

# Bronchiolitis obliterans caused by CMV in a previously healthy Asian infant

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**SUMMARY:** Byun S-Y, Kim M-J, Lee Y-S, Kang E-J, Jung J-A. Bronchiolitis obliterans caused by CMV in a previously healthy Asian infant. *Turk J Pediatr* 2014; 56: 316-319.

Cytomegalovirus (CMV) is currently the most common cause of congenital infection and the leading infectious cause of brain damage and hearing loss in children. Perinatal CMV infection rarely causes clinical manifestations in normal individuals and usually follows a benign course in immunocompetent infants. However, ~15-25% of infected preterm infants may develop pneumonia, hepatitis or sepsis-like illness, bradycardia, hepatosplenomegaly, distended bowel, anemia, or thrombocytopenia. Bronchiolitis obliterans (BO) is a rare, fibrosing form of chronic obstructive lung disease that follows severe insults to the lower respiratory tract and results in narrowing and/or complete obliteration of the small airways. In non-transplant children, the most common form of BO is a severe lower respiratory tract infection, especially of adenovirus. We experienced a case of a 37-day-old male who was diagnosed as BO on chest computed tomography (CT) after CMV pneumonia. To our best knowledge, this is the first case of BO caused by CMV pneumonia in a healthy infant.

**Key words:** healthy infant, CMV pneumonia, bronchiolitis obliterans.

Human cytomegalovirus (CMV) is a member of the Herpesviridae family of DNA viruses and is responsible for a wide range of diseases in neonates and immunocompromised patients<sup>1</sup>. Although 15~25% of perinatally infected preterm infants may develop clinical illnesses such as pneumonia, hepatitis or sepsis-like illness, bradycardia, hepatosplenomegaly, distended bowel, anemia, or thrombocytopenia<sup>1,2</sup>, it is usually associated only rarely with clinical illness in term infants and usually follows a benign course in immunocompetent infants<sup>3,4</sup>. Bronchiolitis obliterans (BO) is a rare, fibrosing form of chronic obstructive lung disease that follows severe insults to the lower respiratory tract and results in narrowing and/or complete obliteration of the small airways<sup>5</sup>. BO in children is most often seen following a severe lower respiratory tract infection, usually of adenovirus<sup>6</sup>.

To date, there has been no published report of BO due to CMV pneumonia in a healthy infant. We report the first case of BO, which was confirmed on chest computed tomography (CT), caused by CMV pneumonia in a healthy infant.

## Case Report

A 37-day-old male was admitted to the hospital with a seven-day history of cough, rhinorrhea and one-time fever. He was born at 40 weeks of gestational age by normal spontaneous vaginal delivery. His birth weight was 3,280 g. On admission, his temperature was 37.9°C, respiratory rate 40/min, and oxygen saturation 96%. On the physical examination, breath sounds were relatively normal, and there was no hepatosplenomegaly. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) on admission were 222 IU/L and 247 IU/L, respectively. Results of reverse transcriptase polymerase chain reaction (RT-PCR) kit (RV7 detection<sup>®</sup>, Seegene; Seoul, Korea) for seven respiratory viruses (influenza A & B, adenovirus, metapneumovirus, respiratory syncytial virus (RSV) A/B, rhinovirus A, parainfluenza virus 1/2/3) from nasal aspirate were negative. Serum anti-CMV immunoglobulin (Ig)M antibody was positive and anti-CMV IgG antibody was negative. CMV PCR from the urine was 342,284 copies positive, and CMV was isolated from urine. CMV PCR from the maternal breast-milk was 610 copies positive. Serum

