

Case Report: A Case of Diabetic Ketoacidosis Following Chikungunya Virus Infection

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Abstract. Chikungunya is a mosquito-borne viral disease that has recently become endemic in the Caribbean, including the island of Puerto Rico. We present the case of a 50-year-old Puerto Rican man who traveled to St. Louis for business and was diagnosed with acute chikungunya virus infection with atypical features causing diabetic ketoacidosis. This case highlights the need to keep tropical infectious diseases on the differential diagnosis in appropriate individuals and the ways in which tropical infectious diseases can masquerade as part of common presentations.

INTRODUCTION

Chikungunya is a mosquito-borne viral infection, characterized by fever and acute polyarthralgias.¹ There is no drug for treatment or vaccine for prevention available.² Chikungunya virus is an alphavirus of the *Togaviridae* family that is transmitted by mosquitoes of the genus *Aedes* (mainly *Aedes aegypti* and *Aedes albopictus*).³ First isolated in 1952, chikungunya has reemerged in the past decade, causing widespread epidemics in 2005–2006 in the islands of the Indian Ocean and southern India.⁴

There is evidence that the chikungunya virus strain that circulated during the Indian Ocean epidemic had acquired a mutation, which made transmission by *Ae. albopictus* possible.⁵ This species of mosquito is found in a more temperate climate than the traditional vector *Ae. aegypti*. The first locally transmitted case of chikungunya in the Americas was on the Caribbean Island of Saint Martin in December 2013. Since then, there have been 1,975 confirmed cases in Puerto Rico as of August 12, 2014, and 1,100 cases in the United States, including 272 in Florida as of October 1, 2014.^{6,7} Most of the U.S. cases have been associated with travel to an endemic area; however, 11 cases of local transmission were reported in Florida.⁷

With the recent outbreak of chikungunya in the Americas, imported cases among returning travelers in the United States will likely continue to increase. With ongoing interest in neglected tropical diseases, especially as some have spread to nonendemic regions, we seek to present a case of diabetic ketoacidosis (DKA) in a traveler with chikungunya from a chikungunya-endemic area.

CASE REPORT

A 50-year-old Puerto Rican man with type 1 diabetes mellitus and hyperlipidemia visiting St. Louis, MO on a business trip presented to our hospital on the third day of his trip complaining of 2 days of subjective fever, weakness, diffuse myalgias, nausea, and large-volume diarrhea. He denied recent or ongoing arthralgias. Symptoms started 1 day after landing in the United States. He took over-the-counter acetaminophen (paracetamol) with some relief. He denied recent travel outside of Puerto Rico or the United States. Additional

history revealed several mosquito bites in Puerto Rico prior to the day of travel. In addition, he denied sick contacts, dietary changes, or abdominal pain. Home medicines included simvastatin 40 mg by mouth (PO) daily, insulin glargine 40 units (U) administered subcutaneously at night, and 10 U of subcutaneous insulin lispro three times daily with meals. Per history, he did not take his insulin lispro and self-reduced his insulin glargine dose from 40 to 15 U for the 2 days prior to presentation due to poor PO intake. The patient had no known drug allergies, was single, drank alcohol socially, and denied tobacco or illicit drug use. There was no history of travel to west Africa. The review of systems was otherwise negative except as noted.

Upon admission in the emergency department, the patient's temperature was 36.9°C, heart rate 99 beats per minute, respiratory rate 12 breaths per minute, blood pressure 107/69 mmHg, and oxygen saturation 98% on room air. He was a well-dressed, well-nourished man in mild distress, preferring to keep his eyes closed and was speaking quietly. He had dry mucous membranes and anicteric sclerae. Cardiac exam revealed regular rate and rhythm without jugular venous distension or lower extremity edema. Lungs were clear to auscultation bilaterally, without wheezing. Abdomen was soft and nondistended but with mild tenderness to palpation in the suprapubic area. Murphy's sign was absent, and there was no rebound or guarding. Lymph node exam demonstrated shotty left anterior cervical chain lymph nodes but no other findings. Skin examination revealed no rashes, but the anterior chest wall was mildly erythematous, possibly secondary to recent sun exposure. Musculoskeletal exam, including joint exam, was within normal limits.

