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Case Report

Urinary bladder agenesis and renal hypoplasia potentially related to *in utero* Zika virus infection☆

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ABSTRACT

This case report describes the clinical findings of a 22-year-old pregnant woman with confirmed Zika virus infection, at 16 weeks of gestation, in Sucre, Colombia. Her ultrasound revealed severe oligohydramnios, intrauterine growth restriction, and a complete absence of the urinary bladder of the fetus. The poor prognosis led to the decision to terminate the pregnancy. Autopsy of the fetus revealed severe bilateral renal hypoplasia.

Introduction

During recent years, multiple studies have demonstrated associations between in utero Zika virus (ZIKV) infection and multiple birth defects, particularly microcephaly and others related to the central nervous system (CNS) and the associated congenital Zika syndrome (CZS) (Torres et al., 2016). However, to date, there appear to have been no reports regarding the consequences of ZIKV infection on the development of the lower urinary tract (Rodriguez-Morales et al., 2018).

This case report describes the clinical findings of a 22-year-old pregnant woman with confirmed ZIKV infection, at 16 weeks of gestation, in Sucre, Colombia. Her ultrasound revealed severe oligohydramnios, intrauterine growth restriction (IUGR), and a complete absence of the urinary bladder of the fetus. The poor prognosis led to the decision to terminate the pregnancy. Autopsy of the fetus revealed severe bilateral renal hypoplasia.

Case report

In February 2017, a 22-year-old, internally displaced pregnant Hispanic woman, in the 16th week of pregnancy, presented for her first antenatal care visit at a primary health care center in a small town of the north Caribbean region of Colombia (Majagual, Sucre). She was referred to the Hospital Universitario de Sincelejo (in Sincelejo, Sucre) due to severe oligohydramnios. Her pulse rate was 80 beats/min, blood pressure was 100/70 mmHg, respiratory rate 15 breaths/min, and her temperature was 36.3 °C. A neurological examination was normal. Her abdomen was enlarged, compatible

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with pregnancy. The symphysis–fundal height was 16 cm. Obstetric ultrasound revealed a fetal heart rate of 157 beats/min, and all four cardiac chambers were noted. Ultrasound fetal biometry also revealed decreased fetal movements, decreased amniotic fluid (index <3; severe oligohydramnios), and an anterior placenta (I/III). The estimated fetal weight was 168 g, and anhydramnios and IUGR were detected 4 days later. At this point, a complete absence of the urinary bladder was evidenced. Due to the poor prognosis, the pregnancy was terminated in March 2017, at week 17 of gestation. After obtaining written informed consent from the family, an autopsy was performed on the fetus (Figure 1). Maternal serum specimens were also collected. The patient gave informed consent for research and eventual scientific publication.

This young woman was in her third pregnancy. She had no history of previous miscarriage or abortion and had not had any prenatal consultations. She had experienced no previous related symptoms suggestive of an arboviral infection (she denied fever or rash), was not taking any current medication and had not taken any during the pregnancy, did not report smoking or alcohol consumption, had no other risk factors for fetal death (such as maternal age; she was young), was not of black race, was not overweight pre-gestation, had no preeclampsia, diabetes, or thyroid disease, had not been addicted to any drug during her entire life, had not had any other congenital infections, and had no history of consanguinity or familial genetic abnormalities. Her blood type was A positive. She was not anemic (hemoglobin 13.3 g/dl), had normal glycemia (70 mg/dl), and a normal white blood cell count (8.4×10^9/l).

Tests of the maternal serum were negative for STORCH agents: herpes simplex I and II, *Toxoplasma gondii*, HIV (ELISA), *Treponema pallidum* (VDRL), rubella virus, and human cytomegalovirus. Dengue virus (DENV) IgM and IgG ELISA and chikungunya virus (CHIKV) IgM and IgG ELISA were negative. Reverse transcription (RT)-PCR analysis of the blood sample was negative for DENV and CHIKV, but positive for ZIKV. The neonatal karyotype was normal. The woman lived in an endemic area, but had no presenting arboviral disease symptoms. There were no individuals with signs or symptoms of arboviral diseases living in her house. ZIKV serology was not conducted.

