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Editorial

Fatal Zika virus disease in adults: A critical reappraisal of an under-recognized clinical entity☆

Zika virus (ZIKV) is a flavivirus that was most likely introduced into Latin America back in 2013 (Rodriguez-Morales, 2015), but did not cause identifiable outbreaks until its massive emergence in Brazil in 2015, when it rapidly spread across the Americas and the Caribbean (Weaver et al., 2016). The World Health Organization (WHO) declared the ZIKV epidemic a public health emergency of international concern (PHEC) at the height of the pandemic in 2016 (Rodriguez-Morales, 2015; Rodriguez-Morales, 2018), after identifying clusters of ZIKV-associated Guillain–Barré syndrome (GBS) (do Rosario et al., 2016), and more significantly due to its association with outbreaks of microcephaly among newborn infants in which a causal link between ZIKV infection and birth defects was reliably demonstrated (Rasmussen et al., 2016). The clinical manifestations of congenital ZIKV infection extend beyond microcephaly and comprise a distinct constellation of birth defects and manifestations known as the congenital Zika syndrome (CZS) (Nogueira et al., 2018; Moore et al., 2017).

The ZIKV pandemic in the Americas and Caribbean was known to cause over one million cases and there were reports in which the virus was found to cause severe, life-threatening complications in addition to GBS and CZS, especially among patients with associated comorbidities (Rodriguez-Morales, 2018). From a clinical standpoint, until 2013, ZIKV was generally considered to cause a mild, self-limiting illness, which did not pose a serious public health threat (Rodriguez-Morales, 2015; Rodriguez-Morales, 2018; Martinez-Pulgarin et al., 2016). However, it was not until the first non-perinatal death was identified in a 15-year-old girl from northern Colombia in October 2015, (Arzuza-Ortega et al., 2016) that an increasing number of ZIKV-associated fatalities were reported in the literature.

The case from Malaysia reported by Rajahram et al. (2019) in the current issue of the *International Journal of Infectious Diseases*, confirms that ZIKV infection can result in atypical disease and lead to severe and even fatal outcomes (Rodriguez-Morales, 2018). It also demonstrates, as seen in other studies (Sarmiento-Ospina et al., 2016; Soares et al., 2016; Zonneveld et al., 2016; Azevedo et al., 2016), that this neurotropic virus can disseminate to multiple organs and tissues, in addition to the central nervous system, while inflicting pathological effects. Previous to this report, the majority of fatalities associated with ZIKV infection were almost invariably linked to acute neurological complications (Sarmiento-Ospina et al., 2016; Soares et al., 2016; Azevedo et al., 2016). However, amongst those exceptional fatalities without neurological involvement, the question was raised as to whether ZIKV could cause renal and cardiac involvement, as was observed on autopsy examinations of the case described in this issue. Renal and cardiac complications have been reported in atypical, severe (Villamil-Gomez et al., 2016a; Alvarez et al., 2017), and fatal cases (Hoz et al., 2015; Mercado et al., 2018) of chikungunya virus (CHIKV) infection. Conversely, cases of ZIKV infection with documented renal or cardiac complications have been reported on rarely and have usually lacked detailed histopathological evaluation as well as molecular confirmation of the presence of viral RNA within the renal or cardiac tissues during routine autopsy of fatal cases (Mercado-Reyes et al., 2019).

ZIKV infection has previously been reported to cause cardiovascular compromise as a consequence of systemic infection, as revealed by electrocardiographic and echocardiographic alterations (Villamil-Gomez et al., 2018; Schwartzmann et al., 2017), even including venous thromboembolism (in ZIKV and CHIKV infections) (Ramacciotti et al., 2019), as well as demonstrating myocardial inflammation secondary to viral infection (Villamil-Gomez et al., 2018). Autopsy examinations of a heart transplant recipient who developed ZIKV infection revealed plasma cell infiltrates in the myocardial tissue, along with perivascular and endovascular damage (Schwartzmann et al., 2017).

Nevertheless, publications in the literature on cardiovascular manifestations in adult patients with ZIKV infection are scarce, and the case report by Rajahram et al. (2019) is timely in underscoring how this arboviral infection can produce unexpected clinical complications with renal and cardiovascular involvement. Previous reports have suggested an association between cardiovascular complications and ZIKV during the acute phase of the infection (Villamil-Gomez et al., 2018; Li et al., 2016; Minhas et al., 2017). However, only a limited number of studies have addressed this potential association (Martinez-Pulgarin et al., 2016; Minhas et al., 2017). Findings in patients (Abdalla et al., 2018) and non-human

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primates (Li et al., 2016) have provided evidence that ZIKV has a broad tissue tropism, which includes renal and heart tissues (Rajahram et al., 2019; Li et al., 2016). Nevertheless, further investigations are needed in order to delineate the underlying pathogenic processes in which ZIKV affects myocardial tissue and to characterize the spectrum of cardiovascular manifestations caused by this emerging arboviral infection (Musso et al., 2018).

A review of the literature identified a total of 84 fatal cases of ZIKV infection during the recent pandemic in the Americas (Rodriguez-Morales et al., 2018). However, few of these reported cases underwent an in-depth tissue assessment and molecular characterization during autopsy, as was performed in the case report by Rajahram et al. (2019).

It should be emphasized that the pathogenesis of severe ZIKV infection remains poorly understood. *In vitro* and experimental animal models have provided evidence that antibody-dependent enhancement (ADE) may play a role, but clinical correlates for this phenomenon still need to be confirmed in human ZIKV infection (Ngono and Shresta, 2018; Andrade et al., 2019). Recent studies suggested that preexisting high antibody titers to dengue virus were associated with a reduced risk of acquiring ZIKV infection and disease. In this sense, the landscape of ZIKV immunity that now exists may affect the risks of future transmission (Rodriguez-Barraquer et al., 2019). Additionally, cases with arboviral co-infections/co-detection (dengue and chikungunya) have been reported in Colombia and Brazil (Villamil-Gomez et al., 2016b; Sardi et al., 2016), as well as concurrent infections with other microorganisms such as *Leptospira* (Neaterour et al., 2017) and co-infections with other arboviruses (Mercado-Reyes et al., 2019). Co-circulation with other arboviruses and ADE pose a challenge for physicians and public health authorities, given the potential to confound and delay diagnosis and possibly influence poorer outcomes in patients with previous exposure to other flaviviruses (Ngono and Shresta, 2018). As a result, multiple research networks on ZIKV and arboviruses in general have been established, which can leverage protocols, methodologies, and multidisciplinary approaches to inform treatment, prevention, and control strategies. Although recent advances have greatly contributed to our understanding of ZIKV pathogenesis, systemic involvement and the expanding tissue tropism of this virus and its potential relationship to different lineages highlight important aspects for future investigation. Finally, it is worth considering the setting for vaccine development and preparedness for other emerging arboviruses in Latin America and the Asia-Pacific region, such as Ross River, Mayaro, Oropouche, Madariaga, West Nile, and the Venezuelan equine encephalitis and Eastern equine encephalitis viruses.

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Conflict of interest

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Author contributions

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