Clinical Manifestations Associated with Peripheral Joint Involvement in Patients with Acute Chikungunya Virus Infection

Mariangeli Arroyo-Ávila,¹ Amanda Cabán,¹ Enid J. García-Rivera,² Marisela Irizarry-Pérez,² Hilda Torres,² Héctor Gorbea,³ and Luis M. Vilá^{1*}

¹Division of Rheumatology, Department of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico;

²Endowed Health Services Research Center, School of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico; ³Division of Infectious Diseases, Department of Medicine, University of Puerto Rico

Medical Sciences Campus, San Juan, Puerto Rico

Abstract. Chikungunya virus (CHIKV) causes an acute febrile illness usually accompanied by severe polyarthralgia and polyarthritis. Previous studies have shown that older age, female gender, and some comorbid conditions are associated with chronic CHIKV arthritis. However, the factors associated with acute arthralgia and arthritis are not well known. Thus, we studied the clinical manifestations associated with acute peripheral joint involvement in a group of CHIKV patients from Puerto Rico. Patients with a history of fever for < 7 days evaluated at the emergency department of a university-based hospital were tested for several pathogens including CHIKV. All patients with laboratory-positive CHIKV infection were studied. Demographic features, clinical manifestations, and comorbidities were determined. Patients with and without peripheral joint involvement were compared using bivariable and multivariable analyses. In total, 172 patients with CHIKV fever were evaluated; 52.9% were women. The mean (standard deviation) age was 21.1 years (19.3). Peripheral arthralgia and/or arthritis were seen in 156 (90.7%) patients. In the multivariable analysis adjusted for age and gender, peripheral joint involvement was associated with myalgia (odds ratio [OR] = 4.65, 95% confidence interval [CI] = 1.48–14.72), back pain (OR = 16.77, 95% CI = 3.07–313.82), ocular pain (OR = 8.88, 95% CI = 1.65–165.19), headache (OR = 3.63, 95% CI = 1.06–12.53), anorexia (OR = 5.68, 95% CI = 1.87–18.97), and nausea (OR = 6.88, 95% CI = 2.05–31.49). In conclusion, in this population of patients with acute CHIKV infection, peripheral joint involvement was associated with myalgia and back pain as well as nonmusculoskeletal manifestations such as headache, ocular pain, anorexia, and nausea.

INTRODUCTION

Chikungunya virus (CHIKV) is a single-stranded RNA arthropod-borne virus belonging to the *Alphavirus* genus and is transmitted to humans by mosquitoes from the *Aedes* genus.¹ It is a common cause of virus-induced arthritis in the Eastern hemisphere, with documented epidemics in Africa, southeast Asia, and the Indian Ocean islands.^{1–4} However, CHIKV is a novel virus in the Americas. The first case of local transmission was reported in the Caribbean island of St. Marteen in December 2013.⁵ CHIKV rapidly expanded through the region causing outbreaks in the Antilles, Central and South America, and the United States. In May 2014, the first case of local transmission was reported in Puerto Rico. Since then, approximately 4,500 laboratory-confirmed CHIKV cases have been reported in the island.³

Acute CHIKV fever is usually characterized by an acute febrile illness often associated with severe, debilitating symmetric polyarthralgia and polyarthritis.^{2,4–12} The fever usually resolves within 1 week but the musculoskeletal symptoms may persist for months to even years after the acute illness.^{7,13–21} Several factors have been linked with the development of chronic CHIKV-associated arthritis, including female gender, older age, severity of symptoms in the acute phase, and comorbid conditions such as arterial hypertension, type 2 diabetes mellitus (DM), and osteoarthritis.^{8,13,14,16,17,22} However, the factors associated with acute peripheral joint involvement are not well known. Therefore, we sought to determine the clinical manifesta-

tions associated with acute peripheral arthralgia and arthritis in a group of patients with laboratory-positive CHIKV infection from a university-based hospital in Puerto Rico.

