OWL EYE INCLUSIONS IN PLACENTA

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ABSTRACT

Cytomegalovirus (CMV) infection poses an important public health problem as it may cause serious morbidity and mortality in congenitally infected newborns and immunocompromised patients. Maternal infection during pregnancy represents an elusive area in teratology. It is known that many infections can be transmitted from mother to fetus and the spectrum of effects on the fetus hinges on many factors. Congenital cytomegalovirus disease results from transplacental transmission of the virus during pregnancy with manifestations ranging from subtle sensory neural hearing loss to fulminating multisystem infection leading to eventual death of the newborn. We present a case of intrauterine death in a multipara at 32 weeks of pregnancy, caused by a congenital CMV infection presenting with owl eye inclusions in placenta on histopathology.

Key words: Cytomegalovirus infection, pregnancy, intrauterine death

INTRODUCTION

Cytomegalovirus (CMV) is a DNA virus related to herpes group of viruses and humans are its only host. Infection with CMV can be asymptomatic or can be the source of serious illness in people with weak immune systems. It is the most common congenital infection and causes mental retardation and sensorineural defects. The majority of symptomatic congenital CMV infections follows a primary paternal infection during pregnancy and has a poor prognosis. The virus replicates in the uterus, infects the placenta, and then is transmitted to the fetus. It is believed that about 85 percent of the adults have been infected by CMV at some point in their lives. CMV is found in almost all the organs, body fluids, including semen, saliva, urine, feces, breast milk, blood, and secretions of the cervix and transmitted horizontally as a result of organ donation, blood transfusion, sexual contact, and contact with infected saliva and urine. At least 50% of women of reproductive age have evidence of prior CMV infection.
CASE REPORT

A 27 year old female was diagnosed with Intrauterine foetal death (IUD) at 32 weeks of gestation. She was G3P2L2A0 with an uneventful antenatal period. No other significant history including diabetes mellitus, HIV infection or abnormal antenatal ultrasound was detected. TORCH screen was no done, as the patient did not attend antenatal clinic. First two pregnancies were uneventful and two other siblings are normal without any symptoms/clinical features of CMV infection.

The placenta was submitted for histopathological examination which was grossly unremarkable. Microscopy revealed chorionitis, villitis and cytomegalovirus inclusion bodies (owl eye inclusion) in the placenta. Diagnosis of maternal cytomegalovirus infection was made which could have led to sudden IUD of the foetus.

Autopsy of the fetus was not done due to religious reasons. As the patient could not afford, serology, immunohistochemistry or ultrastructural study was not done. Based on available findings on histopathology which was classical, diagnosis of CMV infection of placenta leading onto IUD was made.

Figure 1. Placenta showing chorionitis and villitis with plasma cell infiltrate. 10x H&E
Figure 2. High power showing basophilic intranuclear inclusions and perinuclear halo suggestive of CMV 40x H&E.

DISCUSSION

Human cytomegalovirus (CMV) is the most common cause of viral intrauterine infection, affecting 0.5-2.5% of all live births in different parts of the world. The prevalence of prior infection is increased in women of lower socioeconomic status. Most pregnant women acquire infection as a result of contact with their own younger children or children in a daycare or pre-school setting and could be the probable cause in our case 1,4. The majority of CMV infections during pregnancy is asymptomatic but can present with a mononucleosis-like illness. Symptoms may include fever, lymphadenopathy, splenomegaly and elevation of peripheral lymphocyte count. The rate of transmission of infection to the fetus differs depending upon whether the woman has a primary or recurrent infection. Transmission to the fetus is about 40-50% if a primary infection. This rate drops to 5% if a recurrent infection. Besides contact with seropositive mothers, blood transfusion is the most important mode of perinatal or postnatal spread of CMV to neonates4–6. The risk of seroconversion during pregnancy averages 2.0-2.5%, ranging from 0.47% to 12.9%. Congenitally infected infants who are still born (approximately 20% of the first
trimester infection) on autopsy show thrombocytopenia, purpura, hydrocephalus with periventricular calcifications, intrauterine growth retardation (IUGR), hepatitis and jaundice, microcephaly, and chorioretinitis. Histopathology usually reveals classical cytomegalic inclusion bodies or owl eye inclusions. Pregnancies with evidence of vertical transmission and definite ultrasonographic findings are at significant risk of severe sequelae.\textsuperscript{1,6–7}

