNA sequencing. Testing to distinguish the infection from dengue and Japanese encephalitis viruses by real-time RT-PCR and testing for dengue by immunochromatography (Dengue NS1 Ag Strip, Bio-Rad) were revealed to be negative. Until the results of the tests for parvovirus B19 IgM and IgG antibodies and PCR/RT-PCR tests for nucleic acid from parvovirus B19 and dengue virus were interpreted, we believed that our patient might be the first case of dengue fever in Toyama prefecture.

Two days after referral, the patient’s fever resolved spontaneously. Three months later, his dengue IgM rapid diagnostic test was negative and his parvovirus B19 IgM was 1.31. According to these findings, the rapid diagnostic test appeared to have been a false positive for dengue fever, and the ultimate diagnosis of the case was parvovirus B19 infection (Table). The patient did not develop late symptoms of acute parvovirus B19, such as cutaneous eruption and rheumatic symptoms.

Discussion

Our case of acute parvovirus B19 infection was difficult to diagnosis for two main reasons. First, a false positive result for dengue IgM was obtained from the rapid diagnostic test. Dengue fever is the most common mosquito-borne viral disease in the world, especially in tropical countries. Travelers in those countries are at risk for acquiring it. They also contribute to its spread to nonendemic areas. An outbreak of dengue fever was recorded in Japan in August 2014 and 162 individuals developed the disease.

Dengue virus infection can manifest across a wide spectrum, ranging from an inapparent illness or mild fever to severe bleeding, thrombocytopenia, and plasma leakage (3-7). Given that symptoms such as a fever, headache, and vomiting are nonspecific, dengue fever can easily be mistaken for other febrile illnesses such as malaria, leptospirosis, yellow fever, Japanese encephalitis, or rickettsial infection (2, 7, 8). Therefore, laboratory confirmation is needed for a definitive diagnosis of dengue fever infection. A variety of laboratory tools have recently become available for diagnostic use (3).

A laboratory diagnosis of dengue fever is established directly through the detection of viral components, such as viral nucleic acid, or indirectly by serologic tests for virus-expressed soluble nonstructural protein 1 (NS1) or specific antibody for dengue IgM and IgG. The sensitivity of each approach is influenced by the duration of the patient’s illness. Because dengue viremia can be detected for 4-5 days after onset of the illness, virus detection using methods such as RT-PCR can be used to diagnose the infection during that period. However, detection of dengue-specific IgM and IgG is not the diagnostic method of choice during this period. Dengue-specific IgM antibody may be detected as early as 4-5 days after the onset of a fever, and IgM levels can continue to increase for approximately 2 weeks and persist for as long as 5-6 months (2, 3, 9). Indeed, the detection of dengue-specific IgM and IgG antibodies is the most widely used test for the diagnosis of dengue fever (10). Commercial kits that use a serologic approach to dengue diagnosis are available. These kits are useful because they are quick and easy to perform (6). The sensitivity and specificity of the diagnosis for dengue fever using the Panbio Dengue Duo Cassette™ are 92% (95% CI 80-97%) and 91% (95% CI 70-98%), respectively (11). The sensitivity and specificity of the Dengue NS1 Ag STRIP Kit and SD BIOLINE Dengue Duo Strip Kit are 71% (95% CI 61-79%) and 99% (95% CI 98-100%), respectively (12).
In our patient, we observed that the dengue rapid diagnostic test became negative on day 83, while parvovirus B19-specific IgM decreased over a natural course. The possibility of a faulty Panbio Dengue Duo Cassette™ lot was ruled out because the two positive results were from different lots. The molecular mechanism responsible for the induction of this phenomenon is unknown. It is not clear whether parvovirus B19 retains an antigen that mimics the dengue virus antigen or whether antibodies from the patient create a false positive through anti-idiotypic antibody reactions.