MATERIALS AND METHODS

Patient population data were collected from the Sentinel Enhanced Dengue Surveillance System (SEDSS) site located at the University of Puerto Rico (UPR) Hospital, Carolina, Puerto Rico. SEDSS was a collaborative study between the Centers for Disease Control and Prevention and several institutions in Puerto Rico, including the UPR Hospital, to establish an acute febrile illness surveillance system. The SEDSS ceased operations at the UPR site on September 30, 2015. In this surveillance, all patients who presented to one of the affiliated health-care facilities with documented fever ($\geq 38.0^{\circ}\text{C}$ or $\geq 100.5^{\circ}\text{F}$) or history of fever lasting ≤ 7 days were included in the study after obtaining informed consent. Serum samples were tested for CHIKV, dengue virus (DENV), and enterovirus by reverse transcription polymerase chain reaction (RT-PCR) in addition to CHIKV and DENV IgM antibodies by enzyme-linked immunosorbent assay. Nasopharyngeal and oropharyngeal samples were tested for influenza A and B, respiratory syncytial virus, human metapneumovirus, parainfluenza 1–4, human coronavirus (229E, OC43, NL63, and HR41), and adenovirus using RT-PCR. Patients were also tested for *Leptospira* by serum microscopic agglutination and for *Burkholderia pseudomallei* by serum and urine type 2 secretion system (TTS) RT-PCR and serum indirect hemagglutination assay.

Demographic features, clinical manifestations, and comorbid conditions were systematically collected in all patients using a case information form. All patients with laboratory-positive CHIKV infection from June 1, 2014 to September

*Address correspondence to Luis M. Vilá, Division of Rheumatology, Department of Medicine, University of Puerto Rico Medical Sciences Campus, P.O. Box 365067, San Juan 00936-5067, Puerto Rico. E-mail: luis.vila2@upr.edu

30, 2014, were included in this study. During this period, the CHIKV epidemic was at its peak in Puerto Rico. The Institutional Review Board of the UPR Medical Sciences Campus approved this study and written informed consent was obtained from all participating subjects according to the Declaration of Helsinki.

Variables. Demographic features, health-related behaviors, clinical manifestations, comorbidities, and clinical outcome were examined. Demographic features included gender and age at study visit. Health-related behaviors including cigarette smoking and alcohol consumption were evaluated. Self-reported clinical manifestations examined included chills, tiredness, arthralgia, joint swelling, back pain, myalgia, rash, ocular pain, abdominal pain, anorexia, nausea, vomiting, diarrhea, headache, dizziness, dyspnea, palpitations, and chest pain. In addition, the presence of joint swelling was determined by medical chart review. Peripheral joint involvement was defined as history of arthralgia or joint swelling or evidence of joint swelling on physical examination. Self-reported comorbid conditions studied were type 2 DM, hypertension, cardiac disease, chronic kidney disease, bronchial asthma, chronic obstructive pulmonary disease, and malignancy.

Vital signs including body temperature and heart rate were obtained from the medical chart. Fever was defined as body temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.5^{\circ}\text{F}$. Tachycardia was defined as a heart rate > 190 beats per minute (bpm) for children younger than 2 years, > 140 bpm for children older than 2 years but younger than 10 years, and > 100 bpm for children older than 10 years and all adults. Bradycardia was defined as a heart rate < 100 bpm for children younger than 2 years and < 60 bpm for children older than 2 years and all adults. Laboratory tests included white blood cell (WBC) and platelet counts, aminotransferase (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) levels, and urinalysis. Leukopenia was defined as WBC $< 4,000/\mu\text{L}$, lymphopenia as lymphocyte count $< 1,500/\mu\text{L}$, severe lymphopenia as $< 1,000/\mu\text{L}$, and thrombocytopenia as $< 150,000/\mu\text{L}$. Elevation of aminotransferases was defined as greater than the upper limit of normal according to the hospital's laboratory reference range; AST > 59 units/L and ALT > 72 units/L. Hematuria was defined as > 5 red blood cells/high-powered field and proteinuria as > 30 mg/dL. Outcome measures included discharge from the emergency department (ED) or admission to the hospital.

