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Successful Treatment of Autoimmune Pulmonary Alveolar Proteinosis in a Pediatric Patient

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Conflict of interest: None declared

Patient: Male, 13
Final Diagnosis: Pulmonary alveolar protinosis (autoimmune subtype)
Symptoms: Dyspnea • general weakness • subfebrile episodes
Medication: Vincristine
Clinical Procedure: Bronchoscopy • bronchoalveolar lavage • CT scan • lung biopsy • GM CSF antibody testing • diagnosis confirmation • therapy with inhaled GM-CSF • bilateral lung transplantation • chemotherapy due to PTLD
Specialty: Pediatrics and Neonatology

Objective: Rare disease

Background: Pulmonary alveolar proteinosis (PAP) is a rare condition characterized by the intra-alveolar accumulation of surfactant-derived material, which impairs gas exchange and results in respiratory insufficiency. Two major subtypes of PAP are autoimmune and non-autoimmune PAP. The diagnosis relies on clinical presentation, ground glass opacities on CT scan, bronchoscopy with PAS stain of BAL fluid (BALF), lung biopsy with PAS-positive material in the alveoli, and the presence of anti GM-CSF antibodies in serum or BALF for an autoimmune subtype. The therapeutic approach to pediatric cases varies according to age and the general clinical state of the child; however, whole lung lavage (WLL) and inhaled or subcutaneous GM-CSF are generally first-line therapy.

Case Report: We report a unique case of an autoimmune type of PAP in a 12-year-old boy, who underwent successful bilateral lung transplantation after inefficacious treatment with GM-CSF, and who developed post-transplant lymphoproliferative disease (PTLD) and was successfully treated with a chemotherapeutic protocol.

Conclusions: Although lung transplantation is a rarely used therapeutic approach for patients with an autoimmune subtype of PAP, in cases of inefficacious treatment with other modalities, lung transplantation should be considered.

MeSH Keywords: Lung Transplantation • Lymphoproliferative Disorders • Pulmonary Alveolar Proteinosis

Abbreviations: **aPAP** – autoimmune PAP; **BAL** – bronchoalveolar lavage; **BALF** – bronchoalveolar lavage fluid; **EBV** – Epstein Barr Virus; **GM-CSF** – granulocyte-macrophage colony stimulating factor; **LTx** – lung transplantation; **PAP** – pulmonary alveolar proteinosis; **PRES** – posterior reversible encephalopathy syndrome; **PTLD** – post-transplant lymphoproliferative disease; **R-CHOP** – rituximab, cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (Oncovin), prednisolone; **SpO_2** – oxygen saturation rate; **WLL** – whole lung lavage

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/897868

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Background

Pulmonary alveolar proteinosis is a rare, interstitial lung disease characterized by the accumulation of lipoproteinaceous material in the alveoli. There are two subtypes of PAP: an autoimmune and non-autoimmune PAP, which can be further subdivided into congenital PAP and secondary PAP. An autoimmune PAP is characterized by production of autoantibodies to granulocyte-macrophage colony stimulating factor (GM-CSF), and accounts for more than 90% of all cases. Congenital PAP is a result of mutations in the surfactant or the GM-CSF receptor subunits, inherited in an autosomal recessive or dominant trait. Secondary PAP is associated with exposure to inorganic dusts and medications, hematological malignancies, or infections.

Autoimmune PAP (aPAP) is rare in the pediatric population, with only a few cases reported in the literature. We report on a unique case of aPAP in a 12-year-old boy who underwent successful bilateral lung transplantation (LTx) and developed post-transplant lymphoproliferative disease (PTLD) and an adverse reaction to chemotherapy treatment.

