A combination of intravenous immunoglobulin and pulse methylprednisolone extended survival in pulmonary alveolar proteinosis with chronic interstitial pneumonitis: a case report

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Summary

Pulmonary alveolar proteinosis (PAP) is characterized by intra-alveolar accumulation of lipoproteinaceous material. The severe chronic pulmonary disease and susceptibility to pulmonary infection is a prominent feature of the disease.

We reported a case of postnatal-onset PAP and chronic interstitial pneumonitis in a girl with chronic respiratory distress since she was 5 months of age. A lung biopsy confirmed the diagnosis. The therapeutic bronchoalveolar lavages, a short trial of granulocyte colony-stimulation factor (G-CSF) and a combination of low dose methylprednisolone and hydroxychloroquine were used at different times without noting satisfactory improvement. Intravenous immunoglobulin (IVIG) and pulse methylprednisolone were given monthly with gradual recovery. She did not require oxygen supplement after 21 months of this combination. Our report suggested that IVIG and pulse methylprednisolone might have a potential role in the treatment of PAP with chronic interstitial pneumonitis. *(Asian Pac J Allergy Immunol 2010;28:200-5)*

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Introduction

Pulmonary alveolar proteinosis (PAP) is a rare cause of chronic lung diseases in children. It is characterized by the accumulation of lipoproteinaceous material in the alveoli.[1-4] PAP is a heterogeneous disease. This condition has a variable clinical course, from spontaneous resolution to respiratory failure and death due to disease progression or superimposed infection.[4] Historically PAP has been categorized as either, idiopathic, acquired or adult-type PAP (90% of total cases), secondary PAP (less than 10% of total cases), or congenital PAP (2% of total cases).[3,4] Significant advances in our understanding of the molecular causes of PAP have been made in the past 10 years that may allow for a more mechanistic classification.

Bronchoalveolar lavage (BAL) with milky appearance of the returned fluid is a key diagnostic feature.[1,2] Open-lung biopsy, the gold standard for the diagnosis of PAP, reveals massive quantities of granular, proteinaceous eosinophilic periodic acid-Schiff (PAS) staining material in the alveoli. Foamy alveolar macrophages and epithelial cells hyperplasia are observed with rare interstitial fibrosis.[1,2,4] In adult-type PAP the architecture of the lung parenchyma is preserved unless there is infection.[1,2] Chest X-ray (CXR) is helpful but nonspecific. The typical CXR demonstrates diffused or patchy bilateral central and symmetric lung opacities, with sparing of the costophrenic angles and apices.[3] High resolution computed tomography (HRCT) of the

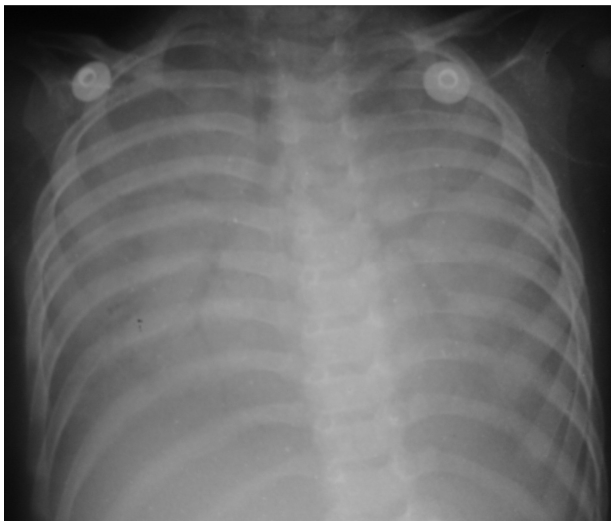

Figure 1. Chest X-ray (CXR) of this patient demonstrated diffused opacities of both lungs, indicating alveolar process. The trachea and air bronchogram were visualized.

lung shows ground glass haziness superimposed by thickened interlobular septa forming geometric shapes, the "crazy paving" pattern. This pattern is highly characteristic of PAP but it is also found in other conditions such as severe infection, heart failure and pulmonary hemorrhage.[3]