An autopsy of the male fetus was performed, with extensive sampling of the lung, heart, liver, kidney, brain, and placental tissues (Figure 1). There were signs of moderate to advanced stage of maceration. The lung structures were compatible with the presumed gestational age. There was a complete absence of the urinary bladder in the fetus. Also, marked hypoplasia was observed in the kidneys (Figure 1). Histopathological findings showed a marked decrease in the thickness of the nephroblast layer, with an arrest in the glomerular migration towards the deepest zones of the cortex (Figure 1). The renal papilla showed a noticeable paucity in the migration and maturation of the collecting tubular system, with severe expansion of the interstitial matrix at the expense of immature mesenchymal tissue (Figure 1). In the brain, viral antigens were localized to glial cells and neurons. Antigens were also seen in the chorionic villi of the obtained placenta. The tissues were positive for ZIKV RNA by RT-PCR.

ZIKV, CHIKV, and DENV real-time quantitative RT-PCR tests were performed. DENV and CHIKV were not detected in any sample, but ZIKV was detected in the placenta and the brain.

Discussion

The ZIKV epidemic in Colombia started in August 2015 and reached its peak in February 2016. After July 2016, the disease was considered to be in the post-epidemic phase. Between 2015 and 2016, more than 100 000 cases were reported in the country (Rodriguez-Morales et al., 2018), with an additional 1901 cases in 2017, the year in which the current case patient was diagnosed.

Given that the full teratogenic potential of ZIKV was not originally known (Torres et al., 2016; Rodriguez-Morales et al., 2018; Valdespino-Vazquez et al., 2019), the severe damage to the lower and upper urinary tract in the case presented here is likely related to this flavivirus infection, although this needs further studies for confirmation. Besides, complete agenesis of the urinary bladder is an extremely rare anomaly, with only a few live cases reported so far (Nazer et al., 2018).

A critical step in understanding the impact and mechanisms of ZIKV infection on human tissue development and the link between ZIKV and birth defects is to identify the cell types that are particularly vulnerable to viral infection in the developing tissues after ZIKV breaches the placental barrier, including those related to the upper and lower urinary tract. In particular, the potential tropism outside the CNS is not correctly understood yet. Studies have reported arthrogryposis, IUGR, uveitis, and retinal degeneration associated with gestational ZIKV infection, and also bilateral renal ectasia (Torres et al., 2016; Rodriguez-Morales et al., 2018; Valdespino-Vazquez et al., 2019). However, there appear to have

