Neonatal Adenoviral Pneumonia - Report of Three Autopsy Cases -

Adenovirus pneumonia, while common in infancy and childhood, is rarely documented but may be fatal in the neonatal period. In regard to the serious outcome and no responsiveness to common ant-viral agents, adenovirus infection should be considered in the differential diagnosis of pneumonia in neonates. We report three cases of fatal neonatal adenovirus pneumonia, all of which were diagnosed by postmortem examination. Two patients were born by cesarean section at 35 or 36 weeks of gestation, and the other was a 5100 gm postmature baby born by vaginal delivery at 43 weeks of gestation. Respiratory insufficiency was detected just after birth or in the immediate postnatal period, and was associated with lethargy and chest X-ray findings of pneumonic infiltration. The postmortem findings of these patients were remarkably consistent and characterized by predominant lung involvement. The lungs showed diffuse massive consolidation with scattered patchy hemorrhage, and histologically revealed multifocal necrotizing alveolitis and/or bronchiolitis, often with hemorrhage. Alveolar lining cells and desquamated cells contained numerous smudge cells and many cells with characteristic inclusion bodies. Electron microscopy revealed that these inclusion bodies consisted of arrays of icosahedral particles of adenovirus. It is unusual that one of the patients, who was born by cesarean section without any evidence of prenatal infection, developed adenoviral pneumonia; this indicates that infection may occur in the immediate postnatal period as well as during passage of the birth canal.
(JKMS 1997; 12: 146~50)

Key Words : *Adenovirus, Pneumonia, Neonate*

Jung-Sun Kim, M.D., Hye Seung Han, M.D., Sun Hoo Park, M.D., Yi Kyeong Chun, M.D., Hoan Jong Lee, M.D.*, and Je G. Chi, M.D.

Department of Pathology and Pediatrics*, Seoul National University College of Medicine, Seoul, Korea

Received : October 15, 1996
Accepted : January 11, 1997

Address for correspondence
Je G. Chi, M.D., Department of Pathology, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-799, Korea
Tel : 02-760-3540, Fax : 02-741-6195

INTRODUCTION

Viruses are responsible for the majority of lower respiratory infections in childhood, including early infancy (1). Adenovirus infection, while common in infancy and childhood, occurs relatively rarely in the neonatal period (2~5). This type of pneumonia may be fatal; it accounted for all of the deaths in a series of viral pneumonia cases in neonates (1). In regard to the serious outcome and no responsiveness to common anti-viral agents, adenovirus infection should be considered in the differential diagnosis of pneumonia in neonates (2). We report three cases of fatal neonatal adenovirus pneumonia, each occurring at a different time, and all diagnosed by postmortem examination.

CASE REPORT

The clinical presentation of each case is summarized in Table 1.

Case 1. A 25-day-old male baby was admitted with dyspnea and lethargy. Because of suspected congenital anomaly, he had been delivered by cesarean section at 36 weeks of gestation. There is no evidence of prenatal infection such as premature rupture of membrane or fetal distress. Dyspnea and systolic murmur were detected on the third day of life. On admission, the body weight was 2,700 gm ; pulse rate was 130 per minute ; respiratory rate was 40 per minute ; temperature was 37.2℃ ; blood pressure was 67/38 mmHg. Arterial blood gas analysis revealed the pH 7.38, pCO_2 85 mmHg, pO_2 51 mmHg, BE 22.1 mmol/l, and O_2 saturation 83%. A chest roentgenogram revealed bilateral pneumonic infiltration. The hemoglobin was 8.7 g/dl, and the white blood cell count was 30,000/mm^3. Serum glutamic oxaloacetic transaminase and glutamic pyruvic transaminase levels were 42 IU/l and 17 IU/l, respectively. *Enterobacter cloacae* was cultured from a series of blood cultures. In spite of the treatment by ceftazidime and amikin, respiratory distress progressed and there was persistent fever. The infant also showed manifestations of disseminated intravascular

Table 1. Clinical data of present 3 neonates with adenoviral pneumonia

	Case 1	Case 2	Case 3
Maternal history	Well	PROM	Well
Route of delivery	CS	CS	V
Gestational age (weeks)	36	35	43
Sex	M	F	F
Body weight (gm)	2,700	1,830	5,100
Apgar score (1/5 min)	not available	2/6	2/7
Onset of symptom (day)	3	0	0
Presenting symptoms	Dyspnea, lethargy	Dyspnea, lethargy	Respiratory distress
Age at death (day)	29	20	30
WBC count (/mm^3)	30,000	27,000	not available
Coagulopathy	+	+	+

PROM indicates premature rupture of membrane; CS, cesarean section; V, vaginal delivery.

coagulopathy. After a series of clinical findings of renal failure and an episode of generalized seizure, he died on the 29th day of life.

