Pediatr Radiol (1993) 23: 373–375

Pediatric Radiology

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Surfactant protein B deficiency: radiographic manifestations

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Received: 25 January 1993/Accepted: 22 March 1993

Abstract. Surfactant is a complex structure primarily composed of phospholipids, but containing essential proteins as well. Congenital deficiency of Surfactant Protein-B (SPB) has recently been documented for the first time in two siblings. The pathologic findings in these infants was that of congenital pulmonary alveolar proteinosis and the radiographic manifestations were strikingly similar to hyaline membrane disease.

Pulmonary surfactant is primarily a phospholipid, but contains multiple proteins and glycoproteins. Deficiency of surfactant in premature infants is the major cause of hyaline membrane disease. Congenital pulmonary alveolar proteinosis is a very rare condition differing pathologically and clinically from alveolar proteinosis of older infants, and thought to be due to a defect in surfactant processing [1]. We wish to report the radiographic findings of two siblings who died of respiratory failure in the neonatal period who had congenital pulmonary alveolar proteinosis and were found to have deficiency of surfactant protein B (SP-B).

Case reports

Case 1

LB was a 3.6 kg full term male, the product of an uncomplicated pregnancy in a 35-year-old gravity 8, para 4, abortus 3 with 3 living children and 3 spontaneous abortions. One live born child died of presumed hyaline membrane disease at 1 month of age. LB was delivered by cesarean section because of failure of progression of labor. Although the Apgars were 8 and 9 at 1 and 5 min, the child developed severe respiratory distress by 10 min. An X-ray obtained at the outside hospital demonstrated bilateral granular infiltrates suggestive of hyaline membrane disease in this term infant (Fig. 1 a). The child was transferred to the neonatal intensive care unit at St. Louis Children's Hospital. More marked ground glass infiltrates were present. Because of failure to respond to maximum medical management of presumed hyaline membrane disease, the patient was placed on extra-corporal membrane oxygenation (ECMO). An additional attempt to wean off ECMO at 8 days (Fig. 1 b) was unsuccessful. However, by increasing dexamethasone dosage the child was weaned off ECMO and returned to respirator therapy. A echocardiogram seven days later was normal. Respiratory therapy continued requiring high ventilatory pressures. All attempts to wean from the ventilator were unsuccessful. The child was then begun on surfactant replacement therapy. However, no significant improvement occurred and at 3 months of age (Fig. 1 c) a lung biopsy was performed. There were pale, eosinophilic proteinaceous secretions and foamy macrophages in the distal air spaces. In addition there was extensive pulmonary interstitial fibrosis. The flocculent material stained periodic-acid-Schiff positive. Gomori methenamine silver and acid fast stains were negative for micro-organisms. Electron microscopy did not demonstrate tubular myelin. These findings were diagnostic of congenital pulmonary alveolar proteinosis. Lung biopsy material was also examined for surfactant and its components and for messenger RNA of surfactant proteins. This revealed increased amount of surfactant protein C and complete absence of surfactant protein B as well as surfactant protein B messenger RNA (mRNA). The details of the immunologic tests for surfactant protein B in these infants are the subject of a prior report [2]. In view of the pulmonary fibrosis and poor respiratory status it was decided the child could not survive pulmonary lavage. Mechanical ventilation was maintained. However, an acute respiratory decompensation occurred at $5^1/_2$ months and the child died.

Case 2

DL, the next-born sibling of Patient # 1 was delivered by cesarean section for prolapsed cord approximately 1 year later. Born after a 40 week gestation he weighed 4.2 kg. Amniocentesis on two occasions during the pregnancy was performed because of findings in Patient # 1. The amniotic fluid demonstrated no evidence of SP-B on either occasion. Apgars were 7 and 8 at 1 and 5 minutes. However, worsening respiratory distress began within minutes. Chest radiographs demonstrated a pattern similar to infant # 1 with diffuse granular infiltrates (Fig. 2 a). The child was intubated but worsening pulmonary status even on prolonged surfactant therapy lead to ECMO. The patient died at 3 weeks of age on ECMO (Fig. 2 b) with deteriorating neurological function. Autopsy in this infant also demonstrated pulmonary findings of congenital pulmonary alveolar proteinosis.