The specific treatment of PAP depends on the form.[1,2,4] Successful lung transplantation was reported in congenital PAP. The treatment in secondary PAP is to manage underlying condition or remove the offending agent. In acquired PAP, whole lung lavage (WLL), granulocyte macrophage colony stimulation factor (GM-CSF) or plasmapheresis were reported to alleviate the symptoms. Supportive treatment is important in all forms which includes supplemental oxygen, antibiotics and respiratory support.[1,2,4]

We reported a case of PAP and chronic interstitial pneumonitis. The patient did not response to bronchoalveolar lavages, a short trial of G-CSF and a combination of low dose methylprednisolone and hydroxychloroquine. Intravenous immunoglobulin (IVIG) and pulse methylprednisolone were given monthly with gradual recovery.

Case report

A 35-week-preterm baby girl was born to a healthy mother who had premature ruptured of membrane. She had no respiratory distress when she was born (APGAR score were 9 and 10).

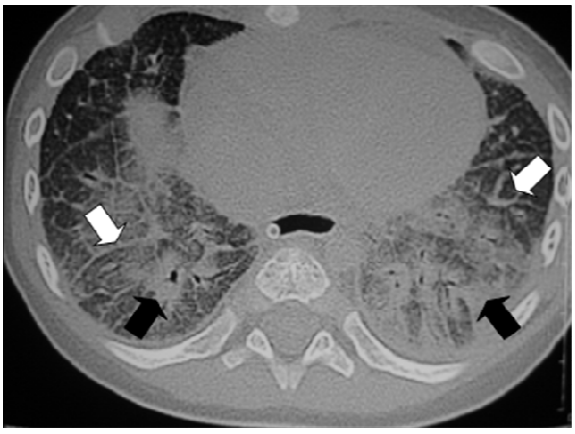

Figure 2a

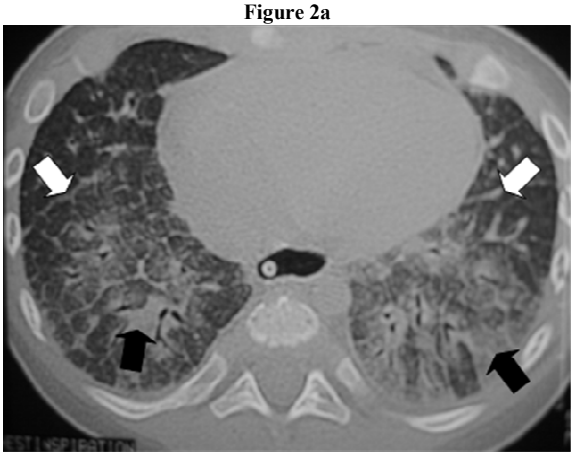

Figure 2b

Figure 2. High resolution CT scan (HRCT) of the lungs of this patient. HRCT at the lower lung level showed areas of consolidation with ground glass appearance in both lungs especially in lower lobes (Fig. 2a and 2b, black arrows). Thicken interlobular septa were demonstrated with white arrows.

On the second day of life, she developed dyspnea with cyanosis and was treated as respiratory distress syndrome. She was intubated for 5 days and required oxygen therapy for 20 days. She was discharged to home on day 39.

At 5 months of age, she was admitted to Siriraj Hospital due to dyspnea and poor feeding. She had central cyanosis (oxygen saturation was 75% in room air) which responded well to oxygen therapy. CXR revealed infiltrations in the right middle and left lower lobes. She was treated with antibiotic without any improvement. Subsequently, *Pneumocystis jiroveci* was detected from gastric wash and trimethoprim-sulphamethoxazole was given with some improvement. Follow up CXR after she was