Case 2. Due to premature rupture of membrane and placenta previa, a female baby was delivered to a 26-year-old woman by cesarean section at 35 weeks of gestation. At birth, the infant weighed 1830 gm and had Apgar scores of 2 and 6 at 1 and 5 minutes, respectively. Dyspnea progressed with cyanosis, necessitating ventilator care. Arterial blood gas analysis revealed the pH 7.06, pCO_2 64.5 mmHg, pO_2 13.4 mmHg, BE -14.0 mmol/l, and O_2 saturation 38.8%. The white blood cell count was 24,700/mm^3. A chest roentgenogram suggested hyaline membrane disease. After ventilator care from the second to the eighth day of life, respiratory difficulty improved, only to recur with pneumonic infiltration on X-ray at the twelfth day. Pseudomonas was cultured from the endotracheal tube. Several blood cultures were negative for bacteria. Though the infant was treated with ceftazidime and amikacin, she continued deteriorated with lethargy, leukocytosis, thrombocytopenia, and oliguria. She expired on the 20th day of life.

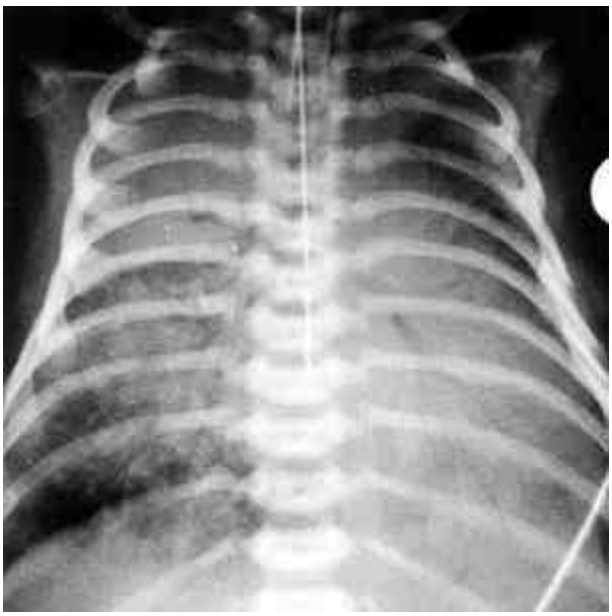

Fig. 1. The chest X-ray showed bilateral pneumonia and cardiomegaly with increased pulmonary vasculature (case 3).

Case 3. A female baby, weighing 5100 gm, was born by spontaneous vaginal delivery at 43 weeks of gestation. The mother had been in good health. Meconium staining and multiple fractures of the right humerus and left clavicle were observed. The baby had Apgar scores of 2 and 7 at 1 and 5 minutes, respectively. She developed respiratory distress soon after birth with a respiratory rate of 75 per minute. A chest X-ray showed bilateral pneumonia and cardiomegaly with increased pulmonary vasculature (Fig. 1). An echocardiogram on the 14th hospitalization revealed a 8 mm-sized patent ductus arteriosus, mild tricuspid regurgitation, aortic narrowing at the isthmic portion, a patent foramen ovale, and concentric hypertrophy of the left ventricle. In spite of antibiotic therapy, she showed no clinical improvement. From the 24th hospital day, she was progressively deteriorated, and died on the 30th hospital day.

On postmortem examination, the lungs of all cases showed massive diffuse consolidation with yellowish nodules and multifocal hemorrhage (Fig. 2). In cases 1 and 2, pleural and pericardial effusion was noted. Microscopically, alveolar spaces were filled with necrotic debris and inflammatory cells, especially polymorphonuclear leukocytes. Some alveoli were lined by eosinophilic amorphous material and showed scattered fresh hemorrhage. Frequently amphophilic intranuclear inclusions were seen in proliferating pneumocytes and des-

Fig. 2. The cut surface of the lung revealed multiple consolidated patchy areas with focal hemorrhage (case 3).

