Zika virus infection in a pediatric patient with acute gastrointestinal involvement

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Abstract

Zika virus (ZIKV) is a mosquito-borne flavivirus, which has been related to severe neurological complications in neonates. However, many clinical aspects of the infection remain unclear, especially in pediatric patients. In this case report we describe the uncommon presentation of ZIKV infection in a pediatric patient with acute gastrointestinal involvement hospitalized in a Brazilian Emergency Unit. Dengue hemorrhagic fever was initially suspected, however, the molecular result for Dengue was negative. Molecular testing for other arboviruses (ZIKV and Chikungunya), revealed positive for ZIKV RNA result in both blood and saliva. The ZIKV load in saliva (6.947 copies/mL) was higher than the vetected ZIKV RNA in plasma (1.945 copies/mL). Additionally, the performed abdominal ultrasound revealed mesenteric lymphadenitis without abdominal retention of fluids. The presentation of this case demonstrates that ZIKV can be involved in a broader range of clinical conditions than currently assumed, including pediatric emergencies, especially in regions with extensive ZIKV outbreaks.

Introduction

Zika virus (ZIKV) is a mosquito-borne flavivirus that has been causing a large outbreak in Brazil since 2014.[1] Although the impact of the infection on pediatric patients is critical due to the relationship between ZIKV and fetal neurological and ocular abnormalities,[2,3] the majority of the infected individuals demonstrate benign febrile condition accompanied by rash, myalgia, and/or conjunctivitis.[4] Still, many aspects of ZIKV infection remain unclear and it is possible that the virus may be involved in a broader clinical spectrum than currently assumed.

Case Report

A male pediatric patient at eight years of age was admitted on March, 29th, 2016 to the Emergency Unit of the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo, city of Ribeirão Preto, São Paulo State, Brazil, with six day history of repetitive high fever for ~four times a day (38.5-39°C), accompanied by frontal headache, retro-orbital pain, photo- and phonophobia.

The retrospective clinical history demonstrated that five days before the hospitalization, the patient presented severe myalgia of the whole body, especially in the legs and was treated with antipyretic drugs. At the time of hospitalization (day #1), diffuse abdominal pain without precise location and two vomiting episodes were registered. The patient denied rash or conjunctivitis. The physical examination demonstrated stable general condition, paleness, no jaundice, adequate hydration status, and eupnea. The skin was without active maculopapular lesions, the respiratory frequency was 28 ipm, heart frequency 110 bpm, blood pressure 109×74 mmHg, and 98% oxygen saturation by pulse oximetry in ambient air. Pulmonary and cardiac examinations showed no changes, except moderate to severe diffuse abdominal pain during palpation. Neurological examination was without meningeal signs, only a mild somnolence was observed. All laboratory parameters were within the normal range, excluding the C-reactive protein, which was highly elevated (11.2 mg/L, high >0.5 mg/L) (Table 1).

Because of ongoing dengue virus (DENV) outbreak by this time in our region, the abdominal pain and the rising hematocrit (33.7% at day #2 to 40.0% at day #4), the medical staff suspected DENV hemorrhagic fever (DHF). Therefore, intravenous hydration was started immediately following well-established DHF-prevention protocol with gradual improvement of the hematocrit. On day #2 of hospitalization (March, 30th), due to the persistent severe abdominal pain and vomiting, the patient was submitted to abdominal ultrasound which showed mesenteric adenitis without fluid leakage in the abdominal cavity (Figure 1). Chest X-ray showed no pulmonary abnormalities. The diagnosis of the mesenteric adenitis was based on the radiologic detection of three or more lymphonodes with at least 5 mm of short-axis diameter in the right lower quadrant, as described previously.[5,6]

At the same day (day #2), in order to diagnose DENV, whole blood was collected and viral RNA was extracted using QIAamp Viral RNA Mini Kit (QIAGEN, São Paulo, Brazil) following the manufacturer´s instructions. DENV TaqMan® real-time PCR was performed with primers and probe detecting all serotypes.[7] The PCR result for

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Contributions: SS conceptualized the study, analyzed the clinical and molecular data and approved the final version of the manuscript; AM, MC and AY revised the manuscript from clinical pediatrics point of view, gathered clinical and radiological data and approved the final version of the manuscript; KO performed molecular quantification of arboviruses, revised the manuscript and approved the final version of the manuscript; DC, and SK permitted the realization of this testing, reviewed and revised the manuscript and approved the final version of the manuscript.