Statistical analysis. Descriptive analyses to evaluate the distribution of variables were performed. Continuous data were summarized using mean or median with its corresponding standard deviation (SD). Categorical data were summarized as frequency and percent. To evaluate the association between peripheral joint involvement with demographic and clinical variables, comparisons of proportions and means between the groups were based on Pearson's χ^2 test, Fisher's exact test (if expected value less than 5), or t test accordingly. Logistic regression models were used to evaluate the association between clinical variables and the presence of peripheral joint involvement adjusting for age and gender. A P value less than 0.05 was considered statistically significant. Data management and statistical analyses were performed using R software v3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From June 1, 2014 to September 30, 2014, 2,691 patients presented with acute febrile illness to the ED; of those, 320 (11.9%) were recruited in the study. One hundred and seventy-two (53.7%) of study participants tested positive for CHIKV, 28 (8.7%) for influenza virus, eight (2.5%) for other upper respiratory tract viruses, and only three (1.0%) for DENV. Among patients with acute CHIKV infection, 156 (90.7%) presented with peripheral joint involvement, whereas 16 (9.3%) did not.

Table 1 shows the general characteristics of patients with acute CHIKV fever. Fifty-three percent were female. The mean (SD) age was 21.1 years (19.3); 65.5% were younger than 16 years. The most common clinical manifestations were fever at ED evaluation (92.9%), peripheral arthralgia/arthritis (90.7%), severe lymphopenia (89.6%), headache (83.7%), myalgia (82.6%), chills (78.3%), tiredness (77.3%), anorexia (68.6%), rash (68.0%), nausea (58.7%), back pain (58.1%), abdominal pain (45.9%), dizziness (44.8%), tachycardia (44.2%), and ocular pain (43.6%). Thirty-three (19.2%) patients were admitted to the hospital.

Table 2 shows the associations of peripheral joint involvement with demographic features and clinical manifestations of acute CHIKV infection. Patients with peripheral joint involvement were more likely to be older (21.3 [± 19.6] versus 8.2 [± 10.3], $P < 0.001$), but no significant associations were observed for age groups or gender. In addition, patients with peripheral joint involvement were more likely to have back pain (63.5% versus 6.2%, $P < 0.001$), myalgia (85.9% versus 50.0%, $P = 0.002$), ocular pain (47.4% versus 6.2%, $P = 0.001$), anorexia (71.8% versus 37.5%, $P = 0.009$), nausea (62.8% versus 18.8%, $P = 0.001$), headache

TABLE 1
General characteristics of patients with acute chikungunya infection

Feature	
Gender, n (%) female	91 (52.9)
Age, mean years (standard deviation)	21.1 (19.3)
Clinical manifestations, n (%)	
Fever on emergency department evaluation	157 (92.9)
Arthralgia/arthritis	156 (90.7)
Lymphopenia ($< 1,000/\mu\text{L}$)	138 (89.6)
Headache	144 (83.7)
Myalgia	142 (82.6)
Chills	130 (78.3)
Tiredness	133 (77.3)
Anorexia	118 (68.6)
Rash	117 (68.0)
Nausea	101 (58.7)
Back pain	100 (58.1)
Abdominal pain	79 (45.9)
Dizziness	77 (44.8)
Tachycardia	76 (44.2)
Ocular pain	75 (43.6)
Vomiting	44 (25.6)
Diarrhea	41 (23.8)
Proteinuria	23 (18.6)
Cough	29 (16.9)
Thrombocytopenia ($< 150,000/\mu\text{L}$)	16 (10.3)
Chest pain	14 (8.1)
Leukopenia ($< 4,000/\mu\text{L}$)	9 (5.8)
Palpitations	6 (3.5)
Bradycardia	5 (2.9)
Dyspnea	4 (2.6)
Outcome, n (%) hospital admission	33 (19.2)

TABLE 2
Association of peripheral joint involvement with demographic features and clinical manifestations in acute chikungunya infection

