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Research Letter

Cytomegalovirus infection and fetal death in one monozygotic twin

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Congenital cytomegalovirus (CMV) infection is symptomatic in approximately 10% of infected neonates and is associated with clinically significant brain damage and sensorineural hearing loss in almost one-half of those infected [1–3]. In addition, neurologic defects will eventually develop in 8–13% of neonates with asymptomatic infections. The prenatal diagnosis of congenital infection is possible; however, there has been much debate about the value of screening for fetal CMV infections. Although CMV-specific hyperimmunoglobulin therapy is possible for the prevention and treatment against fetal CMV infections, no prenatal therapy or vaccine is currently available. There is no accurate means to predict the sequelae of primary infections. Up to 2% of all infants excrete CMV, and attempts to identify and isolate the viral agent are expensive and impractical. Serologic screening is not recommended by the American College of Obstetricians and Gynecologists [4]. Screening for prenatal CMV infection is not mandatory in Taiwan but is performed at the physician's discretion and with the patient's consent. Therefore, the prenatal suspicion and diagnosis of CMV is an enormous clinical challenge for obstetricians.

Primary maternal CMV infection during pregnancy leads to vertical transmission in around 30–50% of fetuses, and the rate of transmission (0.2–1%) is far lower for mothers with secondary infection relatively [5–7]. Only 10–15% of newborns of mothers with primary CMV infection during pregnancy present the typical clinical findings of congenital CMV [8–10]. Although the fetuses can be infected by CMV throughout the whole pregnancy and several studies have suggested that gestational age at infection has no apparent influence on the rate of transmission [11,12], an increased risk of transmission in late gestation was indicated by Bodéus et al [13] and Daiminger et al [14]. Furthermore, a greater risk of symptomatic fetal involvement was noted in infections occurring during the first half of the pregnancy or near the time of conception, whereas infections in the second half result in less sequelae [7,11]. The fetal damage is also more severe in early primary infection than in late infection [7,9].

Although all of the factors influencing the severity of CMV infection are not known, maternal and fetal immune status and viral strain virulence are considered to play a significant role [15]. When CMV affects a twin gestation, both of the twins usually have clinical or laboratory evidence of infection. The data in the literature pertaining to congenital CMV infection in twins, however, are limited [16–21]. Twin gestations represent an interesting model for CMV because of the same maternal influence. Moreover, congenital CMV in monozygotic twins has rarely been reported [17]. Monozygotic twins are genetically identical.

We describe a unique case of congenital CMV in a monozygotic twin gestation, resulting in the intrauterine demise of one fetus and the survival of the other fetus without complications. We have followed the survivor for 8 years as of this writing. This case offers an opportunity to observe a different course of CMV infection amongst twins.

After a period of secondary infertility, a twin pregnancy was achieved in a 38-year-old woman using clomiphene therapy. During the regular prenatal examination, she was shown to have gestational diabetes mellitus and noted to have the familiar marker chromosome. Discordant intrauterine growth of the twins was noted, beginning in the early second trimester, and a difference in the estimated body weight was also recorded beginning in the late second trimester using ultrasound examination. Although the Doppler examination of the umbilical cord flow and amniotic fluid volume were within normal limits, a fetal demise was incidentally diagnosed at 36 weeks of gestation during an ultrasound examination. A low segment cesarean

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section was performed and a live female in the frank breech position was extracted. The body weight was 2,560 g, the length was 43.5 cm, the head circumference was 32.5 cm, and the Apgar scores were 6 and 8 at 1 and 5 minutes, respectively; the second female was a macerated stillborn.

On the initial physical examination, the firstborn was found to be a normal infant. The laboratory data showed nonspecific IgM (14.9 mg/dL), a normal urinalysis, and a mild thrombocytopenia. There was no clinical evidence of congenital infection and the general condition was stable. After counseling with the mother, the fetal demise and placenta were sent for postmortem examination. The body weight was 1,780 g, the length was 46 cm, and the head circumference was 31 cm. The kidneys (Fig. 1A and B) and lungs (Fig. 1C) had inclusion bodies in giant cells suggestive of CMV infection. Immunohistochemical staining for CMV was positive. A single umbilical artery was present, but no other remarkable congenital anomalies were observed. Examination of the placenta, both grossly and microscopically, showed that the fetal membranes were diamniotic and monochorionic (Fig. 1D and E), with the placental plate of the fetal demise smaller than the liveborn. Two placental plates with communicating umbilical vascular branches were found. No inclusion-bearing cells were seen on microscopic examination; however, villous hypervascularity and lymphohistiocytic villitis was noted.

We followed the bottle-feeding liveborn serially. At 4 weeks of age, the serum CMV-IgG titer was 1,741 AU/mL, and the CMV-IgM index (0.18) was negative. At 2 months of age, the CMV-IgG was 1,753.8 AU/mL, but the CMV-IgM index (1.00) was positive. Liver function tests were normal. At 4 months of age, the CMV-IgG was 1,312.8 AU/mL and the CMV-IgM index (0.55) was still positive. The urine culture for CMV was negative, and eye and otologic examinations were also normal at 2, 4, 8, and 12 months of age. Bilateral, multiple, small cerebral subependymal cysts [22] were demonstrated by serial brain echograms beginning at 2 weeks of age. The 1-year-old child showed a normal growth pattern and continues to undergo clinical follow-up every year. The child received psychologic assessment and the Chinese Child Developmental Inventory test was administered at 4 years of age, revealing an intelligence quotient of 147–170%. The 8-year-old child has no clinically significant brain deficits or sensorineural hearing loss as of this writing.