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DENV was negative. Once in the region co-circulated also ZIKV and Chikungunya (CHIKV), the sample was simultaneously quantified for these arboviruses. The detection and quantification of both viruses was performed using primers and probes found in the literature.[8,9] CHIKV quantification demonstrated a negative result. However, ZIKV detection in blood generated a positive amplification with viral load of 1,945 copies/mL. In order to further confirm ZIKV infection, on day #3 of hospitalization a saliva swab was required for viral quantification. The saliva also demonstrated a positive result for ZIKV RNA with higher than plasma viral load (6,947 copies/mL). The patient samples were negative for Influenza, Adenovirus, Epstein-Barr and Cytomegalovirus.

The patient demonstrated favorable evolution, however, once the fever persisted for two more days, his discharge was delayed and hospitalization was continued for more 5 days. On day #8, the patient was discharged without fever and in good general health. Nevertheless, on day #14 he returned with fever and headache and was diagnosed with sinusitis based on a standard othorhinological examination. Treatment with amoxycilin 50 mg/kg/day improved the condition on day#17.

Discussion

In this case report, we demonstrate the detection of ZIKV RNA in blood and saliva of a pediatric patient with acute gastrointestinal involvement. This finding was registered during an extensive DENV/ZIKV outbreak in the region (Ribeirão Preto city is located in the Northeast part of the São Paulo State, Southeast Brazil, 21°10'40''S 47°48'36''E) and demonstrates the possibility of ZIKV to be involved in a wider range of clinical manifestations than already suggested,[2,4] including acute pediatric conditions. In this patient, ZIKV infection was related to gastrointestinal involvement accompanied by mesenteric adenitis (Figure 1) and localized myalgia without exanthema. ZIKV RNA was detected in both plasma and saliva. Salivary ZIKV excretion has been demonstrated by previous studies[10] and it seems a promising noninvasive ZIKV diagnostic tool in emergency room pediatric patients.

The presented case demonstrated atypical presentation of clinically overt ZIKV infection in the affected child with gastrointestinal involvement. Once the infection was associated with mesenteric adenitis, it seems that ZIKV should be contemplated in the differential diagnosis of acute abdominal pain observed frequently in pediatric emergencies. Although in rare cases DENV infection can also lead from moderate to severe abdominal pain, the pathogenesis of DENV abdominal involvement is unclear. One of the possible explanations includes plasma leakage with vascular damage.[11] In our case, we believe that the acute abdominal pain with probable ZIKV etiology was related to an inflammatory process as judged by the enlarged mesenteric lymphonodes without abdominal retention of fluids observed by abdominal ultrasound (Figure 1), and the elevated C-reactive protein.

Another important consideration related to the clinical evolution of this patient was the development of sinusitis, which was diagnosed 10 days after the molecular confirmation of ZIKV. Currently, it is unknown whether ZIKV infection may be associated with secondary bacterial infections. However, in adult patients with confirmed DENV fever, Trunfio *et al.* (2016), demonstrated between 0.18 and 7.0% prevalence of bacterial coinfections. The mechanism which leads to secondary bacterial invasion in DENV is unknown.[12] It can be hypothesized that multiple factors including: i) the neutropenia associated with DENV fever; ii) bacterial translocation due to increased intestinal vascular leakage; and/or iii) breakdown of the skin barrier caused by intense itching of the exanthema are involved. Our patient did not show any of the above mentioned signs and therefore, we suppose that the origin of the bacterial sinusitis in ZIKV may have different immunopathogenesis or might be an occasional finding without relationship to ZIKV infection. However, more studies are needed in order to investigate the immunomodulation during acute ZIKV infection in pediatric patients.

