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Case Report: An Acute Chikungunya Infection and a Recent Secondary Dengue Infection in a Peripartum Case in Ecuador

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Abstract. Dengue virus (DENV) and chikungunya virus (CHIKV) are transmitted by the same mosquito vectors and now co-circulate in many parts of the world; however, coinfections and serial infections are not often diagnosed or reported. A 38-week pregnant woman was admitted to the hospital with a diagnosis of suspected DENV and CHIKV in southern coastal Ecuador. The pregnancy was complicated by mild polyhydramnios and fetal tachycardia, and a healthy newborn was born. The patient was positive for a recent secondary DENV infection (Immunoglobulin M and Immunoglobulin G positive) and an acute CHIKV infection (real-time reverse transcriptase polymerase chain reaction positive) (Asian genotype). The newborn was not tested for either virus. This case resulted in a benign clinical course with a favorable pregnancy outcome.

INTRODUCTION

Dengue virus (DENV, family *Flaviviridae*, genus *Flavivirus*) and Chikungunya virus (CHIKV, family *Togaviridae*, genus *Alphavirus*) are spread by the *Aedes* mosquitoes (*Ae. aegypti* and *albopictus*) and cause illness throughout the tropics and subtropics.[1,2] Illness due to DENV infections ranges from mild febrile illness to severe illness resulting in hemorrhage, shock, and death if fluids are not properly managed.[3] Illness due to CHIKV infections ranges from mild febrile illness to debilitating chronic joint pain.[4] Prior studies indicate the risk of more severe DENV and CHIKV infections during pregnancy.[5–8] However, the ramifications of acute CHIKV infection in the setting of recent secondary DENV during pregnancy are unclear. Here we report the case of a pregnant woman who was admitted to the hospital with a diagnosis of suspected DENV and CHIKV and gave birth. This case occurred during the first epidemic of CHIKV in 2015 in Ecuador.

CASE REPORT

In 2015, a 35-year-old woman who was 38 weeks pregnant was admitted to the emergency department of a hospital in Machala, Ecuador, with a 1-day history of fever, headache, abdominal pain, arthralgia, myalgia, and retro-orbital pain. She was admitted with the diagnoses of gestational hypertension, polyhydramnios, and suspected DENV and CHIKV infections.

The patient had no significant past medical history, and an obstetric history of G3 P2 with two living children. Two months before admission, an obstetric ultrasound showed a 30-week fetus with polyhydramnios (amniotic fluid index [AFI] 23 cm, reference range = 5–22 cm). Eight months before admission, the patient had an obstetric ultrasound within normal limits with an AFI of 12 cm (both ultrasounds available upon request).

On admission, the patient was afebrile, and maximum blood pressure was 130/80 on the first night of hospitalization. Physical examination on admission was unremarkable, with a gravid uterus in right dorsal cephalic position. The patient became febrile overnight, with a maximum temperature of 38.8°C on her second hospital day. Fetal heart rate was 185 beats per minute. She received magnesium sulfate, nifedipine, acetaminophen, and saline (Supplemental Text 1). Laboratory tests throughout the patient's hospital stay are shown in Table 1. On the night of admission, the patient was anemic. Platelet counts and liver enzymes stayed within normal limits over the course of the patient's hospitalization. An obstetric ultrasound taken on day 2 showed a 38-week fetus with polyhydramnios (AFI 25.6 cm) and fetal tachycardia (166 bpm) (Supplemental Text 2). An NS1 test for dengue and a tourniquet test were both negative on day 2. In subsequent laboratory analyses (post hospital discharge), the patient was found to be positive for a recent secondary DENV infection (Immunoglobulin M [IgM] and Immunoglobulin G [IgG] enzyme-linked immunosorbent assay positive) and an acute CHIKV infection (real-time reverse transcriptase polymerase chain reaction [RT-PCR] positive) (Asian genotype) from a blood sample taken on hospital day 3 or day 4 since the onset of the patient's fever. The patient was negative for Zika virus (ZIKV) by RT-PCR. Diagnostic procedures have been described in detail previously.[9]

The patient received one dose of ampicillin on day 2 and continued to have arthralgia and myalgia. On the afternoon of day 2, the patient developed a nonpruritic erythematous spotted rash, with nonelevated borders on the abdomen. There was also tenderness of the extremities to range of motion movements and no peripheral edema. Decreased white blood cell count with lymphopenia was observed on day 3, and from day 3 onward, the patient was afebrile. On day 5, the patient received one dose of misoprostol (25 μg). On day 7, a pruritic rash developed on the patient's hands and lower extremities. Fetal heart rate was 130 bpm.

