Journal of Clinical Virology 69 (2015) 27–29

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Case report

Fatal cases of Chikungunya virus infection in Colombia: Diagnostic and treatment challenges

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ARTICLE INFO

Article history:
Received 10 February 2015
Received in revised form 24 March 2015
Accepted 26 May 2015

Keywords:
Chikungunya
Dengue
Mortality
Clinical feature
Laboratory finding

ABSTRACT

Although Chikungunya infection is emerging as an important public health problem in many countries it is not regarded as a life-threatening disease. Information dealing with fatal cases is scarce. We herein describe three patients with Chickungunya infection who presented with multiple organ failure and died within 24 h of admission. Two cases had positive anti-dengue IgM, but dengue coinfection was rejected based on the clinical features and results of real-time reverse transcription polymerase chain reaction. These cases illustrate the challenges of the diagnosis and management of severe Chikungunya infection.

1. Why this case is important?

Chikungunya infection may cause an overwhelming morbidity. Overall, it is an acute illness whose major signs and symptoms include a sudden-onset fever, skin rash, and a painful and incapacitating arthralgia. However, clinical manifestations are highly variable and may be severe in some cases. Although Chikungunya infection is emerging as an important public health problem in many countries, it is not regarded as a life-threatening disease [1]. Clinical features and the predisposing risk factors for the most severe forms of the disease are still emerging.

Chikungunya has been reported in the Africa, Asia and recently, in the Americas. In addition, imported cases among tourists are identified in several European countries and United States [1]. Around 100,000 cases of Chikungunya fever were reported in late December 2014, in Colombia [2]. In this article, we report a detailed description of three fatal cases with Chikungunya infection. The cases, which were treated in a University-based Hospital in Barranquilla, Colombia, may illustrate the clinical challenges associated to the diagnosis and management of severe Chikungunya infection.

2. Case description

A 71 year-old woman was admitted to the Hospital on December, 2014. She complained of fever, myalgia, incapacitating pain in multiple joints, and diarrhea for four days. In addition, the patient stated that she had lost her appetite and that her urine volume had decreased. There was neither skin rash, nor retroorbital pain. Patient also reported suffering from epilepsy and breast cancer treated 14 years ago.

A physical examination showed dehydration with no signs of jaundice or cyanosis. Her axillary temperature was 37.1 °C; blood pressure 60/30 mmHg, with heart rate of 150 bpm at hospital admission. Her lungs were clear with good air-entry. Her hands were swollen. Pitting edema was present in both lower limbs up to mid-shin. No evident swelling was detected in knee and elbow joints.

Laboratory tests performed upon admission showed important leukocytosis with lymphopenia, hyponatremia, hypoalbuminemia, renal insufficiency, and metabolic acidosis (Table 1). Clotting abnormalities, including major thrombocytopenia, were also detected. Chest X-ray and abdominal ultrasound performed upon admission were normal. Urine findings showed traces of albuminuria and glycosuria.

The patient was diagnosed with an acute bacterial infection and dehydration. She was treated with vigorous crystalloid

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http://dx.doi.org/10.1016/j.jcv.2015.05.021
1386-6532/

Table 1
Clinical and laboratory findings of fatal cases of laboratory-confirmed Chikungunya infection in Barranquilla, Colombia.

	Case 1		Case 2	Case 3
Clinical findings				
Days from symptoms onset	4		8	4
Fever	Yes		Yes	Yes
Skin rash	No		Yes	Yes
Arthralgia	Yes		Yes	No
Hypotension	Yes		Yes	No
Tachycardia	Yes		Yes	Yes
Altered mental status	No		Yes	No
Gastrointestinal symptoms*	Yes		No	Yes
Bleeding	No		No	No
Laboratory findings				
Date (dd/mm/yy)	1/12/14	2/12/14	6/12/14	6/12/14
Hemoglobin (g/dl)	15.7	15.6	17.1	18.3
Hematocrit (%)	42	42.4	51.3	53.5
Total white cells (10^9/L)	29.8	35.1	21.8	52.2
Total lymphocytes (10^9/L)	1.2	1.7	0.7	2.2
15 Platelets (10^9/L)	45	31	167	25
Prothrombin time (sec)	42.3	20.1	27.1	44.4
INR	1.4	1.37	1.53	1.51
Sodium (mmol/L)	127.5	136	129	134
Potassium (mmol/L)	4.86	3.02	6.38	5.79
Urea (mg/dl)	198	71	206	114
Creatinine (mg/dl)	4.34	3.31	6.5	5.33
Total bilirubin (mg/dl)	0.44		1.45	0.7
Aspartate aminotransferase (U/L)	146		276	270
Alanine aminotransferase (U/L)	18		74	30
Alkaline phosphatase (U/L)	265			
Glucose (mg/dl)	98		35	160
Troponin I (ng/ml)	0.68	0.57		
Albumin (g/dl)		1.46	2.62	
Lactate (mmol/L)		5.3	8.6	7.42
Creatine kinase (U/L)		509		1025
Lactate dehydrogenase (U/L)		2418		13620