admitted for 1 month, showed progressive bilateral haziness and alveolar consolidation (Fig.1). HRCT revealed alveolar infiltrations in both lower lung fields with mild thickening of interlobular septa along with ground glass appearance compatible with "crazy paving" pattern. (Fig.2a, 2b). Open lung biopsy demonstrated alveolar infiltration of dense granular eosinophilic material (Fig.3). This substance was compatible with surfactant since it was stained positive to PAS and resistant to diastase (glycogen was digested by diastase but lipoprotein was not). The biopsy established the diagnosis of PAP with chronic interstitial pneumonitis. Other causes of PAP were investigated. HIV antibody and antigen were negative, both cellular and antibody mediated immune functions were intact (CD4 1,700 cell/mm^3, CD8 760 cell/mm^3, IgG 1,027 mg/dl, IgA 57.6 mg/dl, IgM 158.2 mg/dl) and no hematologic malignancy was found. Plasma lysinuric protein was not detected. Genetic analysis of the genes encoding surfactant proteins B and C and member A3 of the ATP Binding Cassette family (ABCA3) did not demonstrate any muations in these genes. (L. Nogee, Johns Hopkins University School of Medicine, personal communication)

After the diagnosis was made, the patient had three episodes of respiratory failure necessitating intubation and intensive care unit (ICU) admission. The triggers were mostly viral respiratory tract infections. Prednisolone (2mg/kg/day) and hydroxychloroquine were administered since she was nine months old without clinical improvement. At 10 months of age, bronchoalveolar lavage (BAL) was performed which revealed milky-frothy fluid. WLL was attempted twice without success because she developed cyanosis during the procedures. At 11 months of age, G-CSF (5 μg/kg/day) was introduced for three weeks without success. She was transferred to the ICU for four times during the age of 11-15 months due to respiratory infections. IVIG (500 mg/kg every 4 weeks) was started at the age of 15 months. Pulse methylprednisolone (30 mg/kg every 4 weeks) was added at the age of 19 months. Interestingly, she had not been intubated since that time. She gradually responded to the treatment and no longer required oxygen supplement after 21 months of treatment. She continued to receive IVIG and pulse methylprednisolone and her condition was relatively stable and remained oxygen independent for 2 years before she died from severe pneumonia with respiratory failure in a local hospital.

Discussion

The three distinct forms of PAP which have been described include congenital, secondary, and idiopathic (acquired or adult) PAP. In 2004, Jacques de Blic reviewed PAP in children and divided PAP into two forms: immediate-onset and postnatal-onset PAP.[1] It was believed that immediate-onset PAP resembles the congenital form. Postnatal-onset PAP may be primary or associated with various diseases, which are similar to idiopathic and secondary PAP, respectively. Postnatal-onset PAP occurs after a postnatal, symptom-free period ranging from a few weeks to several years. Recent advances in molecular biology and genetics have led to a better understanding that the disease pathogenesis is different among these forms.

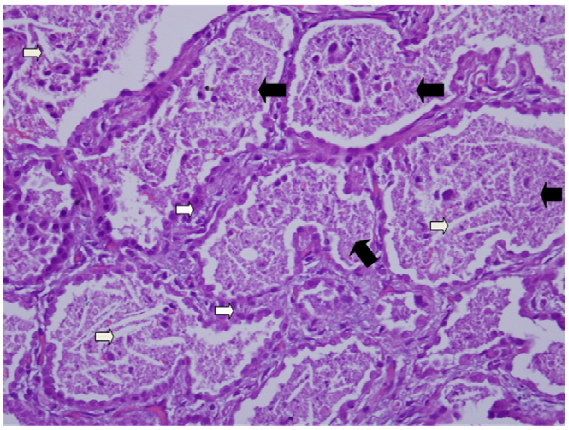

Figure 3. Microscopic findings of lung tissue Lung biopsy showed alveolar infiltration of dense granular eosinophilic material (black arrow) which contained large amount of surfactant protein. This material was periodic acid-Schiff (PAS) positive. There were cholesterol clefts (gray arrow), some foamy macrophages and cell debris within them. The alveolar walls showed slight hyperplasia of pneumocytes type II with scant inflammatory infiltration (white arrow).