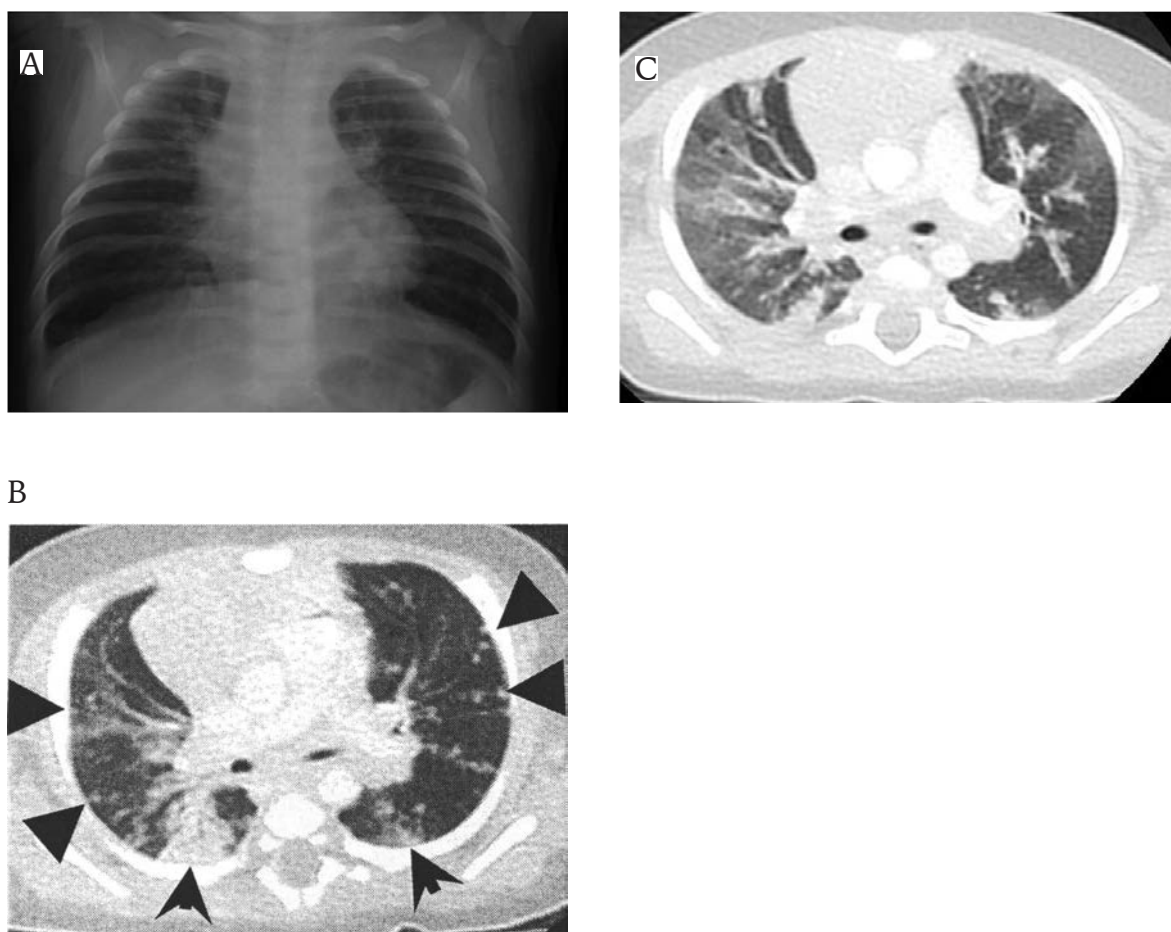
Ig G/A/M levels, C3, C4, CH50 levels, and lymphocyte subsets were normal for his age. On admission day 5, his respiration rate was ~60-70/min, and oxygen saturation was 88% without oxygen. On physical examination, breath sounds were coarse bilaterally with rales, and subcostal retraction was detected. Partial pressure of oxygen in arterial blood (PaO<sub>2</sub>) was 45.3 mmHg, and partial pressure of carbon dioxide (PaCO<sub>2</sub>) was 43.1 mmHg on arterial blood gas analysis. Supine anteroposterior chest radiography showed patch consolidations with ill-defined nodules in both lung fields (Fig. 1A). On the chest CT on admission day 19, bilateral ground-glass opacities, areas of consolidation and small centrilobular opacities were shown in both lung fields, suggestive of BO (Fig. 1B). Even though oxygen saturation was recovered over 95% with oxygen by mask (5 L/min) and inhaled corticosteroid, his respiratory difficulty persisted. We could not confirm CMV pneumonia by detection of CMV in bronchial aspirate due to parental refusal. However, we strongly suspected CMV pneumonitis, and ganciclovir therapy (10 mg/kg, for 6 weeks) was started on admission day 21. After treatment with ganciclovir for two weeks, his tachypnea had improved and oxygen saturation was over 95% without oxygen, but mild subcostal retraction and rales were still present on the physical examination. On further evaluation, there was no chorioretinitis or hearing loss. There was no intracranial calcification on brain CT. After six weeks of treatment with ganciclovir, AST and ALT were 66 IU/L and 18 IU/L, respectively. Urine CMV PCR was negative, and no CMV was detected in urine. CT scans obtained after six weeks showed a decrease in both the extent of consolidations and number of centrilobular nodules. However, the patch areas of ground-glass opacity were still shown in the whole lung fields, suggestive of BO (Fig. 1C). Two months after discharge, mild subcostal retraction and rales remained bilaterally, but his development was normal.

