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Zika Virus Infection Associated With Severe Thrombocytopenia

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Abstract

We report two patients that developed severe thrombocytopenia after Zika virus (ZIKV) infection. The first patient had 1000 platelets/μL and died after multiple hemorrhages. The second patient had 2000 platelets/μL, had melena and ecchymoses, and recovered after receiving intravenous immunoglobulin. ZIKV may be associated with immune-mediated severe thrombocytopenia.

Keywords

Zika virus; thrombocytopenia; fatal; Puerto Rico

In severe cases, dengue and select other flaviviruses (eg, yellow fever and Omsk hemorrhagic fever viruses) are associated with life-threatening hemorrhagic manifestations [1–3]. Zika virus (ZIKV) is a mosquito-transmitted flavivirus closely related to dengue virus

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Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

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(DENV) [4]. After it was first detected in Brazil in 2015 [5], ZIKV rapidly spread throughout the Americas [6]. From 1 November 2015 to 14 April 2016, a total of 683 laboratory-positive ZIKV disease cases were identified in Puerto Rico [7].

Most ZIKV infections are asymptomatic or result in only mild disease [4]; however, Guillain-Barré syndrome and congenital infection leading to severe birth defects, including microcephaly, may result in fatal outcomes [4]. Severe thrombocytopenia has recently been reported to be an uncommon manifestation in patients with ZIKV infection [7–11] (Supplementary Table 1). We report 2 cases of life-threatening severe thrombocytopenia from February 2016 that developed soon after resolution of ZIKV disease.

CASE REPORTS

Case 1

A 72-year-old man with a medical history of untreated hypertension and hyperlipidemia treated with simvastatin presented to an urgent care clinic in San Juan, Puerto Rico, with bloody buccal mucosa that had developed 1 day earlier. He reported 3 days of fever, malaise, and generalized myalgia that had resolved 2 days before presentation. Initial physical examination revealed a blood pressure of 181/90 mm Hg and multiple blood clots in the oral cavity. The patient was given a diagnosis of hypertensive crisis, prescribed oral clonidine, and discharged to home. Soon afterward, he lost consciousness at home and fell backward, hitting the posterior aspect of his head.

The patient was transported to the same urgent care clinic, where he had a blood pressure of 211/111 mm Hg, was pale and diaphoretic, and had active bleeding from the oral mucosa. He was comatose with dilated and unreactive pupils, and his Glasgow Coma Scale score was 4. Laboratory results included a hemoglobin level of 12.8 mg/dL, a white blood cell count of 8.5/μL, a platelet count of 1000/μL, and a serum glucose level of 165 mg/dL; serum liver enzyme and creatinine levels were within normal ranges. The patient was transferred to a local hospital with a presumptive diagnosis of a cerebral vascular accident.

On arrival at the hospital, the patient was intubated, with bright red blood noted in the endotracheal tube. Physical examination revealed petechiae on the extremities, lips, and upper palate and bilateral inspiratory rales and rhonchi. The platelet count was again 1000/μL; platelets were markedly decreased on a smear. Prothrombin and partial thromboplastin time results were within normal limits. Urinalysis showed 8–10 red blood cells per high-powered field. Computed tomography of the head without contrast enhancement revealed a large right subdural hematoma, right-to-left shift of approximately 5 mm, diffuse subarachnoid blood, and a right posterior subgaleal hematoma (Figure 1A). Computed tomography of the chest without contrast enhancement revealed dense patchy pulmonary infiltrates throughout the lungs, most consistent with diffuse alveolar hemorrhage (Figure 1B). Dengue hemorrhagic fever was suspected to be the cause of severe thrombocytopenia, and dengue diagnostic testing was ordered. The patient died 7 hours after admission from the sequelae of diffuse alveolar and multiple intracranial hemorrhages.

An autopsy was declined by the patient's family. Premortem serum sent to the Puerto Rico Department of Health was positive for ZIKV and negative for DENV and chikungunya virus (CHIKV) by reverse-transcription polymerase chain reaction (RT-PCR) (Supplementary Table 2). Anti-ZIKV and anti-DENV immunoglobulin (Ig) M and IgG antibodies were detected with enzyme-linked immunosorbent assay.

Case 2

A 38-year old morbidly obese man (body mass index, 43.6) presented to an urgent care clinic after 2 days of rash, myalgia, malaise, headache, nausea, and fever. Physical examination revealed a blood pressure of 146/85 mm Hg and a generalized macular rash. The patient's complete blood count was normal, including a platelet count of 200 000/μL (Supplementary Figure 1). His rash was ascribed to viral infection; he received oral acetaminophen (500 mg) and intramuscular diphenhydramine (50 mg) and was discharged to home with a recommendation for oral diphenhydramine (25 mg every 8 hours). His symptoms resolved over the next 3 days.