Most cases of congenital PAP are caused by mutations in genes important in the surfactant metabolic pathway, including those in the genes encoding SP-B, ABCA3 and SP-C. This mutation is associated with severe respiratory distress that occurs within the first year of life.[1,4] However, congenital surfactant deficiency such as SP-C deficiency may present in the infancy to adult period.[5] Recently, the mutation in the gene for ATP-binding cassette transporter A3 (ABCA3) has been reported in newborns with fatal surfactant deficiency.[6] Doan et al reported that ABCA3 mutation could be found in newborns and children with PAP, desquamative interstitial pneumonitis (DIP) or non-specific interstitial pneumonitis (NSIP).[7]

Secondary PAP was associated with various conditions involving reduced numbers or functional impairment of alveolar macrophages. Such conditions include some hematopoietic disorders or malignancies, certain infections (e.g. *Mycobacteria*, *Nocardia*, Cytomegalovirus, *Pneumocystis jiroveci*), primary immunodeficiency (e.g. thymic aplasia, IgA deficiency), acquired immunodeficiency (e.g. solid organ transplantation, pharmacologic immunosuppression, HIV infection), lysinuric protein intolerance and inhalation of environmental or industrial materials such as inorganic dust (e.g, silica) or toxic fumes.[1-4]

What was previously thought to be idiopathic PAP is the most common type of PAP. Most patients in this form are adults and 72% have a history of smoking.[2-4] Neutralizing autoantibodies against GM-CSF found in BAL and serum of patients with this disease are the predominant cause.[8-10] However, GM-CSF autoantibodies were not detected in the serum of all children with PAP and were detected in the BAL of only 1/15 children with PAP.[11]

The pathologic finding of lung tissue in our patient also demonstrated chronic interstitial pneumonitis pattern. Pediatric interstitial lung disease (PILD) or interstitial pneumonitis is uncommon in pediatric population. PILD has been classified into ILD of known and unknown etiologies and of unique forms of ILD in infancy. A number of diseases are included in PILD of known etiology; for example, infectious or post-infectious pulmonary disease, and aspiration syndromes. Most of the diseases in PILD of unknown etiology are uncommon such as desquamative interstitial pneumonia, lymphoid interstitial pneumonia, bronchiolitis obliterans, and PAP.[12] The unique forms of ILD in infancy include diffuse developmental disorders, growth abnormalities reflecting deficient alveolarization, specific conditions of undefined etiology and surfactant dysfunction disorders.[13] The corticosteroid is the standard treatment of chronic interstitial pneumonitis.

In our patient, surfactant dysfunction could explain the finding of postnatal-onset PAP and interstitial pneumonitis. As mentioned above, the congenital PAP such as SP-C deficiency could present in infancy period, however, the genetic analysis of SP-B, SP-C, and ABCA3 in this patient were negative. It was also possible that *Pneumocystis jiroveci* infection could cause secondary PAP in this patient or this infection was a result of infectious complication found in PAP.[3] It was unlikely that this patient had immunodeficiency leading to *Pneumocystis* infection since his HIV antibody and antigen were negative, T cell numbers and Ig levels were in the normal range.

PAP has been treated successfully with WLL since the early 1960s, and this procedure remains the standard therapy.[2,4] This procedure removes the lipoproteinaceous material in alveoli and decreases anti-GM-CSF antibody as well as immunologic effects on the effector cells, such as the alveolar macrophages or type II epithelial cells.[14] It was reported as a successful treatment of PAP in adolescents and adults with the response rate of 60-84%.[15-17] In infants and children, there was limited information about the efficacy of WLL.[18] This procedure was difficult to perform and not well tolerated in children. In de Blic's report, 21 children with postnatal onset PAP underwent WLL, ranging from 2-16 times.[1] Eight children died despite WLL, six were asymptomatic and seven improved with residual symptomatic and functional impairment.[1] In our patient, WLL was attempted twice at 1 year of age without success, mainly because she could not tolerate the procedure.