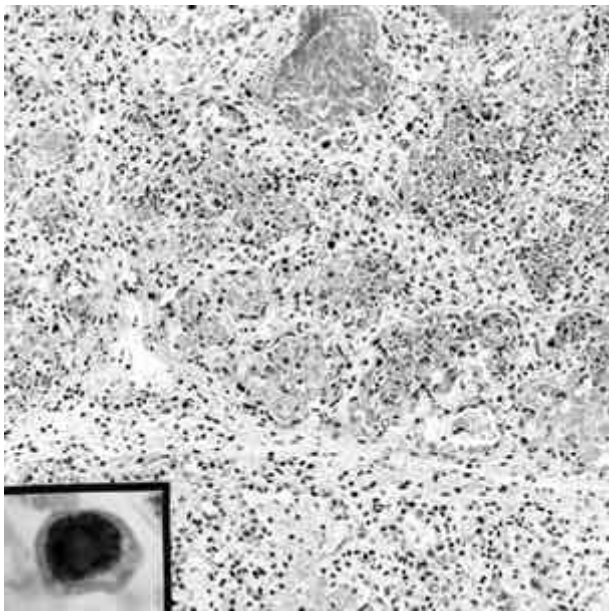

Fig. 3. The alveoli were filled with necrotic exudates, cell debris, and inflammatory cells, in which some desquamated cells were enlarged with amphophilic intranuclear inclusion (inset) (case 1).

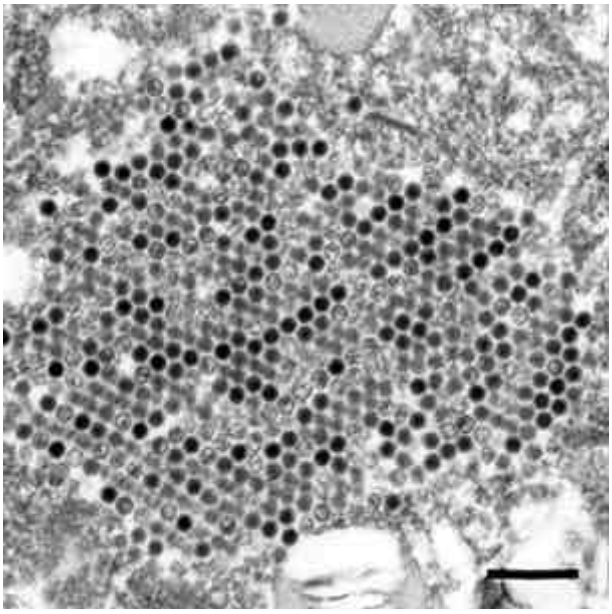

Fig. 4. Ultrastructurally, the characteristic crystalline arrays of adenovirus were detected in the nuclei or cytoplasm of pneumocytes (case 1). Bar indicates 400μm.

quamated cells in the alveoli (Fig. 3), and there were also numerous smudge basophilic cells in the consolidated portion. The bronchial walls were infiltrated by inflammatory cells with focal ulceration. Electron microscopic examination revealed crystalline arrays of icosahedral particles of adenovirus in the nucleus and occasionally in the cytoplasm of pneumocytes in all cases (Fig. 4). In addition, case 1 showed the evidences of sepsis and disseminated intravascular coagulation in multiple organs, including fibrin thrombi in blood vessels, hemorrhagic gastropathy, acute tubular necrosis, thymic involution, and hypoxic ischemic encephalopathy. The liver showed hemosiderosis and fatty change. The brain showed agenesis of the corpus callosum and congenital hydrocephalus. The ductus arteriosus and foramen ovale were patent. Case 2 revealed a patent ductus arteriosus, endocardial fibroelastosis, and centrilobular necrosis and fatty change of the liver. The heart of case 3 revealed a large patent ductus arteriosus, tubular hypoplasia of the aortic arch, endocardial fibroelastosis, and necrosis of papillary muscle. The left kidney showed hemorrhagic infarct of the medulla, with an organizing thrombus in the right renal vein. Multiple petechial hemorrhages were observed in the mucosa of the gastrointestinal tract and urinary bladder.

DISCUSSION

Adenoviruses are 65 to 90 nm-sized, nonenveloped viruses whose genomes consist of double-stranded DNA (6). Many adenovirus infections are subclinical. The adenovirus produces diseases in the respiratory tract, eye, gastrointestinal tract, and urinary bladder. Other organs, such as the central nervous system, may occasionally be

affected. About one-third of the 41 known human serotypes are responsible for most cases of human adenovirus disease (7).