INR = International Normalized Ratio.
* Gastrointestinal symptoms include nausea, vomiting or diarrhea.

hydration and intravenous piperacillin/tazobactam. However, her clinical condition worsened and she required mechanical ventilation; she died within 24 h after admission.

Blood cultures for microorganism growth were reported negative 5 days later. Although laboratory results found anti-dengue IgM upon admission (Panbio Dengue IgM Capture ELISA – Alere®), real-time reverse transcription polymerase chain reaction (RT-PCR) for dengue virus was reported negative 48 h later (Liferiver™ Dengue Virus Real Time RT-PCR Kit Shanghai ZJ Bio-Tech Co., Ltd.). Chikungunya virus was reported positive (cycle threshold value 12) 48 h later on RT-PCR in a serum sample taken upon admission (Liferiver™ Chikungunya Virus Real Time RT-PCR Kit Shanghai ZJ Bio-Tech Co., Ltd.). In addition, serology diagnostic test (IgM) for leptospirosis was negative.

Six days after case 1, a 75 year-old male visited the emergency department complaining of fever, myalgia and arthralgia for 8 days. A family member declared that the patient became somnolent and that the frequency and volume of his urination had decreased. Hypertension and benign prostatic hyperplasia comorbidities were also reported.

After a physical exam, the patient's axillary temperature was 39 °C, blood pressure 60/40 mmHg, and heart rate of 94 bpm. No cardiac or pulmonary abnormalities were found. His lower extremities showed pitting edema. In addition, acrocyanosis and petechial rash on the trunk were evident. There were no signs of swollen joints. There was no evidence of meningeal signs.

As in case 1, laboratory results showed leukocytosis with lymphopenia, hyponatremia, hypoalbuminemia, renal insufficiency, metabolic acidosis and clotting abnormalities. However, there was no thrombocytopenia (Table 1). A diagnosis of sepsis, multiple organ dysfunction and severe dengue was made. Crystalloid hydration with vasopressor support was initiated. Mechanical ventilation was required due to respiratory distress. The patient's condition worsened and died within 9 h after admission.

Anti-dengue IgM and RT-PCR for dengue were negative. Serology diagnostic test (IgM) for leptospirosis also was negative. Chikungunya virus was reported positive (cycle threshold value 20) on RT-PCR. No blood cultures were taken.

Concurrently with the admission of case 2, a 73 year-old female were admitted to the Hospital. She complained of fever, skin rash, nausea, and dyspnea over the past 4 days. The patient did not have underlying diseases. After a physical exam her axillary temperature was 37.5 °C, blood pressure 144/33 mmHg, with heart rate of 136 bpm at hospital admission. No cardiac and pulmonary abnormalities were found. As in case 2, the patient showed acrocyanosis and petechial rash on trunk and lower limbs. Laboratory results were similar to those described in case 1 (Table 1). Her chest X-ray was normal.

Multiple organ dysfunction and severe dengue was suspected. Crystalloid hydration, meropenem and linezolid were initially administered. Despite all of this, the patient's condition worsened, and she required vasopressor and mechanical ventilation. The patient died within 14 h after admission.

Although a serological test for anti-dengue IgM was detected, RT-PCR for dengue was negative. Meanwhile, RT-PCR for Chikungunya virus was positive in serum (cycle threshold value 14). Blood cultures did not show microorganism growth after 5 days of incubation. Similarly, anti-leptospiral IgM was negative.

