Placental Cytomegalovirus Infection

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In the United States, cytomegalovirus is the most common congenital viral infection and the number 1 cause of nonhereditary sensorineural hearing loss. The vast majority of infants may be asymptomatic, especially if cytomegalovirus is contracted later in the pregnancy, and some symptoms may have a delayed onset. Therefore, it is important for the pathologist to identify the common histologic findings to help confirm the diagnosis so the child can be followed for late sequelae. Histologic examination of the placenta is important in live births and in cases of intrauterine fetal demise. Chronic lymphoplasmacytic villitis and fibrotic, avascular villi are the most common findings. When present, Cowdry A intranuclear and basophilic intracytoplasmic inclusions are characteristic. Immunohistochemistry for cytomegalovirus can highlight these inclusions as well as the associated eosinophilic debris. In addition, polymerase chain reaction or viral culture on placental or fetal samples can be performed for confirmation.

Cytomegalovirus (CMV) is a member of the herpesvirus family, which includes other common viruses such as Epstein-Barr virus, herpes simplex viruses 1 and 2, and varicella-zoster virus. Although the exact seropositivity rate of CMV depends upon the population, it is estimated that 60% of adults in the United States are seropositive. Similar to the other members of the herpesvirus family, CMV can go through long periods of latency followed by reactivation of the endogenous strain or by reinfec-tion with a new exogenous strain.

CLINICAL FEATURES

Worldwide incidence of congenital CMV infection is estimated at 0.2% to 2.5% of all live births, and incidence within the United States is estimated at 0.64%. In the United States, congenital CMV infection is the most common congenital viral infection, affecting 20 000 to 80 000 live births per year. Although CMV is a well-known cause of intrauterine fetal demise, there are few data regarding the specific incidence of CMV infection in intrauterine fetal demise cases. The few published studies available report the incidence of CMV in intrauterine fetal demise cases to be 15% to 16%.

Rates of vertical transmission from mother to fetus are higher with primary viral infection (30%–50%) than with reactivation (1%–3%). Risks of vertical transmission and subsequent sequelae also vary with the gestational age at the time of infection. Although the rate of vertical transmission is lower earlier in pregnancy, the risk to the fetus is greater. If the fetus is infected early in gestation, especially during the first trimester, the developmental abnormalities that manifest are more severe. During the third trimester, the likelihood of neonatal disease is low, even though the risk of vertical transmission is increased in comparison with early pregnancy. This somewhat paradoxical observation can be explained by the passive transmission of maternal CMV-specific neutralizing immunoglobulin G antibodies, which increases with gestational age.

Only a minority of children (10%) are symptomatic at birth, with symptoms including petechial rash, jaundice, hepatosplenomegaly, microcephaly, lethargy, hearing impairment, and thrombocytopenia. Those who are asymptomatic at birth, however, may show delayed onset of symptoms. Congenital CMV infection is the number 1 cause of nonhereditary sensorineural hearing loss.

In the antenatal period, CMV can be transmitted through vaginal secretions and breast milk. The latter has been shown to be more likely in the setting of preterm infants because of the decreased levels of passively transferred maternal antibodies when an infant is born prematurely.

GROSS PATHOLOGY/HISTOPATHOLOGY/LABORATORY FINDINGS

There are no specific gross findings in the placenta. The placenta may appear normal or there may be opacity of the fetal membranes, thickened vessels within the umbilical cord, or edematous, friable cotyledons. The most frequently identified placental histopathologic abnormality of congenital CMV is lymphoplasmacytic chronic villitis. Examination of villi may reveal the characteristic cytomegaly with intranuclear and intracytoplasmic inclusions (Figure 1, A and B). The classic intranuclear inclusions are of the Cowdry A type. They are eosinophilic with a surrounding clear halo and appear glassy or smudged. In contrast, the intracytoplasmic inclusions are basophilic and are usually not as prominent. Inclusion...
sions are most frequently seen in the endothelial cells or Hofbauer cells (macrophage-like cells within the stroma of the villi), which may show marked hyperplasia. Eosinophilic necrotic debris may also be found in affected villi.

Another frequent finding is fibrotic, avascular villi with hemosiderin deposition. Early reports of CMV-infected placentas describe vessels within the chorionic villi that show decreased luminal size, loss of cellular detail, fibrosis, and calcification. As the virus infects endothelial cells leading to the destruction of fetal vessels, villi may be completely avascular and fibrotic, hence the description of “pink chorionic villi” in the literature. Vascular destruction then causes red blood cell extravasation and subsequent hemosiderin deposition (Figure 2, A and B). Other nonspecific findings that can be seen include delayed villous maturation, lymphoplasmacytic deciduitis, and chorioamnionitis.

Although the majority of the histologic findings seen in CMV are not specific, any of the above features should prompt further evaluation for congenital CMV infection with immunohistochemical studies. Cytomegalovirus immunohistochemistry will highlight both intranuclear and intracytoplasmic inclusions and may highlight eosinophilic necrotic debris within the villi and infected cells that do not show classic viral cytopathic effect (Figure 3, A and B).

