Short Communication

Chikungunya in kidney transplant recipients: A series of cases

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A B S T R A C T

Chikungunya (CHIK) is a mosquito-borne virus (CHIKV) infection that recently appeared in the Americas and thousands of confirmed cases have been reported in Brazil since the first autochthonous cases were reported in September 2014. We reported four cases of CHIK in kidney transplant recipients. The diagnosis was confirmed by positive CHIKV real-time polymerase chain reaction in two cases and positive CHIKV-IgM serology in two patients. The time between transplantation and CHIKV infection ranged from 2 to 11 years. All of them had arthralgia, and 3 of them had fever. Other symptoms were mild conjunctivitis, rash, and retro-orbital pain. Kidney function remained stable in all cases. In three patients prednisone doses were temporarily increased and the symptoms disappeared concurrently with the increase of the dose. As for the fourth patient, the prednisone dose remained unchanged and yet she improved. Other immunosuppressive drugs were not changed for the four cases. As far as we know, there are only two previously reported cases of CHIK among solid organ transplant recipients besides the four cases reported here. Despite the small number of cases, we can speculate that the use of immunosuppression might have played a role in the paucity of symptoms and the gradual complete recovery with no complication.

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Introduction

Chikungunya (CHIK) is a disease caused by an alphavirus (chikungunya virus – CHIKV) transmitted to humans primarily through the bites of the main vectors A. aegypti and A. albopictus (Staples et al., 2009; Caglioti et al., 2013). In 2013, the virus emerged in the Americas; since December 2013, over 1.7 million cases of CHIK were reported involving over 44 countries (Campion et al., 2015). In Brazil, the first cases of autochthonous CHIK were reported in September 2014, and since then, over a thousand confirmed cases have been reported, mainly in the northeastern region (Azevedo et al., 2015). Brazil now accounts for 94% of confirmed cases of CHIK disease in the Americas (Collucci, 2016).

CHIKV is a highly debilitating disease characterized by an abrupt onset of high fever, headache, diffuse rash, myalgia and prostration (Pialoux et al., 2007). The most impressive clinical symptom is the presence of a prominent polyarthralgia, (sometimes with severe arthritis) that can last for weeks, months or even years after the cessation of the acute phase of the disease bringing a serious motor disability and affecting the quality of life (Schilte et al., 2013; Javelle et al., 2015). The word “chikungunya” comes from Makonde, a language spoken in Tanzania, and means “that which bends up” in reference to the severe arthralgia and arthritis (Pialoux et al., 2007). Atypical manifestations include myocarditis, meningoencephalitis, respiratory, renal and hepatic failure (Economopoulos et al., 2009). There is no specific antiviral treatment and management is based on supportive care. Severe CHIK and death are uncommon and associated with old age, usually over 65, and underlying medical conditions, such as immunosuppression (Economopoulos et al., 2009). CHIKV infection, however, may also cause severe disease and death in young, previously healthy individuals.

Abbreviations: CHIK, Chikungunya; CHIKV, Chikungunya virus.
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individuals as well (Economopoulou et al., 2009; Lemant et al., 2008).

We describe here four cases of CHIK among kidney transplant recipients (KTR) during the Brazilian outbreak of the disease between 2014 and 2016.

Material and methods

KTR with clinical suspicion of CHIK attending in a single center (Hospital das Clínicas of University of São Paulo Medical School) located in São Paulo city, southeastern Brazil, were investigated to confirm the diagnosis. Suspicion of CHIK arose due to the presence of typical symptoms including arthralgia, which was not explained, by other conditions, as well as patients who have visited endemic areas up to two weeks before the onset of symptoms. Confirmatory laboratory diagnosis was made by detection of CHIKV RNA by real-time polymerase chain reaction (RT-PCR) in plasma samples targeting the structural region of the genome as previously described (Lanciotti et al., 2007) and/or detection of CHIKV-IgM and -IgG antibodies using monoclonal antibody-based capture enzyme-linked immunosorbent assay (using the Euroimmun kit, Lubeck, Germany). CHIKV RT-PCR was performed at the Molecular Biology Laboratory of the Central Laboratory Division at Hospital das Clínicas and CHIKV serology was performed at the Diagnósticos da América (DASA) Laboratory. Nucleic acids were extracted with the Virus DSP Kit in the automated platform QIASymphony.