Conclusions

In this case report we describe ZIKV infection in a pediatric patient with abdominal mesenteric inflammation hospitalized in the emergency room. The clinical aspects of this case were compatible mainly with gastrointestinal involvement without exan-

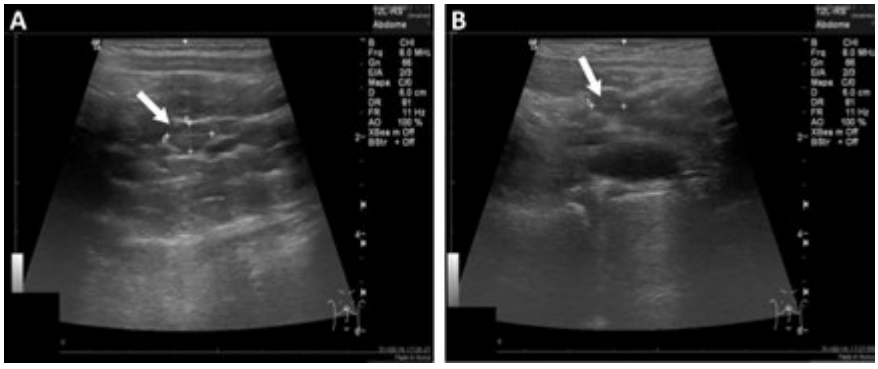

Figure 1. Radiological findings.

Table 1. Biochemical and hematologic parameters of the Zika virus infected pediatric patient during hospitalization.

Clinical parameters	Days during hospital hospitalization			
	Day #1	Day #2	Day #3	Day #4
Alanine Transaminase (IU/L)	33	16	N/A	N/A
Aspartase Transaminase	33	33	NA	N/A
Creatinine (mg/dL)	0.5	N/A	N/A	N/A
C-reactive protein (mg/dL)	N/A	N/A	11.2	8.34
Serum ionic calcium (mg/dL)	N/A	N/A	1.2	N/A
Serum potassium (mg/dL)	N/A	5	4.6	N/A
Serum sodium (mg/dL)	N/A	133	133	N/A
Platelets (×103, cells/mm^3)	216	195	185	249
White blood cells (×10^3, cells/mm^3)	8.12	8.74	9.20	7.30
Hematocrit (%)	33.7	30.6	40.0	34.0
Hemoglobin (g/dL)	11.8	10.8	13.1	11.0

N/A, not available.

thema. We therefore believe that ZIKV should be considered in the differential diagnosis of acute abdominal pain in pediatric patients, which is one of the most common complaints during acute pediatric emergencies.

References

1. Zanluca C, de Melo VCA, Mosimann ALP, et al. First report of autochthonous transmission of Zika virus in Brazil. Mem Inst Oswaldo Cruz 2015;110:569-72.
2. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects - reviewing the evidence for causality. N Engl J Med 2016;374:1981-7.
3. Ventura CV, Maia M, Dias N, et al. Zika: neurological and ocular findings in infant without microcephaly. Lancet 2016;387:2502.
4. Lazear HM, Diamond MS. Zika virus: new clinical syndromes and its emergence in the Western Hemisphere. J Virol 2016; 90:4864-75.
5. Macari M, Hines J, Balthazar E, Megibow A. Mesenteric adenitis: CT diagnosis of primary versus secondary causes, incidence, and clinical significance in pediatric and adult patients. AJR Am J Roentgenol 2002;178:853-8.
6. Patel NB, Wenzke DR. Evaluating the patient with right lower quadrant pain. Radiol Clin North Am 2015;53:1159-70.
7. Huhtamo E, Hasu E, Uzcátegui NY, et al. Early diagnosis of dengue in travelers: Comparison of a novel real-time RT-PCR, NS1 antigen detection and serology. J Clin Virol 2010;47:49-53.
8. Lanciotti RS, Kosoy OL, Laven JJ, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis 2008;14:1232-39.
9. Lanciotti RS, Kosoy OL, Laven JJ, et al. Chikungunya virus in US travelers returning from India, 2006. Emerg Infect Dis 2007;13:764-7.
10. Musso D, Roche C, Nhan TX, et al. Detection of Zika virus in saliva. J Clin Virol 2015;68:53-5.
11. Khor BS, Liu JW, Lee IK, Yang KD. Dengue hemorrhagic fever patients with acute abdomen: clinical experience of 14 cases. Am J Trop Med Hyg 2006;74:901-4.
12. Trunfio M, Savoldi A, Viganò O, Monforte A d'Arminio. Bacterial coinfections in dengue virus disease: what we know and what is still obscure about an emerging concern. Infection 2016;45:1-10.