### Discussion

Transmission of CMV to newborn infants occurs postnatally by ingestion of CMV-positive breast-milk or infected blood transfusion<sup>1,7</sup>. Approximately 9-88% of seropositive women shed CMV into their milk, and approximately 50-60% of infants fed breast-milk that contains

the virus become infected<sup>8</sup>. The best test for diagnosis of congenital or perinatal CMV infection is isolation of the virus or demonstration of CMV genetic material by PCR from urine or saliva of newborn infants<sup>9</sup>. Because the virus is isolated from infants within the first three weeks of life in congenital CMV infection, it is sometimes difficult to differentiate between congenital infection and perinatal infection in infants more than three weeks of age, unless unique clinical features such as chorioretinitis, intracranial calcification, microcephaly, and/or hearing loss are present<sup>1</sup>. Although a four-fold rise in IgG titer in paired sera or a strong-positive IgM anti-CMV may be a common finding suggesting infection, serologic assays cannot confirm the diagnosis of CMV infection in neonates because IgG anti-CMV detected in newborn infants reflects transplacentally acquired maternal antibody, which can persist for up to 18 months of age<sup>1,2</sup>. Further, IgM assay has both false-positives and false-negatives<sup>10</sup>. Treatment with ganciclovir for a six-week course can be considered for symptomatic infants with congenital CMV infection involving the central nervous system (CNS), but cannot be routinely recommended<sup>1</sup>. However, ganciclovir may be beneficial in critically ill infants with symptomatic perinatal CMV infection<sup>11</sup>.

Adenovirus has been documented as the leading infectious cause of BO worldwide<sup>5,6</sup>. Less common infectious causes of BO are RSV, measles, influenza, parainfluenza, and *Mycoplasma pneumoniae*<sup>5,6</sup>. Patients with severe adenovirus pneumonia have been shown to have immune complexes containing adenovirus antigen in the lung and increased levels of interleukin (IL)-6, IL-8, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )<sup>12,13</sup>. A recent study showed correlated, increased levels of neutrophils and IL-8 in bronchoalveolar lavage fluid from patients with BO following measles, suggesting a role for IL-8 as a chemoattractant and activator of neutrophils. In addition, the authors reported increased levels of CD8 $\beta$  T-cells, suggesting a role for T-lymphocytic inflammation in the pathogenesis of BO<sup>14</sup>. The diagnosis of BO in children can be made with confidence based on clinical presentation, fixed obstructive lung disease on pulmonary function testing, and characteristic changes of mosaic perfusion, vascular attenuation, and



**Fig. 1.** A 37-day-old male presenting to hospital with cough and rhinorrhea. (A) Supine anteroposterior chest radiography shows patch consolidations with ill-defined nodules in both lung fields. (B) On the chest CT, bilateral ground-glass opacities, areas of consolidation (arrow), and small centrilobular opacities (arrowheads) are shown in both lung fields, suggestive of bronchiolitis obliterans. (C) CT scans obtained after 6 weeks show a decrease in both the extent of consolidations and number of centrilobular nodules. However, the patch areas of ground-glass opacity are shown in the whole lung fields.

central bronchiectasis on chest high-resolution computed tomography (HRCT)<sup>5</sup>. In fact, the diagnosis of BO may have been missed by lung biopsy due to sampling error, as previously reported<sup>15</sup>. No universally accepted protocol has been established for the treatment of BO<sup>5</sup>. The use of corticosteroid therapy and prolonged course of oral azithromycin may be helpful in patients with BO<sup>16,17</sup>.

In our case, the parents refused any invasive procedure because of his young age. Thus, we could not confirm CMV pneumonia by detection of CMV in bronchial aspirate or confirm BO by HRCT or lung biopsy. Nevertheless, we strongly suspected BO secondary to CMV infection

because his respiratory difficulty and abnormal findings on chest radiography were markedly improved following ganciclovir therapy.

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