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Fatal Adenoviral (Type 7) Respiratory Disease in Neonates

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Two cases of fatal neonatal adenoviral type 7 respiratory disease are described. The clinical, laboratory, x-ray, and pathological features of these two neonates and those reported in the literature are highlighted. Suggestions are made regarding how to diagnose this disease early so that the patients can be isolated and further spread of the disease prevented.

BRONCHOPNEUMONIA and chronic pulmonary disease in infants and young children are known to be caused by various types of adenoviruses, particularly type 21.[1–4] Adenovirus type 7 and type 3 also have been involved in serious and sometimes fatal lung disease in infants and children.[5–10] However, adenoviral infection occurs relatively rarely in neonates, except during sharply defined epidemics. Fatal adenoviral respiratory disease has been reported in term and preterm neonates.[11,12] The purpose of this communication is to report two more isolated cases of fatal neonatal respiratory disease caused by adenovirus type 7. The clinical, laboratory, roentgenologic, and pathologic features of these two cases and other neonatal cases reviewed from the literature will be described.

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Case Reports

Case 1. A 4.3-kg, term, white male infant was born by spontaneous vaginal delivery ten hours after rupture of membranes and with meconium-stained amniotic fluid. The Apgar score was 4 and 8 at one and five minutes. The mother had no antenatal, natal, or postnatal problems. The infant developed symptoms and signs consistent with meconium aspiration syndrome which resolved by the 4th day, except for persistence of tachypnea. He became febrile (100–100.2°F) from the 6th day onwards, and on the 10th day his temperature was 103°F. Blood, cerebrospinal fluid, tracheal aspirate, and stool were sent for bacterial and viral culture, and he was started on chloramphenicol. Cerebrospinal fluid analysis was normal. His condition deteriorated, and he was transferred to the intensive care unit. By the 16th day, the infant was on 100% oxygen with maximal ventilatory support, and chest x-ray showed bilateral diffuse infiltrates (Fig. 1). Prothrombin time was 13.2 seconds (control 12 seconds), partial thromboplastin time 87.5 seconds (control 28.8 seconds), fibrinogen 95 mg/dl, SGOT 545 u/l, and SGPT 122 u/l. All initial and subsequent cultures were negative, except for *Candida albicans* in the gastric as-

pirate. On the 18th day, while on artificial ventilation, physical examination revealed no murmur and no organomegaly. Chest x-ray showed massive consolidation of both lungs. CSF analysis was normal. The infant expired the next day. The results of WBC counts, with differentials and platelet counts done at various days of age, are given in Table 1.

Adenovirus type 7 was isolated from the TA obtained on the 10th and 14th days of age. Blood, cerebrospinal fluid, and stool cultures were negative.

Pathological examination. The lungs showed marked fibrinous airway and interstitial pneumonitis with focal interstitial fibrosis and red refractile (probably viral) inclusions in reactive alveolar lining cells and fibrinous pleuritis. Widespread mycotic ulcerations were seen in the trachea with penetration of the organism to the cartilage (morphology consistent with *Candida*).

Examination of the heart revealed pericardial effusion and patent ductus arteriosus.

The liver and spleen were enlarged and congested with ischemic infarcts.

The brain showed widespread gliosis of the cerebral white matter, and focal subarachnoid hemorrhages of the left temporal lobe-tip and the cerebellar hemispheres.

Case 2. A 1.9-kg, white female infant was born by spontaneous vaginal delivery, with rupture of membranes for 7½ hours and clear amniotic fluid. Apgar score was 7 and 7 at one and five minutes. Physical examination revealed a female infant of 34 weeks gestation with grunting and nasal flaring. The infant received routine care and developed mild jaundice, which was controlled with phototherapy. On the 5th day, she was lethargic and developed apnea and bradycardia (without cyanosis) responding to mild stimulation. A blood culture and spinal tap were done. Cerebrospinal fluid analysis was normal. Chest x-ray was unremarkable. She was started on penicillin and kanamycin. At the 8th day of age, the infant was lethargic and slightly dusky with mild retractions, and was vomiting formula. Chest x-ray showed extensive perihilar granular pattern with air bronchogram in the left upper lobe. Blood gases showed mild hypoxia and respiratory acidosis.

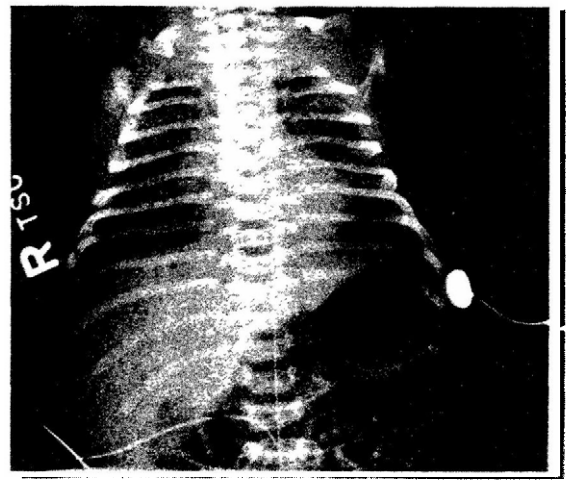

FIG. 1. Chest x-ray (anteroposterior view) showing bilateral diffuse opacities. There are diffuse air bronchograms.