Ninety percent of congenitally infected infants are asymptomatic at birth; however, 10-15\% of the latter are at risk of developing a multitude of developmental abnormalities, such as hearing loss, mental retardation, delay in psychomotor development, chorioretinitis, optic atrophy, seizures, expressive language delays, and learning disabilities. The clinical consequence for the infected offspring appears to be worse when infection takes place before 20 weeks' gestation. Interestingly, when primary maternal infection occurs in the third trimester of pregnancy, the risk of transplacental transmission is much higher – 75 to 80\%. However, the risk of serious fetal injury is very low.\textsuperscript{1,6}

The placenta and fetus present a substantial challenge to the maternal immune system. Vigorous local immune responses can potentially activate maternal anti-fetal allograft immunity but a less than adequate local immune response would allow pathogens to enter the placenta and gain access to an immature fetal immune system that is ill-prepared to respond to them. Irrespective of their etiology, the resulting immune responses can lead to adverse outcomes such as intrauterine fetal demise, premature delivery, fetal growth restriction, and organ-specific damage to the developing conceptus.\textsuperscript{7–8}

Prenatal diagnosis for CMV is difficult as 95\% of women do not have any specific clinical findings and the others may present with a non-specific viral syndrome features. Methods which can be used in a suspicious case include serology, amniocentesis (I trimester), percutaneous umbilical cord blood sampling (II trimester) and ultrasound (II and III trimesters). The presence of IgM antibody or the virus in culture can be determined in amniotic fluid or fetal blood while ultrasound can detect some of the structural anomalies associated with congenital CMV, such as IUGR, hydrops, microcephaly, hydrocephaly, and intracranial calcifications. It has been indicated that high levels of alpha feto protein in the maternal serum may be a marker for fetal infection. Detection of viral DNA through Polymerase chain reaction is possible.\textsuperscript{3,6–9}

Newborns are usually screened for congenital CMV infection by isolation of virus from a urine or saliva or by serological study. Prenatal diagnosis of congenital infection allows the close observation of congenitally infected infants in the first years of life. Such follow-up of these cases will, in turn, mean rapid detection and correction of hearing loss, reducing the risk of secondary developmental disorders. Fetal CMV infection-in the absence of cerebral lesions or severe biologic abnormalities-has been associated with a good prognosis.\textsuperscript{6–9}

Ultrastructural findings of human bone marrow fibroblasts infected by CMV include thickening and conspicuous invagination at multiple focal sites along the inner nuclear membrane. Also many viral particles were seen associated with this envelope demonstrating what are known as pseudoinclusions or nuclear envelope proliferations as possible stages of exiting by the viral particles.\textsuperscript{10}
Various studies have used various methods for diagnosis of CMV infection. Studies have used various methods including histopathological, biochemical and microbiological. The various studies are as shown in Table 1.

Table 1: Various studies in diagnosis of CMV and method used.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No of positive cases</th>
<th>Method used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ko et al 5</td>
<td>2000</td>
<td>3</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Lone et al 14</td>
<td>2004</td>
<td>306</td>
<td>Serology</td>
</tr>
<tr>
<td>Sheevani et al 13</td>
<td>2005</td>
<td>297</td>
<td>Serology</td>
</tr>
<tr>
<td>La torre R et al 2</td>
<td>2006</td>
<td>84</td>
<td>Serology and estimation of Placental thickness by ultrasound</td>
</tr>
<tr>
<td>Murayama et al 11</td>
<td>2010</td>
<td>46</td>
<td>Isolation of CMV genome from amniotic fluid specimens.</td>
</tr>
<tr>
<td>Iwasenko et al 12</td>
<td>2011</td>
<td>20</td>
<td>DNA extraction of CMV from placenta and other tissues and diagnosis using PCR and immunohistochemistry</td>
</tr>
</tbody>
</table>

Regarding the preventive aspect, pregnant women with young children should maintain a good hygiene whereas if infected, mother to fetal transmission is probably preventable using CMV hyperimmune globulin or drugs like ganciclovir or its derivatives.

CONCLUSION

Every attending physician and obstetrician should be aware of the possibility of a primary or even recurrent congenital CMV infection that could be a reason for sudden unknown fetal death. Prenatal diagnosis provides the optimal means for both diagnosing fetal infection (amniocentesis) and identifying fetuses at risk of severe sequelae (ultrasound examination, fetal blood sampling), thus allowing proper counseling. During blood transfusion, leucodepleted blood which is equivalent to CMV seronegative blood should be used especially in neonates.

To minimize the disease burden resulting from CMV congenital infection, the use of a vaccine seems the only logical approach. In view of the complexities involved in the development of a safe and protective vaccine, we believe that the prenatal diagnosis described above provides the optimal means for not only diagnosing fetal CMV infection, but also for defining pregnancies without a significant risk of severe sequelae and thus guiding the patient as to whether her pregnancy can be continued with a high level of confidence.

REFERENCES
Owe eye inclusions in placenta