GM-CSF was reported to be a successful treatment in a subset of idiopathic PAP who had autoantibodies which neutralized GM-CSF.[19-22] The clinical response to subcutaneous GM-CSF therapy was 43-48%.[21,22] Some patients required dose escalation to attain clinical improvement. Aerosolized GM-CSF was also demonstrated to be an effective therapy in a small series of

idiopathic PAP.[23] Tazawa et al reported that inhaled GM-CSF restored alveolar macrophage function and reduced anti-GM-CSF activity.[24] However, GM-CSF could not displace WLL because a subset of clinical responder to GM-CSF still required WLL.[22,25] In pediatric populations, there are few case reports of GM-CSF therapy. Price et al reported a 13-year-old girl with PAP who was successfully treated with inhaled GM-CSF after the failure of WLL.[26] Yamamoto et al also reported a combination treatment of WLL and GM-CSF inhalation in a 9-year-old girl with idiopathic PAP.[27] The optimal dose and duration of GM-CSF therapy was unclear. The suggested dose of subcutaneous GM-CSF from the trials was 5 μg/kg/day for 6-12 weeks.[21,22] In our patient, G-CSF was used due to the unavailability of GM-CSF in Thailand. The patient did not show any improvement during a 3-week course of subcutaneous G-CSF and the therapy was stopped due to financial concerns.

The susceptibility to pulmonary infection is an important feature of PAP.[2] This may be due to alveolar macrophage dysfunction or the microbial growth medium provided by intra-alveolar proteinacious material.[3] The defects of alveolar macrophages chemotaxis, adhesion, phagocytosis and microbial killing were observed in PAP.[2,16] Recent studies in idiopathic PAP demonstrated that the GM-CSF signaling pathway had an important role in terminal differentiation and functions of alveolar macrophages via the transcription factor PU.1. These functions included surfactant degradation, expression of pathogen pattern-recognition receptors, toll-like signaling, phagocytosis, and bacterial killing.[28] Moreover, impairment of antimicrobial functions of neutrophils was reported in PAP patients with GM-CSF autoantibodies.[29] Superimposed infections were found in 13% of all PAP.[28] Most of the infections result from opportunistic organisms such as *Nocardia*, *Candida*, *Cryptococcus neoformans*, *Aspergillus*, Cytomegalovirus, tuberculous and nontuberculous *Mycobacteria*, *Histoplasma capsulatum*, *Pneumocystis jiroveci* and *Streptococcus pneumoniae*.[3]

Our patient suffered from severe pneumonia requiring ventilatory support on several occasions. IVIG and pulse methylprednisolone improved her clinical symptoms and oxygen requirement. This might suggest a potential role of IVIG and corticosteroid in the treatment of PAP and chronic interstitial pneumonitis. The mechanisms of action of IVIG are complex. Anti-inflammatory effects of IVIG involve the modulation of function and expression of Fc receptors, interfering with complement activation and the cytokine system, and modulation of T and B cell activation, differentiation and effector functions. Antibodies in IVIG enhance opsonization and endorse phagocytosis as well as antibody-mediated cellular cytotoxicity. The specific antibodies can also neutralize pathogens.[30] There were two PAP case reports from Japan and Turkey showing the clinical benefit from IVIG.[31,32] However, unlike our patient, those patients had hypogammaglobulinemia.

The natural history of PAP is variable probably due to the heterogeneity of the disease. Mortality rate was gradually reduced since the introduction of WLL. In the postnatal-onset PAP, mortality rate was 35% in a 5-year follow-up period.[1] Causes of death are mainly due to respiratory failure (72%) and infection (18%).[16]

Although lower respiratory tract infections were markedly decreased in our patient at the introduction of regular IVIG and pulse methylprednisolone, she nonetheless died from severe pneumonia and respiratory failure. This might be the result of the underlying functional impairment of macrophage and the immunosuppressive effect of steroid. Therefore, the side effects of high dose steroid should be concerned and closely monitored. The decision to use IVIG and pulse methylprednisolone in PAP with chronic interstiltial pneumonitis should be done on a case by case basis.

In summary, we reported a case of PAP with chronic interstiltial pneumonitis. The combination of IVIG and pulse methylprednisolone extended survival of this patient indicating a potential role of these immunomodulatory agents.

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