Results

CHIKV infection was diagnosed in four patients from January to March 2016. The results are shown in the Table 1 and Figure 1. All patients had travelled to northeastern region of Brazil during the last two weeks before the onset of the symptoms. All patients reported arthralgia and presented full recovery after acute disease.

Discussion

There are only two cases of CHIK reported among organ transplant recipients. The first case was a 45-year-old Malaysian-Chinese man after a liver transplantation for hepatitis-B cirrhosis, on azathioprine and prednisolone, who developed CHIK seven years later, complicated by encephalitis, with complete recovery. He had no joint manifestation (Kee et al., 2010). The second case was a 48-year-old Dominican woman 6 years after a kidney transplant due to HIV-associated nephropathy, who developed high fever, diarrhea, and nausea for two days, and persistent headache, fatigue, myalgia, and bilateral symmetrical severe arthralgia after CHIKV infection. One month later she presented at the hospital afebrile but with persistent arthralgia and difficulty in walking. No severe manifestation occurred and she recovered well (Dalla Gasperini et al., 2015). In addition, there is only a brief citation of three KTR among 610 atypical case of CHIKV infection during the Réunion Island epidemics, but with no information about clinical manifestations nor outcome (Economopoulou et al., 2009).

We describe here four cases, which occurred among KTR. All patients acquired the disease while travelling to northeastern region of Brazil (Paraíba, Pernambuco and Alagoas states), where the epidemic started and where the incidence of CHIK was among the highest in the country at that time. The incidence of CHIK in the northeastern region increased from 11.4 cases/100,000 inhabitants in March 2015 to 56.0 in March 2016, contrasting with the incidence in the state of São Paulo: 0.1 to 3.5 cases/100,000 inhabitants in the same period (Brazil. Secretaria de Vigilância em Saúde, 2015, 2016).

The clinical picture was the typical one, except for one patient who had no fever, arthralgia was mild and transient and no one had arthritis or persistent pain. None of them developed any severe manifestations; all had full recovery with no complications.

Table 1

<table>
<thead>
<tr>
<th>Gender; age (years)</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male; 33</td>
<td>Female; 41</td>
<td>Female; 58</td>
<td>Female; 69</td>
<td>Male; 53</td>
</tr>
<tr>
<td>Living (related)</td>
<td>Deceased</td>
<td>11</td>
<td>Deceased</td>
<td>Living (unrelated)</td>
</tr>
<tr>
<td>Parába</td>
<td>Pernambuco</td>
<td>Parába</td>
<td>Alagoas</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Pred 5 mg + AZA, 100 mg + TAC 4 mg</td>
<td>Pred 5 mg + MPS 1080 mg + TAC 6 mg</td>
<td>Pred 5 mg + TAC 2 mg + EVL 3 mg</td>
<td>Pred 5 mg + MPS 720 mg + TAC 2 mg</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>Fever</td>
<td>Arthralgia</td>
<td>Arthritis</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Knees; migratory</td>
<td>Polyarthralgia mainly in arms</td>
<td>Polyarthralgia, knees and hands</td>
<td>Polyarthralgia</td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Polyarthralgia, knees and hands</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Management of prednisone</td>
<td>Pred 20 mg tapered to 5 mg in 3 mo</td>
<td>Pred 20 mg tapered to 5 mg in 1 mo</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Full recovery. Arthralgia ceased after pred higher dose. Diabetes developed.</td>
<td>Full recovery. Arthralgia ceased after pred higher dose.</td>
<td>Full recovery. Arthralgia ceased spontaneously after 1 mo</td>
</tr>
<tr>
<td></td>
<td>Pred 10 mg for 1 mo</td>
<td>Pred 10 mg tapered to 5 mg in 1 mo</td>
<td>Pred 10 mg tapered to 5 mg in 1 mo</td>
<td>Full recovery. Arthralgia ceased after pred higher dose.</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>RT-PCR</td>
<td>Positive</td>
<td>ND</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Time after onset of symptoms</td>
<td>8 days</td>
<td>–</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td>CHIKV-IgM/IgG antibodies</td>
<td>6.7/2.4</td>
<td>6.6/2.7</td>
<td>ND/ND</td>
</tr>
<tr>
<td></td>
<td>Time after onset of symptoms</td>
<td>22 days</td>
<td>64 days</td>
<td>5 months</td>
</tr>
</tbody>
</table>
Prednisone was increased at the attending doctor’s discretion in three cases; in one case (case #3) the patient did not look for medical attention during the disease and no change in the immunosuppression was made.

