



Early Fetal death by Dengue: Anatomopathologic and Immunohistochemical Description

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Introduction

Several arboviruses are known to cause miscarriages, foetal death, and premature labor, as well as teratogenic alterations in both humans and animals^[1]. The occurrence of Dengue during pregnancy is accounted for in literature as early as 1948^[2,3]. In Brazil, DENV infection has been considered a public health issue for the last 30 years^[4,5]. Rio de Janeiro state has been through periodic epidemics since then and is considered an endemic region for this infection. In the last 5 years, 19 articles regarding human vertical transmission have been published, among which 8 articles confirmed vertical transmission. However, anatomopathological descriptions have not been found in foetal death.

Case report

Pregnant woman, 32 years old, Niteroi city resident, Rio de Janeiro state, searched medical assistance at the local public hospital on May 31, 2010 due to vaginal bleeding that eventually progressed to miscarriage. Her clinical condition was compatible with dengue fever, with hemorrhagic manifestations, no signs of capillary extravasations, laboratory confirmation through ELISA-IgM. Foetus at 12 weeks of gestation according to last menstrual period. The material was forwarded to anatomopathological and immunohistochemical analysis.

Placental weight and disk measurements and some of the characteristics of the fetal membranes, including color and transparency, were evaluated. The distribution and size of the chorionic vessels were evaluated in the fetus. The color and appearance of the placental lobes and tissue sections were examined. The color and thickness of the funicular vessels and Wharton's jelly were evaluated in the umbilical cord and the abnormalities recorded. After examination, the placental tissues were excised, and seven sections were obtained: from the umbilical cord, two cross-sections at opposite ends and a longitudinal section in the median region; from the membrane, a cross-section of the membrane roll; and from the placental disk, a sample

of the cord insertion site and a sample from the middle and outer disks as well as of any other sites considered relevant. All the tissues sections were stained with hematoxylin-eosin (HE).

The fetal membranes, umbilical cord, chorionic plate, villi, intervillous space, and decidua basal is were examined under a light microscope.

Immunohistochemistry was conducted with the murine IgG2A monoclonal anti-DENV complex (MAB8705; clone D3-2H2-9-21; Millipore, Billerica, Massachusetts) diluted 1:300 in phosphate-buffered saline and incubated overnight.

Paraffinized liver tissue from a patient who died from DENV was used as the positive control for the immunohistochemical analysis. For the negative immunohistochemical control, 2 different procedures were incorporated:^[1] paraffinized liver tissue from the patient who had died of dengue, suppressing the monoclonal antibody, the primary antibody of the incubation step, using only the diluent solution (bovine serum albumin) and^[2] paraffin-embedded placental tissue of patients without infectious disease on which the full technique was performed (without the deletion of the MAB).

Microscopic examination of the placenta revealed multifocal intervillitis and positive immunostaining on trophoblast and decidua. Microscopic study showed no evidence of inflammatory response at the level of several foetal organs

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(Figure1), corroborating with foetal age.

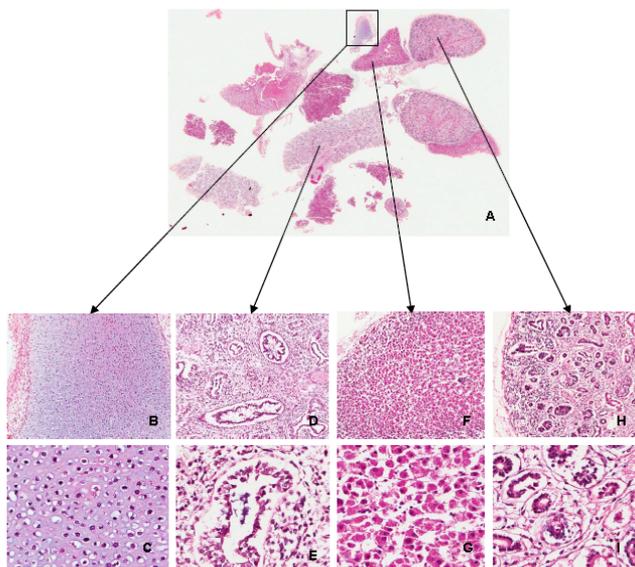


Figure 1: Microscopy - Fetus with gestational age of 12 weeks
Fetus with gestational age of 12 weeks; abortion occurred during the period of maternal viremia. A. Microscopy - Cartilage, lung, adrenal and kidney, Hxe 0.5 x; B. Cartilaginous tissue Hxe 10x; C. Cartilaginous tissue Hxe 40x; D. Pulmonary tissue Hxe 10x; E. Pulmonary tissue Hxe 40x; F. Adrenal tissue Hxe 10x; G. Adrenal tissue Hxe 40x; H. Renal tissue Hxe 10x; I. Renal tissue Hxe 40x.