ANCILLARY LABORATORY STUDIES

Additional laboratory tests to confirm congenital CMV infection can be performed on the placenta or the fetus. If performed on the fetus, testing should be done while the fetus is in utero or within the first 3 weeks of life, as congenital and postnatal infection cannot be differentiated after 3 weeks of age. The most common tests for congenital CMV are viral culture or polymerase chain reaction (PCR) performed on urine, saliva, or amniotic fluid. Although viral culture of neonatal urine has historically been considered the gold standard, real-time PCR has shown increased sensitivity and is becoming more common. Several studies have compared PCR testing and immunohistochemical staining of the formalin-fixed, paraffin-embedded placental tissue. Although neither is as sensitive as PCR testing of the urine, both are diagnostic options after the first 2 to 3 weeks of life, when testing of the infant’s urine is no longer recommended. Additionally, it should be noted that the detection of CMV by PCR in the placenta does not always correlate with its detection in the fetus and vice versa. Studies have shown the presence of
CMV by PCR in a placenta without the presence of CMV in the fetus, suggesting that the placenta may, at times, be a protective barrier to CMV transmission.23,24

DIFFERENTIAL DIAGNOSIS

As noted above, most of the histologic features seen in congenital CMV are nonspecific. Chronic villitis can be caused by other non–herpes family infections, including Toxoplasma gondii, rubella virus, and Treponema pallidum. Most chronic villitis is eventually classified as chronic villitis of unknown etiology.25(pp2333–2334) However, chronic villitis of unknown etiology is most frequently lymphohistiocytic, as opposed to the lymphoplasmacytic inflammation seen in CMV. Before a diagnosis of chronic villitis of unknown etiology is made, infectious etiologies should be ruled out, as chronic villitis of unknown etiology is a diagnosis of exclusion.

Other members of the Herpesviridae family, including varicella-zoster virus and herpes simplex virus, can also produce viral intranuclear inclusions. Cytomegalovirus, however, is the only member of the family where both intranuclear and intracytoplasmic inclusions are seen. Varicella-zoster virus and herpes simplex virus are also more likely to produce a necrotizing villitis rather than the lymphoplasmacytic villitis seen in CMV.18,26

Fibrotic, avascular villi similar to those seen in CMV infection are also a hallmark of fetal thrombotic vasculopathy. Fetal thrombotic vasculopathy is defined by identifying 2 foci of 15 avascular/karyorrhectic terminal chorionic villi or by identifying 45 affected villi total.25 Although originally thought to be due to an underlying coagulopathy, fetal thrombotic vasculopathy is more often due to some form of umbilical cord abnormality that causes a functional obstruction. These cord abnormalities include velamentous insertion, thin cord, kinking, hypercoiling, and entanglement.25 Therefore, attention to the gross pathology of the placenta and umbilical cord is also important for ruling out fetal thrombotic vasculopathy. In addition, assessment of the distribution of fibrotic villi can aid in diagnosis. Because fetal thrombotic vasculopathy is caused by an obstructive mechanism, the fibrotic villi are found in a vascular distribution, which is not the case for CMV.

TREATMENT AND PROGNOSIS

As discussed above, the prognosis of congenital CMV infection depends in part on when during pregnancy the infection is acquired. Of live-born infants who are symptomatic at birth, 50% to 80% will develop cognitive impairment, 30% to 60% will develop sensorineural hearing loss, 20% to 35% will develop visual impairment, and 30% to 60% will develop neurodevelopmental, behavioral, and neuromuscular disorders.1,3 Furthermore, a subset of children who were initially asymptomatic at birth will go on to develop late-onset sequelae, most commonly sensorineural hearing loss.3

Historically, the treatment for congenital CMV infection is antiviral therapy, consisting most often of intravenous ganciclovir.27 However, increasingly common is the use of the oral prodrug valganciclovir, and there is ongoing evaluation of acyclovir and its oral prodrug valacyclovir in the setting of pregnancy.27 Ganciclovir treatment may be reserved for only those infants with severe organ involvement or central nervous system involvement.7 This is because side effects of ganciclovir administration include neutropenia and risk of infection.28 It is not currently recommended to give treatment to asymptomatic infants to prevent long-term sequelae. However, there is some recent evidence that ganciclovir can prevent progression of hearing loss at 6 months of age when started in the neonatal period and administered for more than 6 weeks.2 In addition, treating with valganciclovir has been shown to improve not only hearing outcomes but also long-term developmental outcomes.29

SUMMARY

Cytomegalovirus infection is common throughout the world, with high seropositivity rates among adults in the general population. Although congenital CMV infection has a fairly low incidence in the United States, it is important to recognize because of the significant morbidity and mortality associated with symptomatic disease. Furthermore, there is increasing evidence that infants who appear asymptomatic at birth may still develop long-term sequelae, most notably sensorineural hearing loss, and that the incidence of this hearing loss due to congenital CMV infection may be higher than previously thought. Microscopically, the placenta may

![Figure 3. A, Intranuclear viral inclusions and eosinophilic debris highlighted on immunohistochemistry. B, Intranuclear viral inclusion within villous stromal cells (monoclonal mouse anti-cytomegalovirus, clone CCH2 ÷DDG9, 1:100 dilution, original magnifications ×20 [A] and ×40 [B]).](image-url)
show lymphoplasmacytic villitis and avascular, fibrotic villi. Even if the classic intranuclear and intracytoplasmic inclusions are not seen, an immunohistochemical study for CMV can be beneficial, as it will highlight infected cells and eosinophilic debris within the villi. Although PCR and viral culture of fetal urine or saliva are the best ways to identify congenital CMV infection, histopathologic findings are important to recognize, especially within the asymptomatic population.

References