Hematogenous spread appears to be the most likely pathway of vertical transmission and the placenta is the main entrance for CMV to the fetuses [23]. It is presumed that women who transmit CMV to the fetuses might have defective immunologic responses [24,25]. But some suggested that placenta might also play an important role in vertical transmission as the protective factor by producing interferon when challenged [26] or acting as a nonspecific barrier [27].

The factors influencing the severity of CMV are not known, although maternal and fetal immune status, viral strain virulence [15], and reinfection with different strains [1] are considered to play a role. Based on maternal and fetal symptoms and signs alone, it is often difficult to suspect prenatal CMV infection. Thus, the present case of a CMV-infected twin gestation provides an interesting model for discussion because genetically identical fetuses are simultaneously exposed to the same maternal influence. However, the perinatal outcome was quite different.

In this case, it is clear that the smaller fetus was affected more severely by the intrauterine-acquired CMV infection than the larger fetus. The combination of growth retardation and intrauterine viral infection causing an impaired immunologic response might explain the difference in fetal involvement amongst the twins. The absence of an apparent infection might suggest a more effective fetal immune response in the

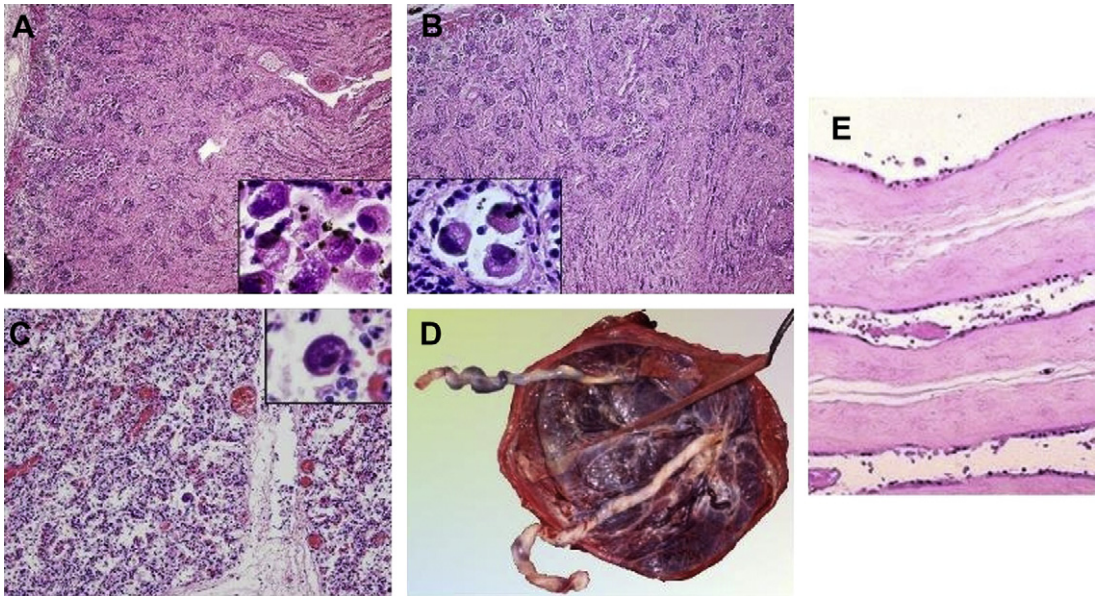

Fig. 1. (A and B) Multiple cytomegalovirus intranuclear viral inclusions are illustrated in the right and left kidneys, respectively and (C) in the lungs in (H&E stain). Magnification was 200× for (A–C) and 400× for the small window. (D) A gross image of the diamniotic, monochorionic placenta is shown. (E) Monochorionic dividing membrane of placenta composed of two amnia without intervening chorion is shown. H&E = hematoxylin and eosin.

surviving twin because fetal age at exposure, viral stain, and maternal immune status are assumed to have been identical in both twins.

It is generally thought that the placenta is the main portal for CMV and that placental infection following maternal viremia is the initiating step in fetal infection [23]. In the present case of twins with the same placenta, only one twin was severely infected. Because the placenta was exposed to the virus at that same time and with the same viral load, both twins would be infected by transplacental spread of maternal viremia. Thus, the placenta of the infected twin may have not acted as a barrier to viral transmission. The placental vascular communication between the twins contributing to the discordant outcome cannot be established with certainty. The serologic diagnosis is complicated by maternal transplacental IgG antibody and the common occurrence of perinatally acquired disease, making studies after the first few weeks of life inconclusive in establishing the diagnosis of congenital CMV.

Our case shows that intrauterine-acquired CMV infections involving monozygotic twins with the same genotype can result in totally different outcomes, even if they are simultaneously exposed to the same maternal influence. We postulate that there are not only maternal factors, placental barriers, viral load or virulence but some other unknown factors affecting fetuses infected with CMV from maternal infection. Influences of unknown factors (such as the relationship between the virus and its environment or the interaction of maternal and fetal immune systems) on the vertical transmission rate are unclear, and further investigations are needed to improve our knowledge of congenital CMV infection.

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