On day 8 the patient gave birth. The patient received oxytocin (three doses of 10 unit intervals at 10:20, 17:47, and 18:00) and saline. The patient had a vaginal birth at 40 weeks of gestation to a female newborn with a weight of 3,400 g, length 47 cm, and Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. No complications at birth were reported and the newborn had a normal physical examination. No diagnostic tests were run on the newborn for DENV, CHIKV, or ZIKV. One day postpartum,

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TABLE 1
Laboratory values during hospitalization of DENV and CHIKV coinfection

		Day-	Day 1	Day 1	Day 2	Day 3	Day 7	Day 7	Day 8	Day 9
Parameter	Reference	Time-	20:01	20:03	15:31	13:41	11:09	11:17	22:35	8:53
Hematocrit (%)	37.0–52.0		32.2		28.2	29.9		33.5	56.3	35.2
Hemoglobin (g/dL)	12.0–18.0		10.4		9.1	9.5		10.9	19.4	11.1
RBC (10^6/μL)	4.20–6.10		3.99		3.51	3.66		4.2	5.62	4.37
MCV (fL)	81.0–99.0		80.7		80.3	81.7		79.8	100.2	80.5
WBC (10^3/μL)	4.80–10.60		8.04		8.39	4.13		6.22	15.6	8.03
Neutrophils (%)	37.0–72.0		85.8		86.9	71.7		73.1	53.2	72.4
Lymphocytes (%)	20.0–50.0		7.2		7.7	17.4		19.5	34.1	19.6
Monocytes (%)	0.0–10.0		6.2		5.2	10.2		6.1	9.0	5.9
Eosinophils (%)	0.0–4.0		0.7		0.1	0.2		1.0	3.2	1.2
Basophils (%)	0.0–1.0		0.1		0.1	0.5		0.3	0.5	0.9
Platelets (10^3/μL)	130–400		227		188	190		201	228	216
ALT (U/L)	10–41			6.3		10.4	28.7			
AST (U/L)	10–50			19.9		40.4				
Glucose (mg/dL)	74–106			77.5			54.5			
Urea (mg/dL)	10–55			10.2						
Creatinine (mg/dL)	0.6–1.2			0.4			0.41			
Uric Acid (mg/dL)	2.4–7.0			4.1			5.6			
Total proteins (g/dL)	6.6–8.7						5.56			
Albumin (g/dL)	3.5–5.2						3.25			
Globulin (g/dL)	2.0–3.5						2.31			
Bili-total (mg/dL)	< 0.9						0.58			
Bili-direct (mg/dL)	< 0.2						0.24			
Bili-indirect (mg/dL)							0.30			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bili = bilirubin; CHIKV = chikungunya virus; DENV = dengue virus; MCV = mean corpuscular volume; RBC = red blood cells; WBC = white blood cells.

the patient had hypogastric pain and moderate vaginal bleeding, and the patient was discharged on day 11.

DISCUSSION

In 2015, when the first cases of CHIKV were reported from the city of Machala, 4.8% of individuals who were clinically diagnosed with DENV infections were found to have had a recent DENV infection and an acute CHIKV infection, including the case presented here.[9] Evidence that single mosquitoes can carry both DENV and CHIKV exists, including a single live capture of a coinfected mosquito.[10,11] There have been reports of coinfection of CHIKV and DENV with variable laboratory values and symptoms.[1,5,6] Coinfections with ZIKV, DENV, and CHIKV have also been reported, representing the challenge of diagnosing these arboviral infections, especially for high-risk groups, such as pregnant women in endemic areas.[12]