One day after the patient's illness resolved, petechiae and bloody ulcers developed on his tongue and buccal mucosa (Supplementary Figure 2). A day later he presented to a hospital emergency room. Physical examination findings were unremarkable, except for a blood pressure of 159/98 mm Hg and generalized petechiae. The patient was given a diagnosis of denguelike syndrome, given intravenous fluids, and admitted for care. His chest radiograph was unremarkable, and his platelet count was 2000/μL, with platelets markedly decreased on the smear. He was given 2 units of platelets, oral acetaminophen (500 mg), and intravenous methylprednisone (60 mg every 6 hours) and ceftriaxone (2 g/d). Dengue diagnostic testing was ordered.

The next morning, the patient had melena and ecchymoses on his arms and abdomen. He was given an additional unit of platelets and transferred to the intensive care unit. That afternoon, his platelet count was 6000/μL. Because he was not responding to platelet transfusions, his severe thrombocytopenia was ascribed to immune thrombocytopenic purpura. The dose of intravenous methylprednisone was increased to 80 g every 8 hours, and intravenous immunoglobulin (IVIG) treatment was started at 40 g/d for 5 days. Over the next 3 days, the patient's vital signs remained stable, and he had no evidence of plasma leakage, shock, or additional hemorrhagic manifestations. His platelet count rose steadily, and he was transferred from the intensive care unit to the inpatient ward on day 5 of hospitalization. On day 6 he was discharged to home in good condition with a prescription for oral prednisone tablets (20 mg 3 times daily for 42 days).

Blood chemistry values were obtained only on day 4 of hospitalization and were normal except for a mildly elevated alanine transaminase level (64 U/L). Titers were negative for human immunodeficiency virus types 1 and 2, as were blood and urine bacterial cultures. A serum sample collected at hospital admission was positive for anti-ZIKV IgM antibody, negative for anti-DENV IgM antibody, and negative for ZIKV, DENV, and CHIKV by RT-PCR (Supplementary Table 2). Convalescent-phase serum, saliva, and urine specimens collected 46 days after illness onset were negative for ZIKV nucleic acid. The same convalescent-phase serum specimen was positive for anti-ZIKV IgM antibody and negative

for anti-DENV IgM. Plaque reduction neutralization test performed on both serum specimens demonstrated a 4-fold rise in anti-ZIKV antibody titer and prior DENV infection (Supplementary Table).

DISCUSSION

These 2 cases along with previous reports [9, 10] suggest an association between ZIKV and severe thrombocytopenia. Neither of the 2 cases described here nor a case from Suriname [10] had evidence of involvement of the other hematologic cell lines, preexisting bleeding disorders, or severe liver disease that would explain the patients' severe thrombocytopenia. In case 1, a normal prothrombin and partial thromboplastin time argue against disseminated intravascular coagulation as the cause of severe thrombocytopenia. In patient 2 and the Surinamese patient [10], interventions for immune thrombocytopenic purpura (ie, IVIG) were associated with clinical improvement. Lack of available medical history or details of clinical course from 3 fatal cases with severe thrombocytopenia in Colombia [9] and 4 cases of immune thrombocytopenic purpura during the ZIKV outbreak in French Polynesia [11] preclude interpretation of the relative contribution of ZIKV infection, preexisting medical conditions, and clinical interventions to patient outcome. Investigation of additional cases of severe thrombocytopenia in Puerto Rico is ongoing to better characterize the mechanism of association with ZIKV infection.

Both cases presented herein are noteworthy in that bloody lesions in the buccal mucosa developed 1 day after resolution of an acute febrile illness with generalized rash. The Surinamese patient had onset of hematomas 10 days after an acute illness with fever and rash; however, her platelet counts did not reach their nadir (10 000/μL) until 29 days after illness onset [10]. We therefore suspect that the mechanism of severe thrombocytopenia in these cases may be immune mediated, because ZIKV infection has been associated with other immune-mediated processes (eg, Guillain-Barré syndrome) [4]. Nonetheless, because diagnostic testing for evidence of other infections (eg, human immunodeficiency virus and hepatitis C virus) and autoimmune disease was not performed for all 3 patients with ZIKV infection and severe thrombocytopenia, other causes cannot be ruled out.