Clinical feature	Patients with arthralgia/arthritis N = 156	Patients without arthralgia/arthritis N = 16	P value
Gender, <i>n</i> (%) female	83 (53.2)	8 (50.0)	1.000
Age			
Mean years (SD)	21.3 (19.6)	8.2 (10.3)	< 0.001
0–16 years, <i>n</i> (%)	98 (62.8)	14 (93.3)	0.100
17–55 years, <i>n</i> (%)	43 (27.6)	1 (6.7)	
> 55 years, <i>n</i> (%)	15 (9.6)	0	
Clinical manifestations, <i>n</i> (%)			
Fever on ER	144 (93.5)	13 (86.7)	0.290
Chills	120 (79.5)	10 (66.7)	0.320
Tiredness	123 (78.8)	10 (62.5)	0.20
Musculoskeletal manifestations			
Back pain	99 (63.5)	1 (6.2)	< 0.001
Myalgia	134 (85.9)	8 (50.0)	0.002
Rash	108 (69.2)	9 (56.2)	0.400
Ocular pain	74 (47.4)	1 (6.2)	0.001
Gastrointestinal manifestations			
Anorexia	112 (71.8)	6 (37.5)	0.009
Nausea	98 (62.8)	3 (18.8)	0.001
Vomiting	41 (26.3)	3 (18.8)	0.760
Diarrhea	39 (25.0)	2 (12.5)	0.360
Elevated AST	19 (14.5)	0.0	0.230
Elevated ALT	7 (5.3)	0.0	1.000
Neurological manifestations			
Headache	136 (87.2)	8 (50.0)	0.001
Dizziness	75 (48.1)	2 (12.5)	0.007
Seizures	4 (2.6)	0	1.000
Cardiorespiratory manifestations			
Dyspnea	4 (2.6)	0.0	1.000
Palpitations	6 (3.8)	0.0	1.000
Chest pain	13 (8.3)	1 (6.2)	1.000
Tachycardia	72 (46.1)	4 (25.0)	0.120
Bradycardia	4 (2.6)	6.2	0.390
Renal manifestations			
Proteinuria	19 (17.4)	4 (26.7)	0.480
Hematuria	4 (2.6)	0.0	1.000
Hematologic manifestations			
Leukopenia (< 4,000/ μ L)	8 (5.8)	1 (6.2)	1.000
Lymphopenia (< 1,000/ μ L)	123 (89.1)	15 (93.8)	1.000
Thrombocytopenia (< 150,000/ μ L)	16 (11.5)	0.0	0.380
Outcome, <i>n</i> (%) hospital admission	29 (18.6)	4 (25.0)	0.510

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ER = emergency room; SD = standard deviation.

(87.2% versus 50.0%, $P = 0.001$), and dizziness (48.1% versus 12.5%, $P = 0.007$). No significant differences were observed for chills, tiredness, rash, vomiting, diarrhea, elevated liver enzymes, cardiorespiratory or renal manifestations. Also, no significant associations were seen between groups in terms of admission to the hospital.

The associations between peripheral joint involvement and selected comorbidities are shown in Table 3. We found no significant differences for type 2 DM, hypertension, cardiac disease, chronic kidney disease, bronchial asthma, chronic obstructive pulmonary disease, or malignancy.

The multivariable analysis of variables associated with acute peripheral joint involvement is shown in Table 4. Myalgia, back pain, ocular pain, anorexia, nausea, and headaches retained significance.

DISCUSSION

In this population of patients with acute febrile illness and laboratory-positive acute CHIKV infection, we found that peripheral joint involvement was the most common manifestation, present in 91% of patients. In addition, those with

TABLE 3
Associations between peripheral joint involvement in acute chikungunya virus infection and comorbidities

Comorbidity <i>n</i> (%)	Patients with arthralgia/arthritis N = 156	Patients without arthralgia/arthritis N = 16	P value
Type 2 diabetes mellitus	6 (3.8)	0.0	1.000
Arterial hypertension	17 (10.9)	1 (6.2)	1.000
Cardiac disease	6 (3.8)	0.0	1.000
Bronchial asthma	43 (27.6)	2 (12.5)	0.240
Chronic obstructive pulmonary disease	2 (1.3)	0.0	1.000
Chronic kidney disease	0.0	0.0	1.000
Malignancy	1 (0.6)	0.0	1.000

TABLE 4

Clinical manifestations associated with peripheral joint involvement by multivariable analysis

Clinical feature	OR (95% CI)*
Myalgia	4.65 (1.48–14.72)
Back pain	16.77 (3.07–313.82)
Ocular pain	8.88 (1.65–165.19)
Anorexia	5.68 (1.87–18.97)
Nausea	6.88 (2.05–31.49)
Headache	3.63 (1.06–12.53)
Dizziness	4.07 (0.98–27.69)

CI = confidence interval; OR = odds ratio.