3. Other similar and contrasting cases in the literature

Mortality attributed to Chikungunya fever was first reported during the Reunion Island outbreak in 2006. Atypical cases were estimated at 0.3% of all symptomatic cases. Thirty-six percent of the atypical cases were considered to be severe, 14% of those patients were admitted to an intensive care unit and 10% of them died [3]. A variety of atypical manifestations have been reported during the acute Chikungunya infection, such as neurological complications, myocarditis, pericarditis, pneumonia, nephritis, hepatitis and pancreatitis. Hemorrhagic complications are rare [1,3].

4. Discussion

Chikungunya infection severity seems to be markedly influenced by age and the presence of underlying diseases [3]. The patients described in this report were older than 70 years old. Nevertheless, they did not have major comorbidities and in those who had an underlying disease, this was not decompensated.

A misdiagnosis of bacterial sepsis or severe dengue was given in these cases at the emergency department. Leukocytosis found in the present report has not been documented to be associated to Chikungunya infection in recent studies [4–6]. Similarly, clotting abnormalities and major thrombocytopenia are not frequent findings in most of the Chikungunya infections. The presence of these abnormalities in our patients suggests intravascular coagulopathy. Significantly, there was no evidence of severe hepatitis, liver failure or hemorrhagic complications in these cases. Our patients also suffered from severe hypotension and renal failure, which have only been reported in a minority of Chikungunya infections [3]. It is noteworthy that blood cultures taken before administering antibiotics and leptospiral serology were all negatives in our patients. The cases had not risk factors for diseases such as rickettsioses or Q fever.

Coinfections with Dengue and Chikunkungunya have been previously reported [7]. Studies suggest that thrombocytopenia is a useful tool for diagnosis of dengue in this context [8,9]. Although thrombocytopenia was present and anti-Dengue IgM was positive for two of our cases, the possibility of having a Dengue coinfection was rejected based on the results of RT-PCR. In addition, patients did not have systemic vascular leak syndrome (hemoconcentration, pleural effusions or ascites). This may imply that either the patient was recently infected with Dengue or that there was a false-positive result. It is important to highlight that we only had RT-PCR results for Chikungunya and Dengue 48 h after the admission of patients to emergency department, because these tests are performed outside the Colombian Health Institutions. Therefore, a Chikungunya diagnosis should also be considered even for patients with initially positive anti-dengue IgM tests.

Our 3 patients rapidly deteriorated during hospitalization. Mortality ensued within the first 24 h for all cases, despite aggressive intravenous fluids, antibiotic administration, and vasopressor support. The patients showed neurological and respiratory deterioration and required mechanical ventilation and intensive care unit admission. The underlying physiopathology for some of the complications seen in severe Chikungunya infection is not known to a full extent. Although it is suspected that underlying medical conditions and deterioration of a previously unrecognized disorder may play a role, these factors cannot explain what happened to our patients. In the present report, most of the clinical and laboratory data suggested inadequate tissue perfusion. It is probable that hypoperfusion associated organ dysfunction played a role in the adverse outcome. The facts that we did not evaluate the immunological response to the virus or we did not isolate the virus for genetic mutation studies were limitations on this report.

In conclusion, these cases provide information intended for the clinician to be aware of the possibility for severe Chikungunya infection in the regions that are traditionally endemic for Dengue or among international travelers. In addition, the clinical presentation and the course of the illness in severe Chikungunya may be highly variable. In those areas without molecular diagnostic capabilities sensitive and rapid tests are required. The fatal outcome in these patients also highlights the need to better define the therapeutic approaches of severe Chikungunya infection.

Competing interest

All authors: no reported conflicts.

Funding

This work was supported by Universidad del Norte (PE0031/2014DViasus).

Ethical approval

Not required.

Author contribution

All authors had full access to all the data in the study and take responsibility for the integrity of the data. D.V. has contributed to the report concept and has written the manuscript. J.M.H., J.L.A. and H.S.V. have recorded data and have provided a critical revision of the manuscript for important intellectual content. B.B. and S.V. provided aid in interpreting the molecular virology results and other laboratory test, and contributed to the manuscript. All authors have approved the final manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcv.2015.05.021

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Journal of Clinical Virology 70 (2015) 14–15

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Letter to the editor

Mortality and fatality due to Chikungunya virus infection in Colombia

Dear editor,

Chikungunya virus disease (CHIK) began its spread through Latin American countries in 2013, increasing its epidemiological burden and posing an important economic drawback to healthcare systems of most of the affected countries throughout 2014. Foregoing Disability Adjusted Life Years (DALYs) lost estimates reveal that its burden is actually expected to be higher than those reported in previous epidemics [1]. Currently, with ever-increasing reports of severe and fatal cases of CHIK, predicted DALYs are expected to escalate even higher. The case report of de la Hoz et al. [2], highlights the importance of severe and fatal CHIK in new endemic areas of Latin America. However, along these lines we would like to discuss the current status of CHIK mortality and fatality in Colombia, providing estimated rates, based on officially reported deaths during 2014 and up to the 15th epidemiological week of 2015 [3].