Although both patients from Puerto Rico had an illness consistent with ZIKV disease, neither received a diagnosis of suspected ZIKV infection. Instead, as with other cases of ZIKV-associated severe thrombocytopenia [9, 10], both patients were suspected to have dengue owing to severe hemorrhage and thrombocytopenia. Notably, no patient with ZIKV-associated severe thrombocytopenia had evidence of plasma leakage, which precedes the onset of major hemorrhagic manifestations in most patients with severe dengue [1]. This observation suggests that hemorrhage in these patients was the result of severe thrombocytopenia and not prolonged shock, as is more often the case in patients with dengue [1]. Moreover, both the timing and the mechanism of thrombocytopenia in patients with ZIKV infection seem distinct from those in patients with dengue, who most frequently develop thrombocytopenia during the febrile phase owing to direct infection of progenitor cells in the bone marrow and/or destruction of mature platelets [12].

The diagnosis of immune thrombocytopenic purpura in patient 2 and the Surinamese patient [10] triggered treatment with IVIG and a corticosteroid; however, corticosteroids are not recommended for patients with dengue because they are not associated with improved patient outcome [1]. Hence, owing to the lack of available point-of-care diagnostic tests to confidently differentiate patients with ZIKV disease from those with dengue, administration of corticosteroids to patients with suspected dengue or ZIKV disease should be reserved for those who have evidence of immune thrombocytopenic purpura or other complications for which clinical management includes corticosteroids.

Because of known cross-reactivity of antibodies directed against DENV with ZIKV antigen [4], one limitation of this investigation is that patient 2 had only serologic diagnostic evidence of ZIKV infection. Although original antigenic sin has been observed in patients with ZIKV infection and prior DENV infection [13], lack of detected anti-DENV IgM antibody in both acute- and convalescent-phase specimens along with 4-fold increase in ZIKV plaque reduction neutralization titer are together highly suggestive of ZIKV infection. Moreover, although patient 2 did not have ZIKV detected in a urine specimen collected 1½ months after illness onset, such testing may have improved sensitivity for diagnosis of patients with recent ZIKV infection [14]. Similarly, this investigation benefited from the availability of the TrioPlex RT-PCR assay, which simultaneously detects nucleic acid from ZIKV, DENV, and CHIKV and enabled diagnosis of ZIKV infection in patient 1 when dengue diagnostic testing was ordered.

In summary, ZIKV-infected patients with severe thrombocytopenia and hemorrhage may be underrecognized owing to misdiagnosis of severe dengue. Clinicians seeing febrile patients who live in or have recently returned from areas where ZIKV is circulating should be aware that acute ZIKV infection may be associated with immune-mediated severe thrombocytopenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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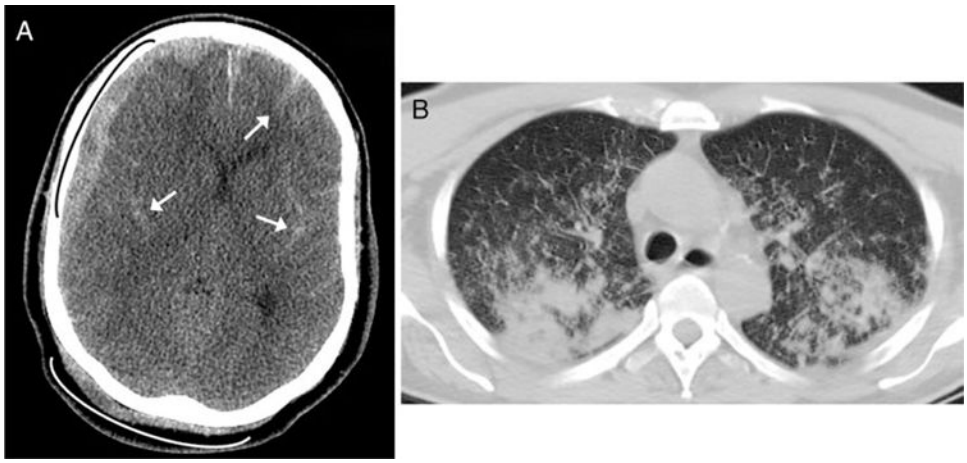

Figure 1.

Hemorrhagic manifestations in case 1. *A*, Computed tomography (CT) of the head without contrast enhancement demonstrating right-sided subdural hemorrhage (*black arc*), diffuse subarachnoid hemorrhage (*arrows*), subgaleal hematoma (*white arc*), and a 5-mm right-to-left midline shift. *B*, CT of the chest without contrast enhancement demonstrating diffuse alveolar hemorrhage.