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Case report

Three atypical lethal cases associated with acute Zika virus infection in Suriname

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ABSTRACT

Acute Zika virus infection usually presents with a self-limiting triad of fever, rash and arthritis. There is limited information on severe or lethal cases. We report three cases of lethal acute Zika infection, confirmed with polymerase chain reaction, in adult patients with some co-morbidities. The patients showed rapid clinical deterioration with hemorrhagic and septic shock, and exaggerated acute and innate inflammatory responses with pronounced coagulopathy, and died soon after admission to the hospital. It remains unclear whether the fatal outcomes were due to acute Zika virus infection alone or to the combination with exacerbated underlying prior disease or co-infection. Nonetheless, the severity of these cases implies that increased awareness for atypical presentations of Zika virus infection, and careful clinical assessment of patients with symptoms of Zika, is warranted during current and future outbreaks.

Introduction

Zika virus (ZIKV) is a vector-borne virus (family *Flaviviridae*, genus *Flavivirus*) transmitted by *Aedes* mosquitos [1]. In 2015 the virus rapidly caused an epidemic in many South and Central American and Caribbean countries [2]. Two geographically distinct lineages (i.e., the African and Asian lineage) of ZIKV exist [1]. The ZIKV strain in Suriname resembles the Asian lineage and the first clinical cases appeared around September 2015 [3].

ZIKV infection usually presents with a mild self-limiting triad of fever, maculopapular rash, and polyarthralgia, sometimes accompanied by bilateral conjunctivitis [1,2]. ZIKV infection has been associated with congenital brain malformations and microcephaly among newborns and neurological complications (e.g., Guillain-Barre syndrome) in adults .[4,5] The exact impact of these complications is now under further investigation, but may indicate increased virulent potential of ZIKV in the Americas. Lethal potential of acute ZIKV infection in adults has been described in a recent report from Colombia [6]. In these cases, underlying prior disease may have contributed to the lethal outcome and host-responses such as severe thrombocytopenia and septic shock were consistently observed. A confirmed severe non-lethal case from Suriname also presented with thrombocytopenia and subcutaneous bleeding [7]. Additionally, a case of lethal ZIKV infection in an adolescent girl with sickle cell anemia suggests an association of a fatal outcome with aberrant vascular responses leading to exacerbation of vaso-occlusive events [8].

Here, we provide a detailed clinical and diagnostic report of three adults presenting with septic shock and multi-organ failure in which ZIKV was the only identified pathogen. With our report we intend to emphasize the need for increased awareness of atypical and severe presentations of acute ZIKV infection during the current and future outbreaks.

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Methods

Real-time PCR

For all RT-PCR analyses, viral RNA was extracted manually from 150 μL of an EDTA-plasma specimen by using the E.Z.N.A. Viral RNA Kit (OMEGA Bio-Tek, Norcross, GA, USA), according to the manufacturer's instructions. CHIKV RT-PCR was performed according to Pastorino et al. with a CHIKV specific primer set targeting a region of the envelope-protein 1 gene of CHIKV (F-CHIK: 5′-AAGCTYCGC GTCCTTTACCAAAG-3′ and R-CHIK: 5′-CCAAATTGTCCYGGTCTTCCT-3′).[9] DENV PCR was performed according to Lanciotti et al. with a primer set specific for the DENV-envelope gene (DEN-F: 5′-TTAGAGG AGACCCCTCCC-3′ DEN-R: 5′-TCTCCTCTAACCTCTAGTCC-3′).[10] For ZIKV PCR, a ZIKV-positive control was obtained from the Arboviral Diseases Branch of the Center for Disease Control and Prevention (Fort Collins, Colorado, USA). RT-PCR for ZIKV was performed according to the protocol of Lanciotti et al., with the following modification: SYBR Green I Dye (Thermo Scientific) was used for detection [11]. For this method, high sensitivity was already shown in studies for detection of dengue and chikungunya viruses [12]. A set of ZIKV specific primers were used: ZIKV 835: 5′ TTGGTCATGATACTGCT-GATTGC-3′; ZIKV 911c 5′CCTTCCACAAAGTCCCTATTGC-3′; ZIKV 1086: 5′ CCGCTGCCCAAC ACAAG-3′; ZIKV 1162c: 5′ CCAC-TAACGTTCTTTTGCAGACAT-3′. Amplification of viral RNA was performed with a LightCycler 480 (LC480) Real-Time PCR system (Roche) and viral load (Fig. 1B) was determined with LC480 software. Nucleotide sequence of the ZIKV envelope was obtained and a phylogenetic tree was constructed with CLC Main Workbench 6 Software by neighbor joining of ZIKV envelope gene sequences of earlier Surinam cases to trace the origin of the ZIKV isolate of our first case (Fig. 1C, branch 21068, 2015, Suriname) [3].

