

## CASE REPORT

### Congenital cytomegalic inclusion disease with disseminated Herpes simplex infection

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#### Abstract

We report a case of congenital cytomegalovirus and Herpes simplex virus infection suspected via ultrasound indicated by the presence of fetal cerebral abnormalities. The pregnancy was electively terminated at 31 weeks of gestation. The postmortem examination of the foetus showed brain with lissencephaly. The histopathological examination revealed numerous enlarged cells containing cytomegalic inclusions and multinucleated giant cells in multiple fetal organs and placenta. Documented evidence of histopathological detection of cytomegalovirus inclusions in multiple organs are very sparse in literature. This case highlights the causal relationship of viral infections in early pregnancy and abnormalities of the central nervous system.

**Keywords:** Cytomegalovirus, Herpes simplex virus, foetus, congenital, lissencephaly

#### INTRODUCTION

Cytomegalovirus (CMV) and Herpes simplex virus (HSV) are wide spread pathogens and the most common cause of intrauterine infections that may lead to foetal malformations. Foetal infections may occur both during the primary infection and during the reinfection or reactivation of the virus, which may even be asymptomatic with the mother.<sup>1,2</sup>

In primary infection of the mother, transplacental spread of CMV to the foetus occurs in 30-50% of cases. In contrast, during the reactivation, the transmission rate is significantly lower and amounts to 0.2-1%.<sup>3</sup> Infection of a foetus with CMV may have various outcomes, from intrauterine death and death in neonatal period, to clinically asymptomatic infections. It is still not clear why the virus replicates in certain foetal tissues and causes damage, while in others, it does not cause damage.<sup>4,5</sup> Foetal damages are more serious if the infection occurs during early gestational period than in the later stage of

pregnancy. There is a proof for direct connection between the gestational age of the foetus at the time of infection and the degree of brain tissue damage, where the infection in the first trimester of pregnancy may lead to significant developmental anomalies of the central nervous system and lissencephaly.<sup>6</sup> Intrauterine HSV infection of the foetus occurs in about 5% of cases, unlike the peripartal and postpartal infections that are more common.<sup>2,3</sup> Intrauterine HSV infection of the fetus most often occurs in first 20 weeks of pregnancy and may result in abortion, preterm birth and the occurrence of various congenital malformations.<sup>7,8</sup>

#### CASE REPORT

During pregnancy, by ultrasound imaging, a 28-year-old secundigravida was diagnosed with central nervous system malformations of the foetus (ventriculomegaly and lissencephaly). In the 31<sup>st</sup> gestational week, the ethics committee allowed the termination of pregnancy. Before

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the feticide, blood tests were performed for virus antibodies and the results showed increased levels of IgG and negative IgM antibodies against CMV and HSV type 1. Antenatal, she was febrile in the 12<sup>th</sup> gestational week.

The foetus and placenta were examined. The foetus was a 37 cm long female and weighed 1220 grams, which corresponded with the gestational age. No external malformations or skin lesions were noted. All internal organs had unremarkable macroscopic characteristics except for the brain, which had almost completely undeveloped, flattened convolutions with smooth surface. The cross-sections of the brain showed widened brain ventricles on both hemispheres. In the occipital and parietal part of the brain there was a bigger area of encephalomalacia of softer and friable consistence, yellow-greenish in colour. This tissue was partially present in the lumen of right lateral ventricle. The described area histologically corresponded to structureless necrotic brain tissue surrounded by area with hyperaemia and the presence of a modest inflammatory infiltrate. In the remaining and preserved brain tissue there were

focally distributed individual, enlarged cells with intranuclear, basophilic and eosinophilic inclusions. Calcifications were multi-focally distributed in the brain tissue. Multinuclear giant cells were noticed in endothelial blood vessels cells.

All other internal organs were in their normal anatomic positions and appeared grossly unremarkable. Cytomegalic inclusions were noticed during the histologic examination of lung, liver and kidney tissue specimens. In kidneys, the cytomegalic inclusions were numerous, dominantly grouped in tubule epithelial cells and the epithelium of the parietal layer of glomerular (Bowman's) capsule (Figs. 1A and 1B). Around the described cells, modest mononuclear inflammatory infiltrate was present. The lung showed foetal atelectasis and passive hyperaemia. Enlarged cells, which correspond to the pneumocytes, with intranuclear inclusions were mostly present freely in alveolar spaces, and were rarely in contact with alveoli (Fig. 2A). In the liver, the virus inclusions were present in both hepatocytes and epithelial cells of the bile ducts (Figs. 1C and 1D). Multinucleated giant