*Adjusted for age and gender.

peripheral arthralgia/arthritis were more likely to have other musculoskeletal manifestations such as myalgia and back pain, as well as nonmusculoskeletal symptoms such as ocular pain, headache, anorexia, and nausea. No associations were seen for major organ involvement, hospitalizations, or comorbidities. To the best of our knowledge, this is the first study that evaluates the clinical manifestations associated with peripheral joint involvement in the acute phase of CHIKV infection rather than those related to chronic joint symptoms.

Several studies have found that older age (> 45 years) and female gender are associated with the development of CHIKV-related chronic arthritis.^{13,16,17,22} In our study, patients with acute CHIKV who had peripheral joint involvement were older than those without joint symptoms. Similarly, other authors have described that pediatric patients with acute CHIKV infection are more likely to experience nonspecific symptoms such as fever rather than the typical clinical features such as arthralgia.²³ In contrast to what is described for chronic CHIKV-associated arthralgia, we found no significant associations between acute peripheral joint involvement and gender.

With regard to the relationship of comorbid conditions with arthralgia/arthritis, several authors have described associations between comorbidities such as osteoarthritis, type 2 DM, and arterial hypertension with the development of CHIKV-related chronic joint symptoms.^{13,14,22} However, we found no associations with the presence of comorbidities including tobacco and alcohol use, type 2 DM, cardiopulmonary or renal disease, or malignancy with acute peripheral joint involvement. This may be partly explained by the relatively large proportion of pediatric patients in our study sample, and consequently, a low prevalence of these comorbid conditions.

Our patients with peripheral arthralgia/arthritis were more likely to experience other musculoskeletal manifestations such as myalgia and back pain compared with those patients without joint involvement. Myalgia is a common symptom in acute febrile illnesses, and therefore, its presence in acute CHIKV is not unexpected; however, its prevalence varies among different studies.^{4,7,11,12,24–26} In a recent cross-sectional study of 30 patients with confirmed acute CHIKV infection in the Caribbean island of Trinidad, myalgia was present in 70%.¹¹ Similarly, Thiberville and others reported muscle discomfort in 74% of patients with confirmed CHIKV infection evaluated at an outpatient setting in Reunion Island; however, only 46% reported moderate to severe myalgia.²⁴ Conversely, a cross-sectional

study evaluating patients with acute CHIKV infection from two rural villages in India reported myalgia in only 25% of the population.⁷ Meanwhile, the presence of back pain during acute CHIKV infection has been infrequently reported in the literature and classically is more associated with dengue fever.^{4,6,7,11,12} In fact, in a study comparing clinical manifestations between CHIKV and DENV infection, none of the patients with confirmed CHIKV infection had back pain, whereas 12.5% of patients with DENV did.¹¹ Interestingly, in our study, back pain was fairly common and seen more frequently in association with acute peripheral arthralgia/arthritis.

Nonrheumatic manifestations are often reported in acute CHIKV infection.^{4,6,7,13,26} In our study, patients with peripheral joint involvement were more likely to have gastrointestinal symptoms, such as anorexia and nausea, compared with patients without arthralgia/arthritis. In general, and consistent with other reports, gastrointestinal symptoms were seen in approximately half of our patients.^{4,15,26} Conversely, neurologic manifestations are variably reported in acute CHIKV, headache being the most commonly described.^{4,11,12,15,25,26} In our population, patients with peripheral joint manifestations were more likely to have headache and dizziness.

Although not associated with peripheral joint involvement, other common manifestations seen in our patients with acute CHIKV were severe lymphopenia (89%), fatigue (77%), and skin rash (68%). Even though these have been reported in other series, their frequency is higher in our population.^{6–9,11,12,25} For instance, Borgherini and others reported that of 157 patients hospitalized with acute CHIKV infection in Reunion Island, 79% had lymphopenia; however, only 39% were in the severe range and 40% had maculopapular rash.⁶ Also, in a prospective study of 203 confirmed CHIKV-infected patients, 50% presented with rash and 49% had fatigue.⁹ Similar to our population, Mattar and others reported that rash was present in 64% of confirmed cases in a recent epidemic in Colombia.¹²

