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Perinatal cytomegalovirus infection complicated with pneumonitis and adrenalitis in a premature infant

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Cytomegalovirus causes pneumonia, hepatitis, thrombocytopenia, and hemolytic anemia. Cytomegalovirus adrenalitis in premature infants, however, is rare. This report described a premature newborn who had progressively worsening hyperbilirubinemia, pancytopenia, and hepatosplenomegaly at the age of 4 days. The baby's mother had prolonged rupture of amniotic membrane for about 8 weeks. The infant received exchange blood transfusion, empiric antibiotics treatment, and mechanical ventilation. Pneumonia and sepsis developed at the age of 18 days. Serum anticytomegalovirus immunoglobulin M and urine virus culture were positive for cytomegalovirus. The baby died at the age of 22 days. Autopsy showed cytomegalovirus infection complicated with interstitial pneumonitis and pulmonary edema, subacute bronchopulmonary dysplasia with interstitial fibrosis, and adrenalitis. We concluded that the functional status of the adrenal glands in cytomegalovirus-infected premature newborns who have unexplained electrolytes imbalance, fever, diarrhea, weight loss, or hypotension should be closely followed because of the possible involvement of adrenal glands.

Key words: Adrenalitis, cytomegalovirus, perinatal infection, premature infant

Cytomegalovirus (CMV) infection is the most frequent congenital infection with approximately 10% of infected infants being symptomatic at birth each year in the United States [1-3]. However, only 5% of infected infants have clinical disease in the newborn period with signs of intrauterine growth retardation, hepatosplenomegaly, thrombocytopenia, pneumonitis, or encephalitis [4,5]. Shen *et al* [6] reported that the cervical and urinary excretion rates of CMV in Taiwan women during the first trimester of pregnancy were similar to those of nonpregnant women. However, as pregnancy proceeded, the cervical excretion rate increased from 13% to 40%, and the urinary excretion rate increased from 1% to 13% [6]. Cytomegalovirus infections acquired perinatally were far more frequent than those acquired transplacentally. The 3 major routes of perinatal transmission of CMV in infants are (1) aspiration of infected cervical secretion at birth [7]; (2) ingestion of CMV-containing breast milk [8]; and (3) transfusion with CMV-seropositive blood [9,10]. Perinatal CMV infection usually results in significant morbidity in infants with very low birth weight [9]. This study reported the case of a premature newborn who had perinatal CMV infection complicated with adrenalitis diagnosed on autopsy.

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Case Report

A 1-day-old girl was delivered at a gestational age of 28 weeks. She had cyanosis and general weakness since birth, and was admitted to the Neonatal Intensive Care Unit of the Tri-Service General Hospital. Her mother was gravida 2 para 2. Rupture of the amniotic membrane had occurred at the gestational age of 20 weeks, and the patient's mother was admitted to the obstetric ward for tocolytic treatment. Intravenous prophylactic antibiotics and steroids were given, and oligoamniosis was noted during hospitalization. The delivery was spontaneous and the infant had Apgar scores of 5 and 7 at 1 and 5 min, respectively. The birth body weight was 948 g (20th percentile), and the body length was 37 cm (40th percentile).

Physical examination revealed microcephaly (head circumference, 24 cm; <10th percentile) and suprasternal and intercostal retraction. Unconjugated hyperbilirubinemia (total bilirubin, 17.8 mg/dL; direct bilirubin, 0 mg/dL) was noted at the age of 4 days, and emergency exchange blood transfusion and intensive phototherapy were administered. Pancytopenia was

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found the next day and granulocyte colony stimulation factor (G-CSF), blood transfusion, and empiric antibiotics treatment with vancomycin and cefotaxime were administered under the impression of neonatal sepsis. Cerebrospinal fluid (CSF) and blood culture showed no bacterial growth, and blood parvovirus B19 immunoglobulin (Ig) M and IgG were negative. Virus culture of CSF was negative. Hepatomegaly with normal liver enzymes and splenomegaly were noted at the age of 11 and 14 days, respectively. Brain sonography at Day 13 revealed an obvious increase in echogenicity of the periventricular white matter and right caudate nucleus, leading to suspicion of transient ischemic change. At 18-day-old, serology screening for rubella virus, herpes simplex virus, syphilis, and blood culture were performed because of abdominal distension, persistent thrombocytopenia, and tachypnea with poor oxygen saturation. C-reactive protein was 7.49 mg/dL (normal range, <0.8 mg/dL). Bone marrow aspiration at 21-day-old revealed normal myeloid hematopoietic cells. Optic fundi showed no retinal lesions or hemorrhage. The patient's condition continued to deteriorate despite blood transfusion, intravenous Ig infusion, and high-frequency positive pressure ventilation (in treating pulmonary interstitial emphysema). The patient died at the age of 22 days. Serum anti-CMV IgM and urine virus culture for CMV were positive at 18- and 22-day-old, respectively. Autopsy revealed subacute bronchopulmonary dysplasia with interstitial fibrosis, septal thickness, and pulmonary edema in lungs; enlargement of nuclei; intranuclear inclusions with halos in alveolar cells of the lungs (Fig. 1), and adrenal glands (Fig. 2); and hepatosplenomegaly. Autolysis was found in the liver,

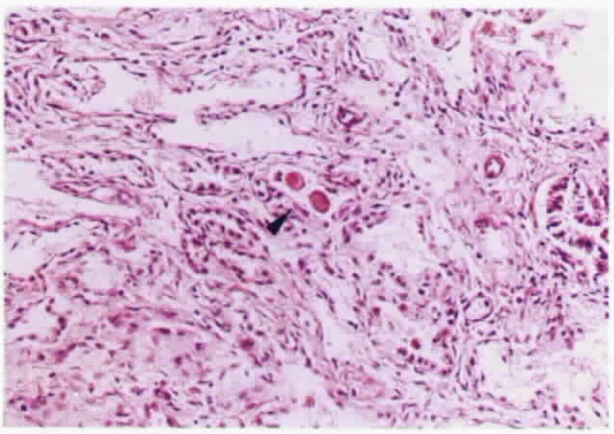

Fig. 1. Microscopy of a lung tissue specimen obtained at autopsy, showing cytomegalovirus pneumonitis, enlargement of alveolar cells and nuclei, and intranuclear inclusions with halos (arrow) (Hematoxylin and eosin, x200).