In the emergency department, the patient's laboratories indicated DKA—blood glucose 311 mg/dL, serum ketones 5.7 mmol/L, 2 + glucose in urine, and anion gap 22 mEq/L. His liver function tests were elevated at alanine transaminase 161 U/L, aspartate transaminase 97 U/L, and alkaline phosphatase 129 U/L. Complete blood cell counts revealed lymphopenia ($0.500/\text{mm}^3$) and thrombocytopenia ($114,000/\text{mm}^3$). His hemoglobin A1C was 10.0%. Electrocardiogram showed normal sinus rhythm, and a chest radiograph showed no cardiac or pulmonary abnormalities.

His DKA was treated with intravenous fluids and an insulin drip, and he was subsequently transitioned to subcutaneous basal-bolus insulin regimen once his anion gap closed. Because of the patient's presentation with fever, nausea, vomiting, and diarrhea, an infectious etiology for his DKA was pursued. Viral respiratory and influenza nasopharyngeal swab was obtained and was negative. Routine blood cultures,

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bacterial stool cultures, stool *Clostridium difficile* toxin, and human immunodeficiency virus were all negative. Given his thrombocytopenia, transaminitis, fever, myalgias, weakness, and location in Missouri, Ehrlichia polymerase chain reaction (PCR) was obtained and was negative. As the patient lived in an area endemic for dengue and recently endemic for chikungunya, dengue immunoglobulin M (IgM) and immunoglobulin G (IgG) as well as chikungunya virus reverse transcription polymerase chain reaction (RT-PCR) were checked. These laboratories were drawn on the fourth day of the patient's illness (and second day of his hospitalization). The choice of testing for each disease (RT-PCR for chikungunya, serology for dengue) was guided by availability through the Missouri Department of Health and the home institution, as neither disease is routinely checked at hospitals in Missouri. Because of the lack of institutional experience, dengue serologies were sent to the Mayo clinic. In retrospect, dengue PCR testing would have been more appropriate; however, it was thought to be unavailable at the time.

Given his negative bacterial cultures and symptoms, a viral syndrome was thought to be the cause of DKA. As such, he was treated with supportive care consisting of intravenous fluids and anti-emetics. His symptoms resolved and his laboratory abnormalities improved over the course of this 3-day inpatient hospitalization in October 2014. After tolerating an oral diet, he was discharged on a new insulin regimen with instructions to follow-up with his primary care physician in Puerto Rico. Weeks after his discharge, dengue serologies were IgG positive and IgM negative, suggestive of remote and not acute dengue virus infection, and chikungunya RT-PCR was positive, consistent with acute chikungunya at the time of hospitalization.

DISCUSSION

The etiology for our patient's DKA was likely an acute infection with chikungunya virus. This was his first hospitalization due to DKA in 15 years. He likely had local transmission of chikungunya virus in Puerto Rico the week leading up to his airplane flight to the United States. As noted in the retrospective analysis of the 2005–2006 Reunion Island chikungunya outbreak, patients with diabetes were more likely to be hospitalized than the patients that did not have diabetes.³ Our patient's medical history of type 1 diabetes mellitus likely placed him at a higher risk of hospitalization.

Malaria and dengue are two of the most common systemic illnesses reported in returning travelers. Chikungunya has received increasing recognition in the Western Hemisphere. Since the first locally transmitted case of chikungunya in 2013 in the Caribbean, the number of cases in Puerto Rico has been growing steadily. Due to travel between Puerto Rico and the United States, the number of imported cases in the United States will likely increase. We suspect presentations similar to our patient's will become more common to returning travelers in the United States. As such, chikungunya must be considered in travelers from Puerto Rico presenting with fever, fatigue, gastrointestinal symptoms, and myalgias/arthralgias.