The infant was placed on a ventilator with 30% oxygen. Penicillin was discontinued, and ampicillin was started. Blood, spinal fluid, and tracheal aspirates were sent for bacterial and viral culture. Cerebrospinal fluid results were normal. By the 11th day, the infant required more oxygen and ventilatory support. Physical examination revealed bilateral rales and liver enlargement, and chest x-ray showed bilateral diffuse interstitial infiltrates. Cardiac evaluation was normal. The infant continued to deteriorate despite multiple antibiotics, oxygen, and maximal ventilatory support. SGOT was 385 u/l and SGPT 92 u/l. The infant expired on the 14th day. The results of WBC counts, with differentials and platelet counts done at various days of age, are given in Table 1. Adenovirus type 7 was isolated from the pooled (8th to 11th day) tracheal aspirates. The cerebrospinal fluid was negative.

Pathological examination. The lungs showed extensive intra-alveolar thickening, fibrin deposition, and cellular disquamation. The interstitium was thickened with

TABLE 1. *The White Blood Cell Counts, with Differential and Platelet Counts of the Neonates at Various Days of Age*

	Age (days)	Leukocytes (/cu mm)	Bands (%)	Segmented (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Platelets (/cu mm)
Case 1								
	1	17,100	14	31	49	3	3	
	10	10,400	6	48	45	1		70,000
	13	8,100	22 (2)*	48	27	11		79,000
	18	21,300	40	30	28	2		50,000
Case 2								
	1	16,600	12	49	35	2		215,000
	5	14,600	37	43	15	5		175,000
	8	18,700	44 (2*, 2†)	26		25	1	
	13	16,200	38 (3*, 4†)	34	21			59,000

* Number of metamyelocytes.

† Number of myelocytes.

chronic inflammatory cells, and red refractile intranuclear inclusions were found. Examination of the liver revealed congestion with no evidence of inflammation. Focal areas of congestion and vascular engorgement were seen in the brain studies.

Discussion

Epidemics of adenoviral illness have been reported in newborns.[13] The manifestations of the illness varied from stuffy nose syndrome caused by type 1 virus to mild diarrhea caused by type 3. Adenovirus type 7 also has been involved in serious and sometimes fatal lung disease in neonates, infants, and children.[8–11] The lung is the most frequently involved organ with type 7 infection. The infants present with severe respiratory disease that, initially, closely resembles respiratory distress syndrome.

The salient features of neonatal adenoviral infection as seen in our infants and those described in the literature are as follows: 1) Temperature instability—term infants tend to have elevated temperatures (101° to 103°F). Premature infants may or may not demonstrate any temperature instability; 2) lethargy; 3) progressive respiratory disease manifested by tachypnea, cyanosis, bilateral rales, and x-ray evidence of bilateral diffuse, interstitial, and alveolar infiltrates, leading to respiratory failure; 4) hepatomegaly, which was evident clinically or on pathological examination on all the infants, and clinically mildly elevated liver enzymes were noted in both of our infants; 5) WBC counts, revealing marked shift to the left with or without leukocytosis; 6) thrombocytopenia, with or without disseminated intravascular coagulations; 7) fibrinous intraalveolar and interstitial desquamative disease with hyaline (red refractile) intranuclear inclusion bodies on pathological examination of the lungs; and 8) isolation of virus from either tracheal aspirate or lung tissue.

The diagnosis of adenoviral infection also can be made by rising complement-fixation antibody titers. Adenovirus can be rapidly detected in respiratory secretion of immunofluorescence technique,[14] by radioimmunoassay (which is convenient and sensitive in the detection of the adenovirus), and by enzymatic assays which are comparable in convenience and sensitivity to radioimmunoassay.[15] The infants reported here were born approximately six months apart. To our knowledge, there were no other adenovirus (type 7) isolates at the time. Both infants were symptomatic by the 5th to 6th day of life, which is within the range of the incubation period. We assume that the infection was acquired at birth, probably by passage through the birth canal, but we did not obtain viral cultures from the mothers. Both mothers were well in the perinatal period. Adenoviruses may be found in the stools and urine in the absence of diarrhea and with or without respiratory symptoms,[16,17] and infants born to such mothers may be potentially at risk for contracting the disease. Maternal antibodies acquired transplacentally may not completely protect against clinical disease.[13]

Neonates presenting with unexplained progressive respiratory disease with elevated band counts, thrombocytopenia, and x-ray evidence of diffuse bilateral interstitial or alveolar disease should have tracheal aspirate obtained for viral cultures and viral antigen detection.

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