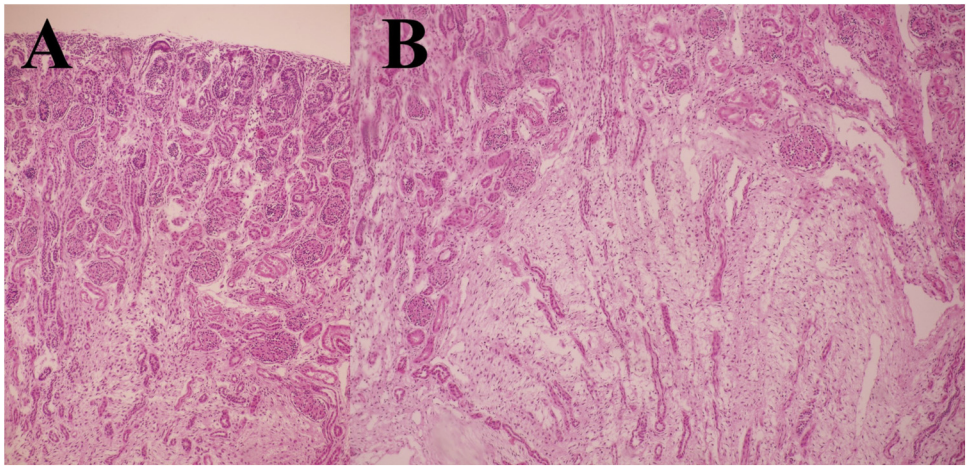

Figure 1. Histopathological findings for the kidneys. (A) Renal cortex showing a marked decrease in the thickness of the nephroblast layer, with an arrest in the glomerular migration towards the deepest zones of the cortex (hematoxylin and eosin stain, 20×). (B) Renal papilla with a noticeable paucity in the migration and maturation of the tubular collecting system, with a severe expansion of the interstitial matrix at the expense of immature mesenchymal tissue (hematoxylin and eosin stain, 10×).

been no reports yet of renal and urinary bladder agenesis related to ZIKV. No reports of previous cases of renal hypoplasia potentially associated to ZIKV are available in the literature.

As found in the case presented here, other studies have reported IUGR and low birth weight in CZS cases (Rodriguez-Morales et al., 2018). Furthermore, a study has reported neurogenic urinary bladder findings in patients with CZS, with most presenting high-risk urodynamic patterns that would lead to renal damage if left untreated (Costa Monteiro et al., 2018). ZIKV RNA has been detected in the kidneys and has been associated with abnormal renal function (Rodriguez-Morales et al., 2018; Valdespino-Vazquez et al., 2019). The presence of viral-like particles in the renal tissues and the isolation of infectious ZIKV from the renal tissues demonstrate that the kidneys are an active site of ZIKV replication in the fetus; this was probably related to the impairment in the development of the kidney of the fetus, leading to renal hypoplasia. Moreover, the renal tubular epithelium appears to be at risk of ZIKV infection (Valdespino-Vazquez et al., 2019). ZIKV replication in the kidneys might explain the continuous viral shedding observed in the urine of some CZS patients (Valdespino-Vazquez et al., 2019).

Urinary bladder agenesis is one of the rarest urinary tract anomalies, with a reported incidence of 1 in 600 000 patients and only 64 cases reported worldwide (Nazer et al., 2018). This defect is usually associated with other severe malformations that are incompatible with life. It has been linked with urogenital sinus injury at weeks 5–7 of embryogenesis (Nazer et al., 2018), which, in the case presented here, would have been caused by the ZIKV infection during the first weeks of pregnancy, as multiple other infectious and non-infectious teratogenic factors were ruled out.

ZIKV epidemics have reminded us of the vulnerability of human beings to emerging infectious diseases, as experienced previously with many other agents. Moreover, ZIKV has also changed the way researchers and physicians deal with flavivirus infections. This advance is due mainly to the severe impact of ZIKV infection during pregnancy and the resulting CZS and other birth defects, which may potentially include urinary tract abnormalities, as seen in the case presented here. As of June 1, 2019, 245 new ZIKV cases had been reported in Colombia.

Even after 4 years of epidemics in the Americas, there remains a knowledge gap about ZIKV infection and its effect on cellular tissues and organs. It should also be highlighted that this is just one case report that suggests a possible association between congenital ZIKV infection and urinary tract abnormalities.

Finally, as was proposed in 2016 by Torres et al. (2016), the cellular tropism of ZIKV and the nature of the cellular receptors that mediate its entry into different tissues, as well as the mechanisms of ZIKV infection and the signaling pathways and antiviral immune response of the host elicited by this virus (Torres et al., 2016), are aspects that still require further study and understanding.

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Ethical issues

Written informed consent was obtained from the patient.

Conflict of interest

All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Author contributions

WVG and AJRM conceived the report, collected data, and analyzed and interpreted clinical data. WVG, DPR, AM, AA, and OBG attended to the patient. HP and MCU performed a systematic review. EAPS performed histopathological studies. AJRM developed the first draft. All authors approved the subsequent draft versions. All authors approved the final submitted version.

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