Our patient had some but not all the classic features of acute chikungunya. Gastrointestinal symptoms of nausea, vomiting, and diarrhea occur in up to 50% of the patients.^{3,8} These symptoms resolved with supportive care in our patient. Like many viral infections, patients infected with chikungunya

virus can demonstrate lymphopenia, thrombocytopenia, and elevated liver function tests.⁹ We originally attributed our patient's transaminitis to his statin. However, he had taken this medicine for over a decade without issue. We now believe this laboratory abnormality was also a manifestation of his acute infection.

A very common feature of chikungunya virus infection is polyarthralgias, mainly in the knee and ankle joints. Among those acutely infected, patients developed arthralgias at rates as high as 87–98% in some case series.¹⁰ In some patients, arthralgias may resolve within 1 week, but 60% of patients may develop chronic arthritis that can last up to 3 years.¹¹ These polyarthralgias can be disabling and severe.⁵ Our patient did not manifest this symptom while hospitalized, and he denied having this symptom prior to hospitalization; it is important to note that the patient was fluent in English, and there were no language barriers. It is critical to recognize arthralgias as part of the viral syndrome and provide acute treatment with acetaminophen. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided initially when there is concern for dengue as it can increase the risk of bleeding.¹² NSAIDs should only be used in adults once dengue has been ruled out or when arthralgias last longer than 1–2 weeks, a clinical manifestation not consistent with dengue.¹² As serology was performed for dengue on the fourth day of illness instead of RT-PCR, there is a small chance that our patient's result was a false negative and that he may have been coinfecting with both viral diseases. There was no remaining specimen upon which repeat testing could be performed for PCR. In addition, as this patient already had IgG present in the acute serum sample, a 4-fold increase in IgG antibody titers between acute and convalescent serum would have indicated an acute secondary dengue infection.¹² However, we were unable to follow up convalescent IgG titers for dengue as he returned to Puerto Rico.

Patients should be educated that these joint pains may persist for a long time after fever resolution and may progress to a destructive arthritis.⁵ There is no current treatment or vaccine for chikungunya; however, as this pathogen is rapidly emerging, efforts are being made to develop a vaccine.² Chang and other recently published a successful phase 1 clinical trial of a virus-like particle vaccine.²

IgM antibody response to acute chikungunya virus infection is detectable between days 2 and 7 after the onset of fever with an enzyme-linked immunosorbent assay test.⁵ An IgG antibody response is typically detectable 1–2 days after IgM becomes detectable, approximately on day 7 of illness.^{13–15} IgG levels can persist for years whereas IgM levels can persist for up to 3–4 months.⁵ Chikungunya virus infections can cause high levels of viremia for 4–6 days after onset of symptoms but can persist up to 12 days.⁹ As such, virus isolation and nucleic acid detection by RT-PCR is possible within 7 days of symptom onset.⁹ As diagnostic tests were sent on day 4 of symptom onset, chikungunya virus RT-PCR was checked and returned positive.

Aedes albopictus, one of chikungunya's vectors, is common throughout the contiguous United States.³ It is possible that local transmission of the virus could spread outside of Florida, where at least 11 locally transmitted cases have been reported.⁷ Consequently, it is critical that clinicians distinguish between imported and locally transmitted cases. Even if there has been no recent travel to an endemic region, those in regions with

recently identified chikungunya cases who have consistent physical examination findings or laboratory abnormalities should be tested. Early recognition of local transmission could lead to evidence-based public health measures, notably vector control, and such interventions could prevent chikungunya from becoming endemic to additional geographic areas.

Received December 27, 2014. Accepted for publication April 13, 2015.

Published online June 1, 2015.

Acknowledgments: We thank the Mayo Clinic for performing dengue serologies and the Centers for Disease Control and Prevention for performing the chikungunya RT-PCR testing.

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