Remarkably, ocular pain, classically associated with acute DENV and infrequently reported in patients with CHIKV, was present in nearly half of patients with confirmed acute CHIKV infection.^{4,12,15,26} It was significantly more frequent in those who had peripheral joint involvement. In agreement with our study, Sahadeo and others compared the clinical manifestations of confirmed CHIKV and DENV infection and described that 40% of patients with confirmed CHIKV had eye pain. In this study, no significant difference in terms of ocular pain was observed when compared with patients with DENV.¹¹ It is important to note that DENV shares certain clinical manifestations with CHIKV such as fever, myalgia, headache, ocular pain, and rash. This makes the diagnosis of both conditions challenging. However, distinguishing between the two has important clinical and therapeutic implications. In the study by Sahadeo and others, those with acute CHIKV infection were more likely to present with arthralgia and rash, whereas leukopenia and thrombocytopenia were more common in patients with DENV infection.¹¹ Similarly, Mohd and others compared the clinical manifestations of patients with acute CHIKV and DENV infections and found that joint pain and rash were independently associated with CHIKV infection, whereas myalgia and elevated AST were associated with DENV infection.²⁵

Interestingly, we found that approximately 20% of patients with acute CHIKV infection had proteinuria. This finding together with the presence of arthralgia/arthritis, myalgia, rash, and lymphopenia may mimic the acute onset of autoimmune connective tissue diseases such as systemic lupus erythematosus (SLE). Furthermore, Miner and others described the presence of antinuclear antibodies (ANA) in three of nine patients with CHIKV infection returning from Haiti, two of which had high ANA titers.²⁷ Besides SLE, CHIKV may mimic other rheumatic diseases, including rheumatoid arthritis (RA) which shares some clinical and immunologic features.^{18,27}

Some limitations in our study should be addressed. First, a thorough rheumatologic examination to determine tender or swollen joint count was not performed in these patients, as it was not part of the primary acute febrile illness study. Second, there is no long-term follow-up data of these patients and thus the course of the disease cannot be studied; however, the primary endpoint of this study focused on the acute phase of CHIKV infection and not its chronic sequela. Third, the study was conducted in a university-based hospital and may not be representative of the entire population of Puerto Rico. Fourth, the majority of subjects recruited in our study were ≤ 16 years of age. Therefore, it is difficult to compare with previous studies performed primarily in adults, including older adults. One possible explanation is that young children with fever might be seen more often at the ED than adults as parents tend to bring their children to the ED even for nonurgent care.²⁸ Because of the discrepancy observed between age groups, in the multivariable analysis the associations with peripheral joint involvement were adjusted for age. Finally, emergency physicians participated in the enrollment of study patients, but due to the overwhelming workload of over 28,000 ED visits seen during the study period of 4 months, only a fraction of patients with acute febrile illness were enrolled possibly missing a significant number of acute CHIKV cases. Nevertheless, our study included a significant number of patients with laboratory-positive acute symptomatic CHIK infection.

In conclusion, in this population of patients from Puerto Rico with acute febrile illness evaluated between June 2014 and September 2014, approximately half had laboratory-positive acute CHIKV infection. Peripheral joint involvement was very common and was more frequent in older patients. The presence of peripheral joint involvement was associated with other musculoskeletal symptoms such as myalgia and back pain and with nonmusculoskeletal manifestations such as ocular pain, headaches, anorexia, and nausea. In contrast to chronic CHIKV arthritis, peripheral joint arthralgia/arthritis in the acute phase was not associated with female gender and chronic comorbid conditions. Physicians should be aware that acute CHIKV infection could present with clinical manifestations similar to other viral infections such as DENV infection and autoimmune connective tissue diseases, including RA and SLE.

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Authors' addresses: Mariangeli Arroyo-Ávila, Amanda Cabán, and Luis M. Vilá, Division of Rheumatology, Department of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico, E-mails: mariangeli.arroyo@upr.edu, amanda.caban@gmail.com, and luis.vila2@upr.edu. Enid J. García-Rivera, Marisela Irizarry-Pérez, and Hilda Torres, Endowed Health Services Research Center, School of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico, E-mails: enid.garcia3@upr.edu, marisela.irizarry@gmail.com, and hilda.torres1@upr.edu. Héctor Gorbea, Division of Infectious Diseases, Department of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico, E-mail: hector.gorbea@upr.edu.

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