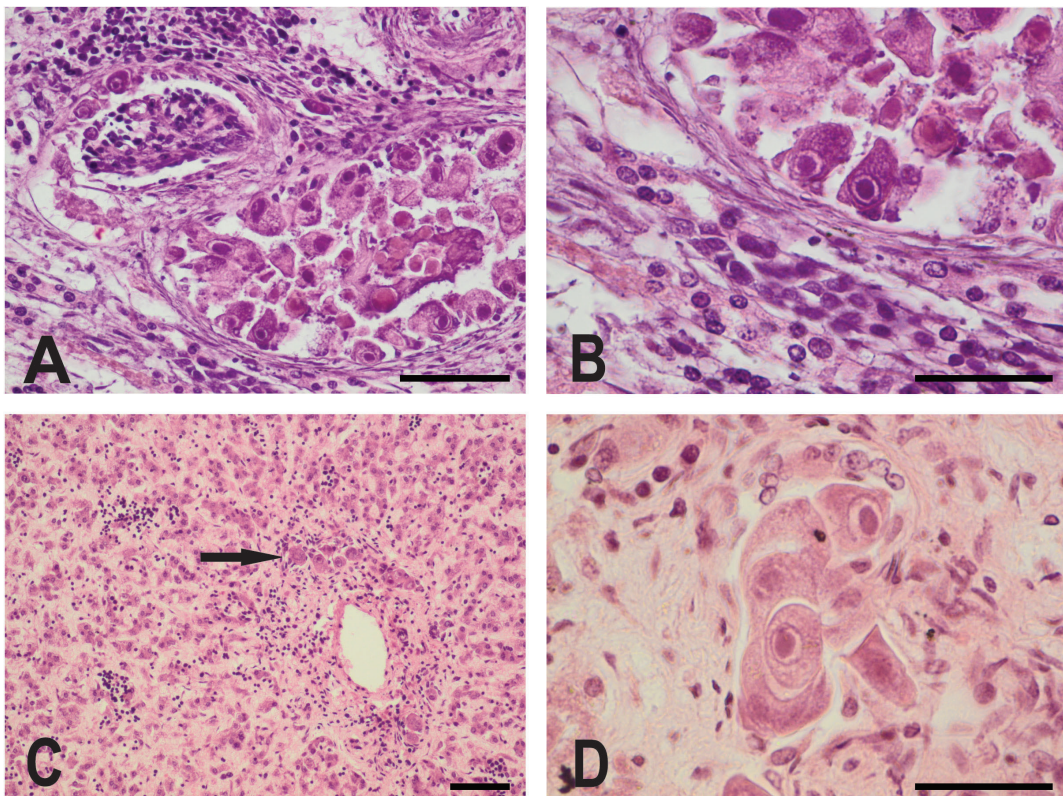


FIG. 1: CMV inclusions in epithelium of Bowman's capsule (A) and renal tubular epithelial cells (A & B). Cells with CMV inclusions in the liver (C & D) (A: H&E, x200; B: H&E, x400; C: H&E, x100; D: H&E, x400).



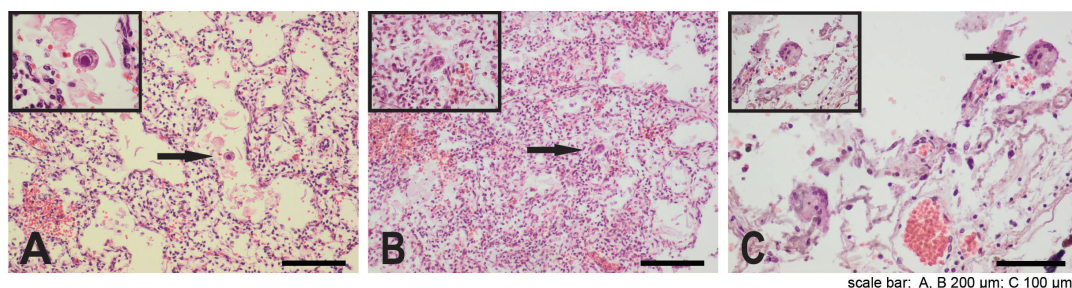


FIG. 2: Pneumocyte in the lung with intranuclear CMV inclusion in alveolar space (A) and multinucleated giant cell (B). Multinucleated giant cell in the brain (C) (A: H&E, x100, insert magnification x600; B: H&E, x100, insert magnification x600; C: H&E, x200, insert magnification x600).

cells were present in all examined organs (Figs. 2B and 2C), as well as in placenta (Fig. 3A).

The placenta appeared to be grossly normal for the gestational age of the foetus. Placental disc was 15 cm in greatest dimension with complete maternal surface, free peripheral membranes and 3 vessels umbilical cord paracentrally inserted. The histologic examination of the placenta revealed mild chronic villitis with focally distributed, modest mononuclear inflammatory infiltrate (mainly lymphocytes with rare plasma cells) in chorionic villi stroma. A few oedematous, partially necrotic villi, were present. In rare cytotrophoblast cells there were CMV inclusions (Fig. 3B). The final diagnosis was cytomegalic inclusion foetal disease with disseminated Herpes simplex infection.

## DISCUSSION

Virus infections during pregnancy are one of the main causes of morbidity and mortality of the foetus. However, they may often pass as asymptomatic in mothers. Cytomegalic infection is the most common intrauterine infection and

represents the most common cause of foetal congenital malformations.