Between 2014 and the 15th week of 2015, 43 fatal cases of CHIK have been reported in the country, with 25 laboratory-confirmed cases (Table 1). Based on the number of deaths and considering the total sum of cases reported as well as the population from those areas where fatal cases have occurred, an overall case fatality rate (CFR) of 0.012% has been estimated herein (Table 1), ranging from 0.000 up to 0.040% (in Cundinamarca department). The overall estimated mortality rate was 0.128 deaths/100,000 population for areas reporting deaths, ranging from 0.000 up to 0.738 deaths/100,000 population (in North Santander department) (Table 1).

As stated by de la Hoz et al. [2], previous studies in other continents have reported fatal and severe CHIK [4–7]. Although fatal cases have not been reported in some important epidemics around the globe, an increased mortality during CHIK outbreaks has been highlighted in countries such as India [8,9] and, in Reunion Island where a CFR of 10.7–27.7% and about 1 death/100,000 population mortality were reported during the 2005–2006 epidemics [10,11].

Severe and fatal cases of CHIK have been an underestimated reality [2,7,10,12,13]. Fatality presents usually in patients over 60 years, with associated comorbidities and with dengue-like manifestations (thrombocytopenia, leucopenia, haemoconcentration and shock). Larger population studies are needed to better define the critical clinical signs and to characterize the diverse spectrum of CHIK symptoms, in order to allow timely recognition and prompt therapeutic interventions aiming to reduce and control disease burden. Public health managers should remain cautious about the possible impact, both from a human and economic standpoint when facing a possible spread of the disease, since an increase in patient mortality remains a plausible scenario. Molecular epidemiology studies are pivotal in order to identify potential strain variability of the virus that may be linked to the development of severe and fatal forms of the disease.

Finally, we would like to acknowledge de la Hoz et al. [2] and Torres et al. [13] in Colombia and Venezuela respectively, for there timely publications on CHIK which represent the first reports in the Latin American medical literature about fatal cases of CHIK.

Table 1
Estimations of CFR (%) and mortality rates due to CHIKV based on officially reported deaths during 2014 and first 15 epidemiological weeks of 2015, Colombia.

Territory	Notified deaths	Ruled out deaths	Deaths under study	Confirmed deaths (2014–2015)	Cases (2014)	Cases (2015)[a]	Population (2015)	CFR (%)[b]	Mortality rate[c] (deaths/100,000pop)
Norte de Santander	13	0	3	10	24,694	5,641	1,355,723	0.033	0.738
Huila	3	0	0	3	2,131	23,806	1,154,804	0.012	0.260
Sucre	3	0	1	2	14,741	6,140	851,526	0.010	0.235
Cundinamarca	7	1	0	6	1,816	13,148	2,680,041	0.040	0.224
Tolima	6	0	4	2	1,772	29,868	1,408,274	0.006	0.142
Cartagena	1	0	0	1	12,279	341	1,001,680	0.008	0.100
Barranquilla	2	0	1	1	4,341	3,952	1,218,737	0.012	0.082
Bolívar	3	0	3	0	18,190	426	2,097,086	0.000	0.000
Cesar	1	0	1	0	797	2,635	1,028,880	0.000	0.000
Santander	3	0	3	0	403	3,478	2,061,095	0.000	0.000
Valle del Cauca	1	0	1	0	375	44,179	4,613,377	0.000	0.000
Total	43	1	17	25	81,539	133,614	19,471,223	0.012	0.128

CFR = case fatality rate.
[a] Until week 15.
[b] (Deaths 2014–2015/Cases 2014–2015) × 100.
[c] (Deaths 2014–2015/Population 2015) × 100,000pop.

http://dx.doi.org/10.1016/j.jcv.2015.07.001

Funding

None.

Competing interests

None of the authors report competing interests.

Ethical approval

Not required.

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15 June 2015

29 June 2015

1 July 2015