The second reason why the diagnosis was difficult was the patient’s clinical condition. Most patients with acute parvovirus B19, such as our patient, have only mild, nonspecific cold-like symptoms. The others have an erythema infectiosum rash and/or arthralgia, which are two classic syndromes associated with parvovirus B19 infection. The most common clinical manifestation in children is erythema infectiosum, causing a “slapped-cheeks” facial rash, whereas the most common manifestation in adults is arthralgia, although either can be seen in both children and adults (13). Even when erythema infectiosum is present, the rash is less characteristic in adults than in children and may be mistaken for other types of rash, including purpura, petechiae, papules, macules, rubella rash, or morbilliform or vesicular rashes. A sevenrequirement scoring system recommended by Nagai et al. may be useful for deciding when to obtain blood samples from a patient for anti-parvovirus B19 antibody testing. The level of CRP is low and without leukocytosis; flu-like symptoms; a rash is observed on the legs; contact with an ill child during his trip; and hypocomplementemia. The possibility of parvovirus B19 infection should be suspected in patients who meet the foregoing criteria.

Our case reinforces the importance of viral nucleic acid, NS1, or IgM seroconversion in the confirmation of presumptive results from the rapid diagnostic test. At the same time, epidemiological information on the prevalence of other infectious agents that cause rashes, such as measles, rubella, enterovirus, and human herpes viruses 6 and 7, may be useful in guiding the interpretation of a positive rapid test result. Furthermore, clinicians must be aware that acute parvovirus B19 infection may cause a false positive reaction in returning travelers who present with febrile illness of unknown etiology. Surveillance studies conducted in endemic regions are also useful. False positive results could mistakenly lead to surveillance for dengue fever if the rapid diagnostic test is the only diagnostic modality used. Our experience with a false positive result from the dengue rapid diagnostic test in a case of acute parvovirus B19 infection has prompted us to point out these indications for the careful and precise diagnosis of dengue fever and to suggest that epidemiological information on the prevalence of other viruses would be useful in guiding the interpretation of a positive result in the dengue rapid diagnostic test (3).

The authors state that they have no Conflict of Interest (COI).

References
1. Rathakrishna A, Sekaran SD. New development in the diagnosis of dengue infections. Expert Opin Med Diagn 7: 99-112, 2013.
2. World Health Organization. Dengue Haemorrhagic Fever: Diagnosis, Treatment, Prevention and Control. 2nd ed. World Health Organization, Geneva, 1997.
3. Tang KF, Ooi EE. Diagnosis of dengue: an update. Expert Rev Anti Infect Ther 10: 895-907, 2012.
4. Potts JA, Rothman AL. Clinical and laboratory features that distinguish dengue from other febrile illnesses in endemic populations. Trop Med Int Health 13: 1328-1340, 2008.
5. Tantawichien T. Dengue fever and dengue haemorrhagic fever in adolescents and adults. Paediatr Int Child Health 32 (Suppl 1): 22-27, 2012.
6. Hemungkorn M, Thisaykorn U, Thisaykorn C. Dengue infection: a growing global health threat. BioScience Trends 1: 90-96, 2007.
7. Gulati S, Maheshwari A. Atypical manifestations of dengue. Trop Med Int Health 12: 1087-1095, 2007.
8. Wilder-Smith A. Dengue infections in travellers. Paediatr Int Child Health 32: 28-32, 2012.
9. Chappuis F, Alirol E, d’Acremont V, Botteau E, Yansouni CP. Rapid diagnostic tests for non-malarial febrile illness in the tropics. Clin Microbiol Infect 19: 422-431, 2013.
10. De Paula SO, Fonseca BA. Dengue: a review of the laboratory tests a clinician must know to achieve a correct diagnosis. Braz J Infect Dis 8: 390-398, 2004.
11. Blacksell SD, Doust JA, Newton PN, Peacock SJ, Day NP.
Dondorp AM. A systematic review and meta-analysis of the diagnostic accuracy of rapid immunochromatographic assays for the detection of dengue virus IgM antibodies during acute infection. Trans R Soc Trop Med Hyg 100: 775-784, 2006.

12. Zhang H, Li W, Wang J, et al. NS1-based tests with diagnostic utility for confirming dengue infection: a meta-analysis. Int J Infect Dis 26: 57-66, 2014.

13. Servery JT, Reamy BV, Hodge J. Clinical presentations of parvovirus B19 infection. Am Fam Physician 75: 373-376, 2007.

14. Nagai Y, Hara N, Maeda T, et al. Human parvovirus B19 infection in 15 adults: two-year Toho University Hospital Study. Kansenshogaku Zasshi (The Journal of the Japanese Association for Infection Diseases) 83: 45-51, 2009 (in Japanese, Abstract in English).

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