CASE REPORT

Pulmonary Alveolar Proteinosis

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Manuscript received: February 6, 2008; Initial review: March 5, 2008; Accepted: May 26, 2008.

Pulmonary alveolar proteinosis is a rare cause of respiratory distress in neonates. We present a 4-month-old infant who presented with progressive respiratory distress since birth and failure to thrive. He was initially treated as a case of diffuse alveolar disease but on open lung biopsy was diagnosed as pulmonary alveolar proteinosis. The child expired at 7 months of age.

Key words: *Pulmonary alveolar proteinosis, Surfactant protein B deficiency.*

Pulmonary alveolar proteinosis is a rare cause of lung dysfunction and respiratory distress in term neonates(1). In several cases, a deficiency or insufficiency of surfactant protein B (SP-B) has been caused by a frame shift mutation in the gene encoding SP-B(2). Mortality rate in infants is 100% on conventional treatment. The only treatment available is lung transplantation.

CASE REPORT

We present a 4 months old male child born of non-consanguineous marriage as a preterm (35 weeks, birthweight 2.2 kg) by cesarean section, to a third gravida mother with history of two abortions in past. She had oligohydramnios in this pregnancy. She also had pulmonary tuberculosis prior to this pregnancy for which she received complete treatment. The baby developed respiratory distress at birth, was intubated and given surfactant. He also developed sepsis and hyperbilirubinemia requiring antibiotics and photo-therapy. He was discharged on day 10 of life. Subsequently child was well according to the parents except for poor weight gain.

He was re-hospitalized at 4 months of age with complaints of poor weight gain for 2-3 months and respiratory distress for 15 days. Chest radiograph revealed bilateral hazy lung fields (***Fig.* 1**) and was managed as bronchopneumonia. Since the child did not improve, and in view of history of tuberculosis in mother and positive Mantoux test, he was started on anti-tubercular therapy (4 drug therapy; HRZS), which he received for around 20 days. CT chest revealed diffuse opacification with air bronchogram in bilateral lung fields except in right middle lobe (***Fig.* 2**). The child did not improve, had persistent oxygen requirement, and was referred to us for further management.

At admission in pediatric intensive care unit, the child was tachypneic, with marked respiratory distress and severe hypoxemia (pH 7.28, pCO_2 51mm Hg, pO_2 34.2 mm Hg, SaO_2 59%). Flexible bronchoscopy showed diffuse congestion of the bronchi but no gross structural anomaly of airways. Broncho-alveolar lavage (BAL) fluid was milky in appearance and was negative for AFB and *Pneumocystis carinii.* Gram's stain and pyogenic culture did not yield any organism. Histopathological analysis revealed numerous lipid-laden macrophages. In view of increasing work of breathing and progressive hyper-carbia (pH 7.23, pCO_2 67 mm Hg, pO_2 100.2 mm Hg, SaO_2: 97%), the child was ventilated. Provisional diagnosis of diffuse alveolar disease was made. He was extubated after 4 days as he started showing gradual improvement. Immunological work up was done to

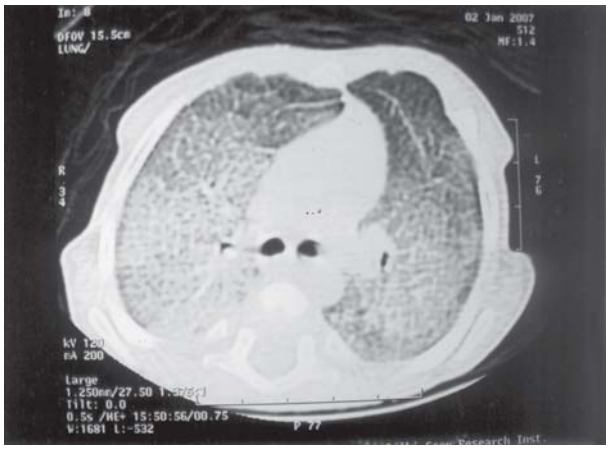

FIG.1 *Bilateral hazy lung fields.*

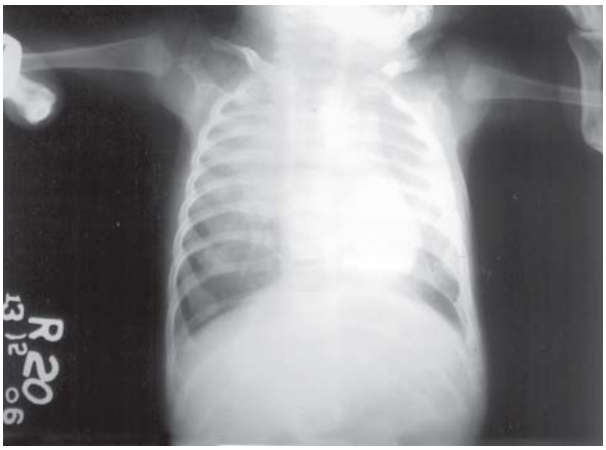

FIG.2 *Diffuse opacification with air bronchogram in bilateral lung fields except in right middle lobe.*

rule out immunodeficiency, ELISA for HIV-1, HIV-2 was negative. IgG was on lower range of normal (210, normal: 200-1000).