Infections caused by Herpes simplex virus are more common in periparturient and postparturient period, but despite the low incidence during the intrauterine period, they are significant because of potentially fatal consequences like foetal death or serious disorder in development.

Prenatal diagnostics comprise ultrasound examination and virological testing of amniotic fluid. Ultrasound imaging may suggest the presence of congenital CMV infection in more than 15% of infected foetuses.<sup>9</sup> Positive virological testing of amniotic fluid cannot determine the outcome of the disease.<sup>2</sup> In the case described above, malformations of the central nervous system in foetus, ventriculomegaly and lissencephaly, were diagnosed via ultrasound.

According to some authors, besides genetic disorders, lissencephaly may also occur because of the intrauterine virus infection of the foetus, where the cytomegalovirus is mentioned as the significant and common aetiological factor which leads to lissencephaly.<sup>9</sup> CMV shows a

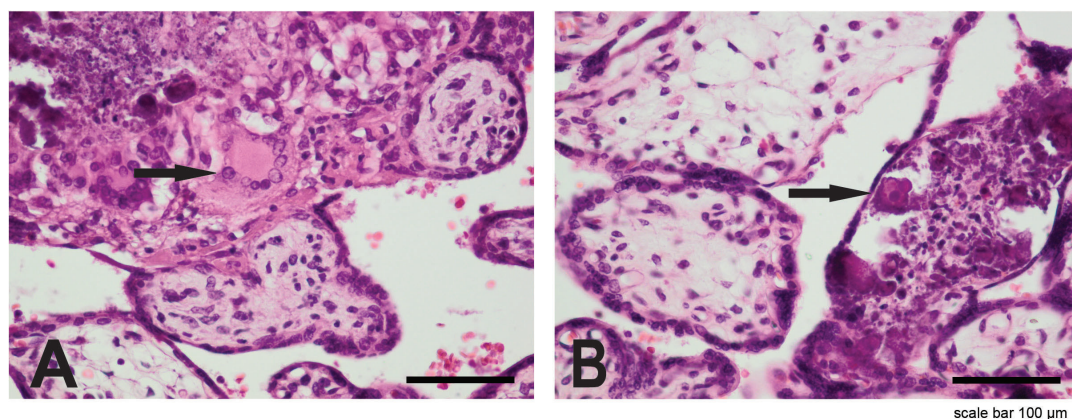


FIG. 3: Multinucleated giant cell (arrow) in the placenta (A). Cells with intranuclear CMV inclusions (arrow) (B) (A: H&E, x200; B: H&E, x200).

pronounced affinity for developing brain tissue, which may lead to development of brain necrosis, lissencephaly, microcephaly, polymicrogyria, hydrocephalus, ventriculomegaly and other brain anomalies.<sup>10</sup> Besides other symptoms (changes on skin and eyes), intrauterine HSV infection most often also lead to neurological disorders like development of encephalomalacia (especially in temporal regions), encephalitis, intracranial calcification and microcephaly.<sup>4</sup> In the case of joint CMV and HSV infection described above, the histological examination of the brain showed larger necrotic areas with calcifications and numerous cells with intranuclear inclusions. CMV shows different level of tropism for different tissues. It is considered that the initial infection affects epithelial and endothelial cells, and is followed by viremia and secondary systemic spread of the virus. Different sensitivity of tissue to infection has impact on the frequency of histological finding on organs.<sup>3</sup> In literature it states that pancreas, kidneys, lungs, liver and brain are organs where cytomegalic inclusions of a cell may be found most often, which corresponds to our findings.<sup>1</sup> In this case, the cytomegalic inclusions are most visible and most abundant in renal tubule epithelial cells.

The inflammatory response around the cells with cytomegalic inclusions was not pronounced in the case presented above. It is considered that the inflammatory infiltrate occurs as an immunologic reaction to infection and that it rarely occurs with foetuses infected by virus in earlier gestational age.<sup>3</sup>

Study showed that CMV is the most significant cause of chronic lymphoplasmacytic villitis.<sup>11</sup> Besides this finding, in the case of CMV infection in foetus, in the placenta one may find thrombosis of chorionic villi capillaries, hemosiderin depositions, chorionic villi and trophoblast necrosis, stromal fibrosis, calcifications, hyalinisation and CMV inclusions. The inclusions are situated in stromal cells of chorionic villi, in capillary endothelium and rarely in syncytiotrophoblast cells.<sup>12</sup> It was pointed out that there is a connection between the degree of inflammatory response of placenta and the severity of inflammatory infiltrate in the brain, where the stronger placentitis is related to more pronounced brain damages.<sup>1</sup> It is assumed that the infection causes placental dysfunction and leads to secondary chronic hypoxemia which results in ischaemia and necrosis of the development of brain tissue.<sup>2</sup>

## CONCLUSION

Foetal central nervous system malformations may occur for various reasons. If ultrasound examination of the foetus showed lissencephaly and ventriculomegaly, one of the possible aetiological reasons may be virus infection, and it is advisable for the mother to undergo serological testing.

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