For Case 2 a 22 multiplex PCR (Pathofinder BV, Maastricht, The Netherlands) for viral and bacterial pathogens was performed on an oro-pharyngeal swab kept in universal transport medium (Copan diagnostics, Italy).

Serologic testing

Serology for chikungunya was performed with an Anti-CHIKV IgM and IgG ELISA (EuroImmun, Lubeck, Germany) and for dengue with the RapidSignal IgG/IgM quicktest (Orgenics, Yavne, Israel), both according to the manufacturers' instructions. Presence of acute or prior HIV infection was performed with the Architect HIV antigen/antibody assay (Abbott). Leptospirosis IgM detection was performed with and Leptocheck (Zephyr Biomedicals, Verna, India).

Ethics statement

We received approval from our institutional ethics committee and obtained informed consent from the patients' family members.

Case reports

Case 1

A 61-year-old Surinamese male with known history of hypertension, treated with atenolol, presented at the emergency room (ER) with a 2-day history of vomiting, watery diarrhea, and arthritis (Fig. 1A). Physical examination revealed tachypnea with hypoxia, tachycardia with hypotension and acrocyanosis of the left upper extremity. During examination the patient appeared unresponsive. Bedside glucose level was low and rapidly corrected

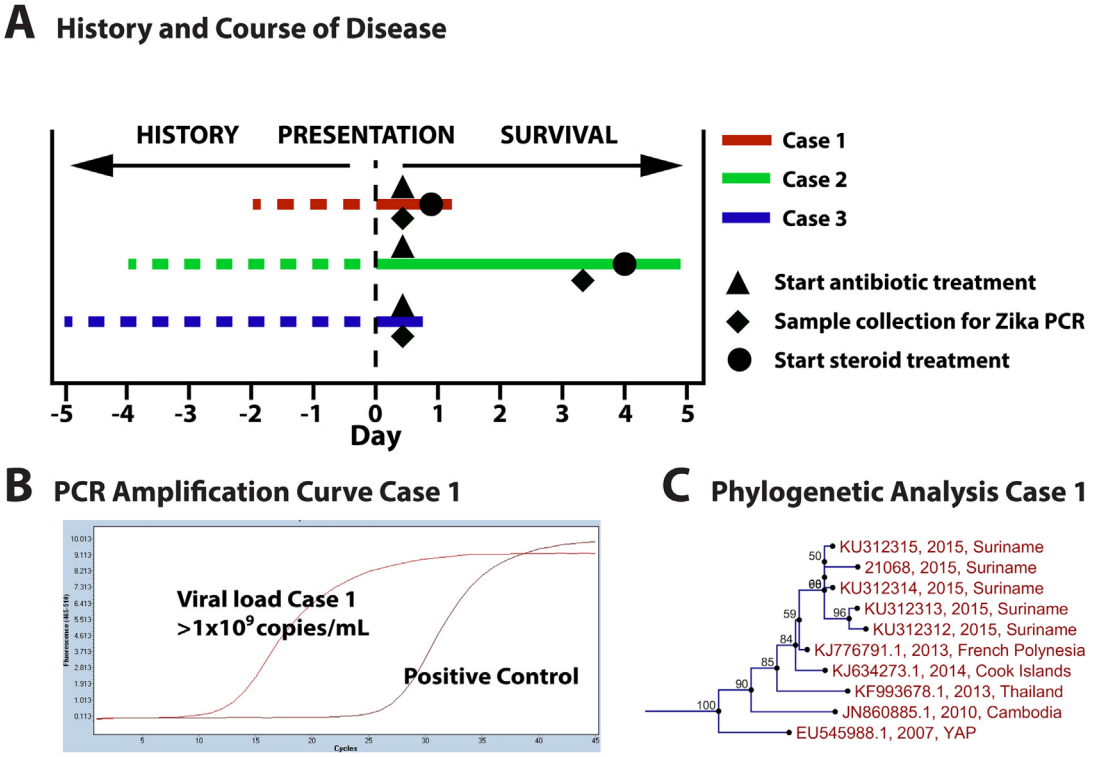

Fig. 1. A. Schematic representation of history and course of disease for all described cases. B. RT-PCR amplification result for ZIKV performed in patient serum of Case 1. C. Phylogenetic analysis of Case 1 constructed from nucleic-acid sequence data from former Surinamese cases by neighbor-joining algorithm.