Tube feeds were gradually introduced and child began to gain weight and maintain saturations under oxygen (SpO_2 92-95% at a flow rate of 2-3 l/min with nasal prongs), with decrease in respiratory distress. In view of low IgG levels child was given a dose of IVIG. Further immunological work up revealed absolute lymphopenia on two occasions absolute lymphocyte count of 2914/cumm; and 1255/cumm) with decreased T cells (873/µL; normal: 2170-6500/µL) and B cells (210/µL; normal 430-3300/µL). Nitroblue Tetrazolium Test (NBT) and immunoreactive trypsin were negative. He remained stable for few days. In view of persistent O_2 dependence, open lung biopsy was done after 40 days of hospital stay. Biopsy showed many distended alveoli containing pale eosinophilic granular material and scattered foamy macrophages, some alveoli showing prominent lining cells and others showing thickening of septa. Presence of diastase resistant and PAS positive alveolar material was suggestive of alveolar proteinosis. Subsequently the child underwent repeated large volume broncho-alveolar lavages, which showed presence of PAS positive material. A trial of surfactant was also given, but there was no improvement in general condition. Baby continued to have poor weight gain with progressively decreasing oral acceptance and increasing O_2 requirements. The child was discharged on request on home O_2 therapy on 68th day after admission. A week later the parents informed about the death of their child.

DISCUSSION

Pulmonary alveolar proteinosis (PAP) is an extremely rare cause of respiratory failure in the pediatric age group that was first described in 1958(1). It is characterized by intra-alveolar accumulation of PAS positive surfactant rich material. The lung architecture is typically preserved(1). Impairment of surfactant clearance as a result of inhibition of the action of GM-CSF may underlie many acquired cases, whereas congenital disease is most commonly attributable to mutations in surfactant protein genes but may also be caused by GM-CSF receptor defects(2,3).

Our patient was a preterm baby with hyaline membrane disease requiring mechanical ventilation and surfactant therapy. The interim time period till readmission with us did not reveal history of respiratory distress, so the diagnosis of immediate-onset pulmonary alveolar proteinosis (congenital variety) cannot be ascertained. Since the child had the onset of complaints at 4 months of age so the disease was a postnatal type of PAP. The largest series of 23 children with postnatal PAP (median age of diagnosis 6 months) was reported in 2004(4). All of symptomatic infants had growth retardation and progressively appearing dyspnea.

The clinical course of congenital alveolar proteinosis and acquired PAP is different although the histopathological appearance is similar. In neonates with congenital variety, the mortality rate associated with conventional therapy is 100%(5). Lung transplantation improves survival. Disease-specific 5-year survival rates are estimated to be 88%. About 80% of deaths occur within the first 12 months. Most cases are transmitted in an autosomal recessive manner(6,7).

There is no specific treatment of PAP. The appropriate management, however, depends on the patient's age at presentation, the severity of symptoms, and the anticipated course of the disease. Mechanical ventilation is often necessary in congenital PAP. Repeated whole lung lavage is the mainstay of treatment for PAP. The aim is to eliminate the material in distal air spaces and restore the permeability of the alveolar-capillary barrier (4). There are no randomized control trials done to assess the efficacy of whole lung lavage but case reports have shown improvement in exercise tolerance and symptoms, pulmonary function, arterial oxygenation and shunt fraction. In children, there is decrease in need for oxygen, respiratory rate and weight gain(8).

The use of whole-lung lavage is less well established in young infants and newborns mainly because of the technical difficulties associated with use of large endotracheal tube(9). The use of surfactant has not been of benefit. Because congenital PAP is a single-gene defect, it may be a candidate disease for gene therapy(4). Intravenous immunoglobulin (IVIG) and GM-CSF therapy do not have a role in congenital form of disease although in adult studies they have shown benefit(4,8,10). Other options include extra-corporeal membrane oxygenation and lung transplantation(4).

Pulmonary alveolar proteinosis is a rare but important cause of respiratory distress. Differential diagnosis that needs to be considered are acute respiratory distress syndrome, interstitial pneumonitis, Pneumocystis carinii pneumonia, typical bacterial pneumonia, hypersensitivity pneumonia, bronchiolitis obliterans, and organizing pneumonia.

Contributors: All the authors were involved in all aspects of manuscript preparation.

Funding: None.

Competing interests: None stated.

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