The laboratory diagnosis opportunity depends on the period of the infection. During the viremic period, usually up to one week from the onset of the symptoms, the diagnosis of the acute infection is based on direct methods, such as RT-PCR, with high specificity. CHIKV RT-PCR reacted specifically with CHIKV RNA and not with related or unrelated viruses (Lanciotti et al., 2007). Over one week of symptoms up to 3 to 6 months, the diagnosis is based on IgM detection and serologic cross-reactivity with related viruses, such as Mayaro fever and other alphaviruses, cannot be ruled out. Nevertheless, the reported sensitivity and specificity of the CHIKV IgM Eurommum assay accomplished are 98 and 97.5%, respectively (Johnson et al., 2016).

CHIK has been used in Brazil since September 2014 (Azevedo et al., 2015) and we were well aware of the existence of the disease. However, we have only identified patients with clinical suspicion of CHIK infection and confirmatory laboratory diagnosis in early 2016. No one was diagnosed until June 2017.

Despite there being only four cases, the absence of severe arthralgia is noteworthy; in some cohorts, about 80% of patients had persistent arthralgia at 4 months, and over 50% had arthralgia and clinically detectable joint swelling at 3 years after their acute infection (Schilte et al., 2013). It is also noteworthy that, although immunosuppression has been pointed out as a risk factor for complicated CHIKV infection, there are several clinical cohorts of CHIKV infection reported with only very few cases of solid organ transplant recipients included in these cohorts (Pialoux et al., 2007; Economopoulou et al., 2009; Lemant et al., 2008).

We can speculate that immunosuppression might have played a role in avoiding severe and persisting arthralgia. There is a possibility that, opposite of what was initially reported (Economopoulou et al., 2009; Kee et al., 2010), immunosuppression might be an influence of a more benign clinical course.

Patients under corticosteroids, such as KTR, might develop a less severe disease. There is some evidence of the benefit of a short period of corticosteroid use but their use in the relief of pain is still debated (Arroyo-Avila and Vilà, 2015). Indeed, there are very few guidelines for treating inflammatory and algic manifestations of CHIK (Simon et al., 2015). In those guidelines prevails the expert opinion over the scant evidence mostly based on the consolidated strategies frequently used to treat inflammatory articular diseases. Among these strategies, the corticosteroids play an important role on inflammatory articular control.

Indeed it is possible to say that the South American CHIKV strain behaves differently than the South Pacific or Caribbean outbreak strains. The genotype identified in Brazil is the East-Central-South-African (ECSA) (Costa-da-Silva et al., 2017) in contrast to the Asian genotype responsible for Caribbean cases. It seems that in the Pacific region a much more complex pattern is in place probably including the Asian, the ECSA and the Indian Ocean genotypes (Petersen and Powers, 2016). Despite that difference, there is no evidence that any of those genotypes could lead to milder case presentations with lesser symptoms. Moreover, reported cases have showed that in Brazil, CHIKV infection in the general population is highly symptomatic; these have eventually been complicated by neurological presentation and death (de Lima Martins and Bernardino, 2016).

Considering the current high number of CHIKV infections which have been reported in Brazil, we believe that CHIK may occur more frequently in organ transplant recipients than we can observe, causing a non-specific and unrecognized disease.

**Conflict of interest**

The authors have no conflicts of interest to declare.

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None.
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