The majority of lower respiratory infections in childhood, including early infancy, are caused by viruses (1). Paisley et al. (8) reported that viruses were responsible for 79% of pneumonias in neonates ; the most common viral pathogen causing pneumonia in neonates was found to be the respiratory syncytial virus (55%), followed by the enterovirus (15%), rhinovirus (15%), adenovirus (10%), parainfluenza virus (7.5%), and the herpes simplex virus (5%) (1). Adenoviral infection, while common in infants and children, occurs relatively rarely in neonates, except during sharply defined epidemics (2~5). The rarity of neonatal adenovirus pneumonia is presumably due to the presence of transplacentally acquired serum adenovirus antibodies (9). Several reports including our cases, in which adenovirus pneumonia was confirmed only after autopsy and was not suspected clinically, suggest that adenovirus infection may occur more frequently in neonates than is generally expected (2, 4, 5).

Neonates with adenoviral pneumonia develop symptoms earlier than patients with other viral pneumonias. The mean onset of adenoviral pneumonia is 6.8 days after birth, while that of other viral pneumonia is 17.1 days ($p=0.02$) (1). In our cases, the onset of symptom occurred within three days after birth. In contrast to the relatively late onset of other viral pneumonias, the early onset of adenoviral pneumonia suggests that the adenovirus may be acquired at or near the time of birth. Several reports suggest that adenoviral infection develops via the birth canal, since most newborns with adenoviral pneumonia were delivered by vaginal route or encountered prenatal problems such as premature rupture of the membrane in cases by cesarean section (2, 3, 10). One of our cases (case 1), however, was born via cesarean section without any prenatal problem, and this suggests that infection might occur during the immediate postnatal period.

Clinical symptoms and signs are nonspecific. Infants with adenovirus infection described by Abzug et al. (1), were lethargic and coughing was not a feature, and these findings were true in our cases. This type of pneumonia manifests radiologically as patchy or confluent pulmonary consolidation, usually seen in bacterial pneumonia, more frequently than other viral pneumonias (11). Neonatal adenoviral pneumonia may be fatal ; it accounted for all of the deaths in a series of viral pneumonia cases in neonates (1). In addition, the devastating potential of adenovirus disease in newborns has been described in several reports (2, 12). Diagnosis is usually based on a demonstrable rise in serum antibody titer or isolation of the virus from nasal or tracheal aspirates. Rapid diagnosis is also possible by immunofluorescent or immunohistochemical studies of aspirates with a monoclonal pan-adenovirus anticapsid protein (2, 13).

The histopathologic findings of adenovirus pneumonia were first described by Goodpasture et al. (14). Microscopically, the involved lungs present with necrotizing bronchopneumonia with hemorrhage. Because of infiltrates of polymorphonuclear leukocytes and deposition of necrotic debris in alveoli, it can be difficult to differentiate it from bacterial pneumonia, rather than from viral pneumonia mainly showing mononuclear cell infiltrates. Pneumocytes and desquamated cells with amphophilic intranuclear inclusions and the appearance of smudge cells are so characteristic to make the diagnosis (15). Out of viral pneumonias, herpes pneumonia has to be considered in differential diagnosis because it occasionally present with necrotizing tracheobronchitis and bronchopneumonia with the intranuclear inclusions similar to those of adenoviral infection (16). It is helpful to diagnose that herpes pneumonia shows the typical "ground glass" appearance of the nuclei and no smudge cells. In all our cases, definite diagnosis was also made by electron microscopy. The ultrastructural appearance of the adenovirus is unique. the virus is organized into small crystalline arrays within the nuclei, and the diameter of individual virions ranges from 65 to 90 nm (17). Other viruses that form intracellular crystalline arrays, such as the poliovirus and coxsackie virus, are much smaller in the order of 23nm in diameter (18). The diagnosis of adenovirus infection using DNA hybridization performed in situ and polymerase chain reaction on fixed tissues recently became feasible (2, 19, 20). These methods can be used to confirm a specific viral infection in cases showing non-diagnostic histologic features (21). In cases of disseminated adenoviral infection, pathologic changes could be detected in the liver and the brain in addition to the lung (10, 22). The liver was enlarged and congested, and frequently contained areas of inflammation and/or necrosis. Abnormalities in the brain included congestion, gliosis, and focal hemorrhage. These liver and brain findings may be due to the adenovirus itself, as well as, to disseminated intravascular coagulopathy.

Adenovirus infection does not respond to interferon or other present-day antiviral drugs, although type-specific hyperimmune serum could be effective if administered early in the infection. For this reason and because of the often fatal outcome of this disease, its possibility should be considered in the differential diagnosis of pneumonia in neonates and infants in spite of its rarity (2). We therefore suggest that tracheal aspirate for viral culture and viral antigen detection should be obtained from neonates with unexplained respiratory disease (3).

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