It is critically important to assess the risks of CHIKV and DENV infections during pregnancy. Common practice by the public health sector in Ecuador and other resource-limited settings is to screen for one pathogen at a time, until a positive test result emerges, although triplex PCR protocols are increasingly being implemented. As a result, coinfections are less commonly documented. Mercado et al.[6] reported a case of a CHIKV and DENV coinfection during the 37th week of gestation, similar to the case presented here; however, the patient developed a hemorrhagic stroke at 4 days postpartum, and later died of nosocomial sepsis. In addition, a coinfection of ZIKV, DENV, and CHIKV during pregnancy (at 14 weeks gestation) has recently been reported in Colombia.[13] DENV infection during pregnancy increases the risk of severe dengue, and peripartum CHIKV infection has been associated with a 48.7% vertical transmission rate of CHIKV with subsequent risk for neonatal encephalopathy.[3,14]

The case presented here adds to the limited body of case reports of serial or concurrent arboviral infections during pregnancy.[6,13] The patient displayed several features typical of both DENV and CHIKV infections (including fever, rash, retro-orbital pain, and myalgias) and an overall benign course. Of note, the blood sample used to run diagnostics in our affiliated laboratories was drawn on the fourth and final day of the patient's fever (hospital day 3). This sample was negative for DENV by RT-PCR, which precluded DENV serotype identification, and it is possible that the window of viremia was missed.[15] DENV IgM is usually detectable by day 4 of infection, and although there is well-documented cross-reactivity among *flaviviruses* such as DENV and ZIKV, DENV IgM and IgG positivity appears reliable in the setting of CHIKV infection.[1,15–17] It is unlikely that the antibody response was due to a ZIKV infection, as the subject tested negative for ZIKV by PCR, and this subject was enrolled 7 months before the first ZIKV case was confirmed in this region.

Laboratory abnormalities in this patient (Table 1) included anemia, likely dilutional because of pregnancy, and possible hemoconcentration on the day of delivery, although there was lack of concurrent signs of plasma leakage typical of DENV infections.[3,18] Ultrasound at admission showed fetal tachycardia and polyhydramnios with an AFI of 25.6 cm; however, this patient already had a slightly increased AFI of 23 cm 2 months before her admission. Polyhydramnios is found in around 1% of all pregnancies, and although it may be associated with fetal anomalies and infections, it is often idiopathic, especially in mild polyhydramnios (AFI 25–30 cm) as seen in this case.[19,20] Polyhydramnios has been previously reported in a DENV case complicated by postpartum hemorrhage.[21] In the case presented here, it is possible that the CHIKV and recent DENV infections may have complicated an otherwise idiopathic polyhydramnios. Notably, the patient had been afebrile and normotensive for 5 days when she gave birth to a newborn with a normal physical examination. Although the peripartum period has increased risk for DENV and CHIKV vertical transmission, the newborn was not tested in this case.[14,15] Fortunately, the newborn did not show signs such as fever or

prostration, which were reported in all vertically transmitted CHIKV cases in one study.[14]

There appears to be a tendency for severe cases of DENV and CHIKV to be reported in pregnancy.[5–8] To our knowledge, this is the first documented Ecuadorean case of acute CHIKV after secondary DENV infection in pregnancy, and it shows a mild clinical picture. In early 2016, a high rate of arboviral coinfection (CHIKV, DENV, and/or ZIKV) was detected in the cerebrospinal fluid of 16 suspected arboviral cases in Guayaquil, Ecuador.[22] With lack of access and timely reporting of both PCR and serology, accurate identification and reporting of future arboviral infections may be limited. Management of a suspected arboviral infection in pregnancy would be enhanced by increased access to molecular diagnostics in endemic areas, which would facilitate better diagnosis, reporting, and research. Given the risks associated with DENV versus CHIKV treatments (e.g., antiplatelet agents used in CHIKV increasing the risk of hemorrhage in DENV patients), as well as the neonatal and neurological complications associated with ZIKV infections, accurate diagnosis and careful treatment of these febrile syndromes is important.[1,3,15,17] We would recommend testing for all three pathogens (DENV, CHIKV, and ZIKV) when one is suspected, especially for pregnant women in endemic areas. Here we report a benign clinical course, albeit during an 11-day hospitalization, in a peripartum woman with an acute CHIKV infection after a secondary DENV infection.

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