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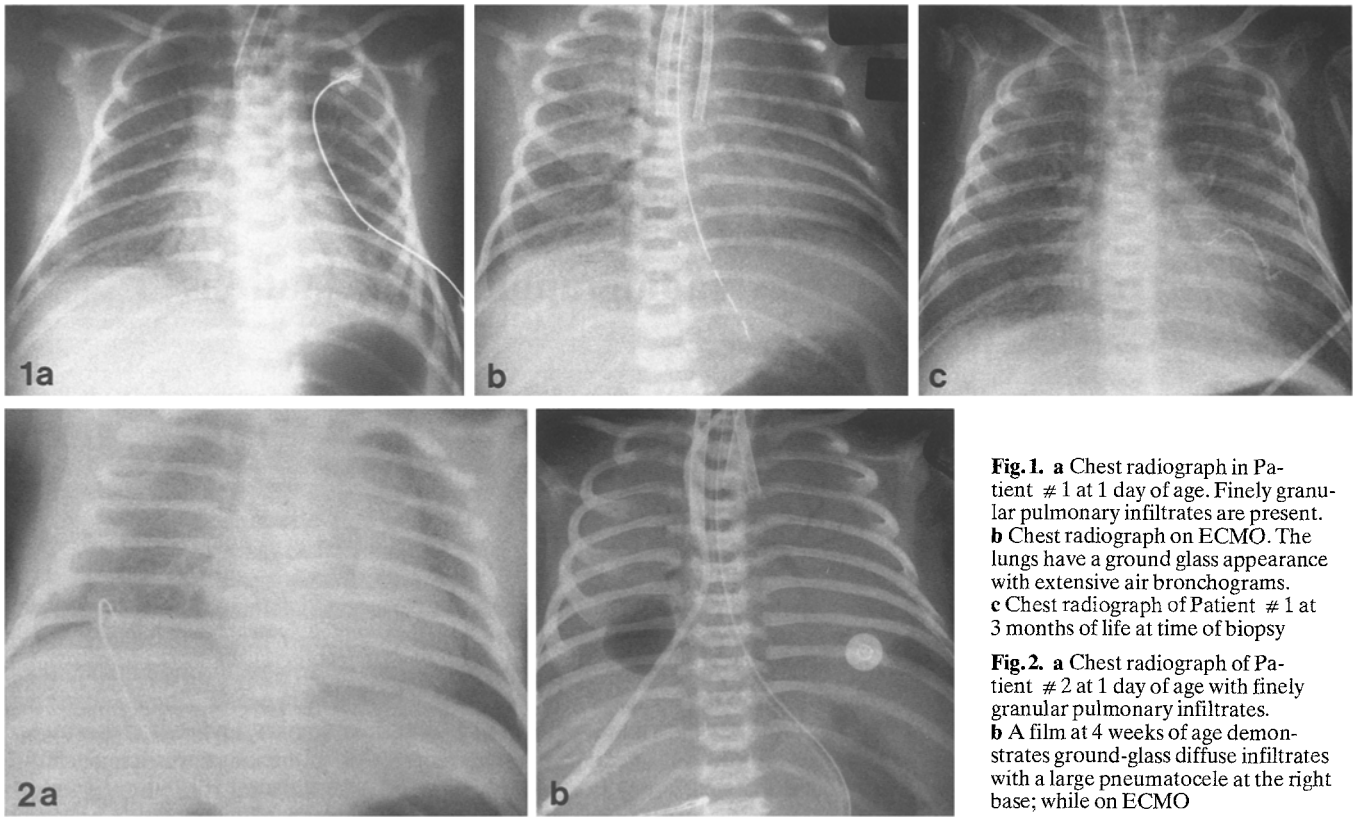

Fig. 1. **a** Chest radiograph in Patient # 1 at 1 day of age. Finely granular pulmonary infiltrates are present. **b** Chest radiograph on ECMO. The lungs have a ground glass appearance with extensive air bronchograms. **c** Chest radiograph of Patient # 1 at 3 months of life at time of biopsy

Fig. 2. **a** Chest radiograph of Patient # 2 at 1 day of age with finely granular pulmonary infiltrates. **b** A film at 4 weeks of age demonstrates ground-glass diffuse infiltrates with a large pneumatocele at the right base; while on ECMO

Discussion

Congenital pulmonary alveolar proteinosis (CPAP) is a very rare disease described in approximately twenty patients in the first days of life with normal immune function [1, 3–5]. CPAP presents as severe, persistent, unresponsive respiratory distress at birth which has been uniformly fatal [1]. CPAP has been thought to be an autosomal recessive condition [1].

CPAP differs in several significant ways from pulmonary alveolar proteinosis (PAP). PAP in older children presents most often as failure to thrive, immune deficiency, particularly thymic alymphoplasia, recurrent infections but not initially as respiratory distress [6, 7]. PAP originally described by Rosen [8] in 1958 is characterized by the accumulation of lipoproteinaceous material in the alveoli and distal airways of older children and adults. This amorphous material contains lipid, protein and carbohydrate with positive periodic-acid-Schiff staining. In PAP patients multilamellated structures are present in the alveoli and called tubular myelin because of their resemblance to normal tubular myelin secreted by type II pneumocytes. This material is not present in neonates with CPAP. Interestingly surfactant protein B is necessary to form normal tubular myelin [9].

Surfactant protein B is an 8,000 Dalton molecular weight hydrophobic protein synthesized by alveolar type II pneumocytes. The surfactant protein B mRNA is only expressed in lung tissue and is detectable in lung tissue at 13 weeks of gestation and becomes increasingly abundant with advance in gestational age reaching 50% of adult levels by 24 weeks of gestation [2, 10–14]. Therefore, it appears that our case and perhaps other cases of CPAP is associated with and probably due to deficiency of surfactant protein B.

The striking similarity of the radiographic findings of infants with CPAP to hyaline membrane disease has been commented upon previously [1]. This similarity is particularly interesting and perhaps not unexpected given the biochemical abnormality demonstrated in these infants. The radiographic finding of granular lungs with air bronchograms resembling hyaline membrane disease persisted longer (greater than 3 months) than these would have in hyaline membrane disease. This persistence in surfactant protein B deficiency may be due to the continued production of abnormal surfactant which fills the alveoli resulting in a prolonged appearance resembling hyaline membrane disease. This persistent finding of granularity with air bronchograms may be helpful in distinguishing hyaline membrane disease from surfactant protein B deficiency. Although a rare disease, CPAP with surfactant protein B deficiency should be considered in full term infants with persistent pulmonary disease resembling hyaline membrane disease particularly if there is a history of prior respiratory deaths of full-term newborns siblings.

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Continued from p. 368

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continued on p. 383