The immunohistochemical study of the foetus revealed immunostaining on the pulmonary covering epithelium, renal tubular covering epithelium and ependymal epithelium (Figure 2).

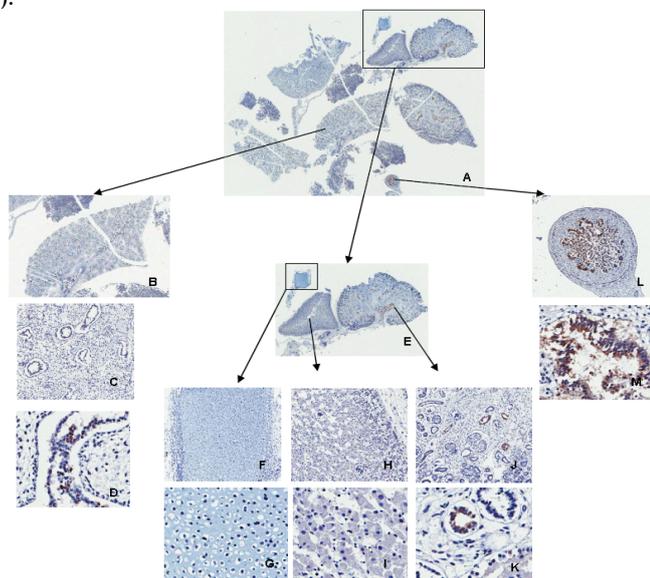


Figure 2: Immunohistochemistry - Fetus with gestational age of 12 weeks

Fetus with gestational age of 12 weeks abortion occurred in the period of maternal viremia. Positive immunostaining confirming vertical transmission. A. Immunohistochemistry (IHC) 0.5 X; B. Pulmonary tissue: positive immunostaining on coating epithelium 1.0 x; C. Pulmonary tissue: positive immunostaining on coating epithelium 10x; D. Pulmonary tissue: positive immunostaining on coating epithelium 40 x; E. Cartilaginous, renal and supra renal tissue (IHC) 1.0 x; F. Cartilaginous tissue: absence of immunostaining 10x; G. Cartilaginous tissue: absence of immunostaining 40x; H. Suprarenal tissue absence of im-

munostaining 10 x; I. Adrenal tissue absence of immunostaining 40x; J. Renal tissue: positive immunostaining in tubular lining epithelium 10x; K. Renal tissue: positive immunostaining in tubular lining epithelium 40x; L. Nervous tissue: positive immunostaining in ependymal epithelium 5.0x; M. Positive immunostaining in ependymal epithelium 40x.

Discussion

In countries that suffer from endemic infections by DENV, the greatest challenge is the differential diagnosis with gestational diseases such as HELLP Syndrome in pregnant women and neonatal sepsis[6].

In previous years two cohort studies and one systematic review with meta-analysis showed evidence for association between DENV infection and low birth weight, and prematurity[3,7,8]. It is believed that during DENV infection both viremia and hemodynamic alterations might be responsible for the damages caused to the foetus, including concepts loss.

In this report the microscopic study of the placenta evidences important inflammatory response at the placenta (multifocal intervillitis) and presence of viral material on trophoblast and decidua. No evidence of inflammatory response was seen amongst several foetal organs, in accordance with the literature, considering that the fetal immunological system at this gestational age does not respond to most varying forms of aggression[9,10]. However, the immunohistochemical study of the bronchial, bronchiolar and alveolar covering epithelium, renal tubules covering epithelium and ependymal epithelium showed positive immunostaining, proving the presence of viral material in the fetus.

Conclusion

Even though we have several literature reports of perinatal transmission of DENV we still need more studies that can associate DENV infection with conceptus loss, especially in countries with endemic DENV infection and of pregnant women that travel to these countries.

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