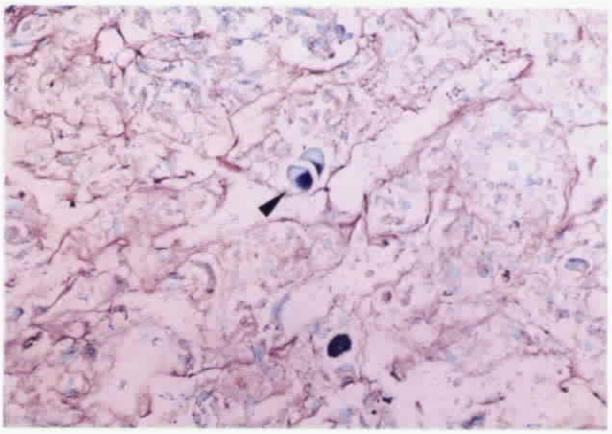

Fig. 2. Gomori methenamine silver stain of an autopsy specimen from the patient's adrenal glands, showing intranuclear inclusions (arrow) (x400).

intestines, stomach, pancreas, and brain. Maternal serum was negative for anti-CMV IgM but positive for anti-CMV IgG 8 weeks after delivery.

Discussion

Weller and Hanshaw [11] reported that the abnormalities found most frequently in infants with cytomegalic inclusion disease were hepatomegaly, splenomegaly, jaundice, petechiae, and microcephaly. Cytomegalovirus pneumonitis, retinitis, and gastrointestinal disease are common among immunosuppressed infants and can be fatal. For newborns, the major risk for CMV is in the seronegative infant who acquires CMV from the mother's primary infection that occurs during pregnancy. About 30% of symptomatic, congenitally infected neonates die during infancy [12].

Intrauterine acquisition accounts for only 0.5% to 2.2% of CMV infection in young infants [13]. The most common routes of perinatal CMV transmission are ingestion or aspiration of cervicovaginal secretions at the time of delivery, or ingestion of breast milk after delivery [7,14,15]. The incubation period of perinatal CMV infection ranges from 4 to 12 weeks [14]. Loss of passively acquired antibody and early excretion of virus appear to be associated with symptomatic CMV infections in premature infants of seropositive mothers [16]. In the case presented in this study, the baby's mother had prolonged rupture of the membrane for about 8 weeks, and perinatal transmission of CMV to the infant by infected cervical secretion or intrauterine acquisition by maternal viremia was thus a likely route of transmission.

Benson *et al* [10] reported about 25% of exchange-transfused neonates become infected with CMV. Some studies described the onset of infection, which was

usually asymptomatic, as occurring at 4 to 12 weeks after exposure to blood products [17,18]. The patient in this study received exchange blood transfusion because of hyperbilirubinemia at the age of 4 days, and transfusion-associated CMV infection was therefore unlikely.

Virus excretion into colostrum and milk is much less frequent during the first few weeks following delivery [19]. Transmission of CMV from breast milk is related to the duration of breast-feeding, and a previous study found that no infant breast-fed for less than 1 month became infected [19]. In this patient, breast-milk feeding began at the age of 4 days, but the early signs of CMV infection were apparent only at the age of 5 days.

Pneumonitis, a common clinical manifestation of perinatal CMV infection, is usually not a part of the clinical presentation of congenital CMV disease. Alford *et al* [13] estimated that diffuse interstitial pneumonitis occurs in less than 1% of congenitally infected infants even when the most severe cases were considered. Perinatally acquired CMV infection can cause severe, protracted pneumonitis and are associated with the development of bronchopulmonary dysplasia in premature infants, which considerably worsens the prognosis [20]; and CMV-infected babies may have an increased risk of developmental defects of the nervous system. The use of combined treatment with ganciclovir and high-dose IVIG or CMV Ig appears to significantly alter the outcome of CMV pneumonia [21,22]. As a result of delayed diagnosis of CMV infection until the age of 21 days, the patient died on the next day despite empiric IVIG treatment.

Immunosuppressed patients, especially those with acquired immunodeficiency syndrome, may have endocrinopathies such as adrenal insufficiency and adrenal necrosis with low Na/K ratio (<30) due to CMV infection [23,24]. Medline search using the keywords "adrenal gland disorder/premature" found no reported cases of adrenalitis in premature infants with CMV infection. The histopathologic characteristics of CMV adrenalitis vary considerably, ranging from involvement of few cells to large areas of extensive coagulation necrosis. The pathogenesis of this distinct tropism for the adrenal gland by CMV remains unknown [24].

In summary, perinatal CMV infection in immunosuppressed premature infants with systemic involvement can be fatal. Early diagnosis and treatment may improve life-threatening conditions. Patients with CMV infection may have complications of adrenalitis or adrenal insufficiency, which can present difficulties in prompt diagnosis because of their nonspecific clinical features, although they can often be confirmed on autopsy. Further evaluation of the functional status of the adrenal glands is indicated in neonates with unexplained electrolytes imbalance, fever, diarrhea, weight loss, or hypotension.

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