Case Report

In 2002, a four-year-old Caucasian boy with a history of frequent respiratory infections and prominent cough was hospitalized due to a second bilateral pneumonia. At the time, all laboratory findings were adequate for his age, and a bronchoscopy exam revealed a normal shape and course of bronchial tree. During a follow-up period of four years, no significant abnormalities of into the lung function were noted. In May 2006, during the second hospitalization, due to prolonged cough and respiratory infection, a second bronchoscopy confirmed the normal structure of bronchial tree and BAL fluid (BALF) analysis was nonspecific. However, the lung function tests showed a restrictive pattern. A CT scan revealed only emphysematous changes in apical parts of lung and the presence of hilar lymphadenopathy. Although emphysematous lung changes typically present an obstructive pattern on lung function tests, our patient had a continuous restrictive pattern in his lung function tests. At that time, therapy with inhaled corticosteroids was introduced and the patient was in a good clinical condition with adequate oxygen saturation rates (SpO_2). Further diagnostic procedures were planned; however, the patient discontinued his regular follow-up visits due to father's death.

In the following three years, the patient developed dyspnea and general weakness with subfebrile symptoms. The patient's father's death was reported to be due to undefined interstitial lung disease. Considering the patient's family history and the newly reported deterioration of the patient's condition, a second CT scan was performed. The scan revealed

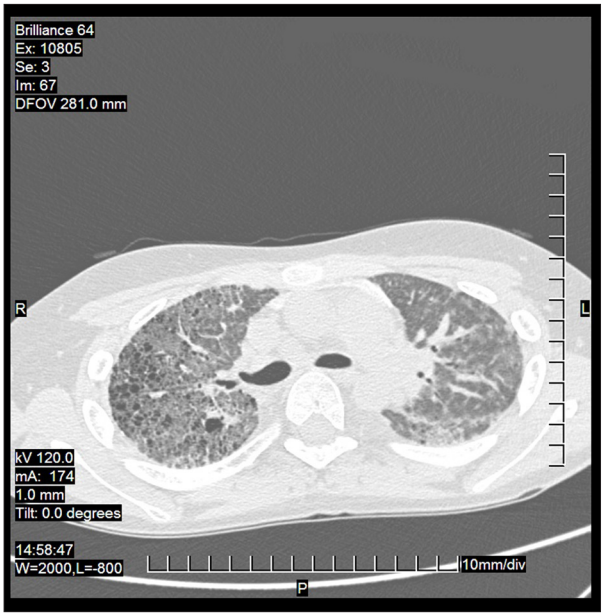

Figure 1. CT scan: bilateral areas of ground glass opacities with reticulation, predominantly distributed in the upper pulmonary fields.

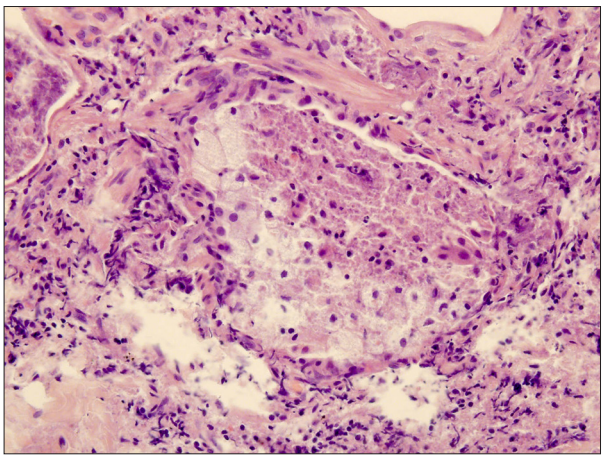

Figure 2. Lung biopsy specimen showing dilated and distorted alveolar spaces filled with PAS-positive granular material, with focally present cholesterol crystals and foamy macrophages and thickened alveolar septa.

extensive, diffused ground glass opacities predominantly distributed in the upper pulmonary fields, without signs of pulmonary fibrosis suggesting interstitial lung disease (Figure 1). Histopathological examination of lung biopsy tissue revealed dilated and distorted alveolar spaces filled with PAS-positive granular material, with focally present cholesterol crystals and foamy macrophages and thickened alveolar septa, which led to a PAP diagnosis (Figure 2). For further differentiation of PAP subtype, blood samples for GM-CSF antibody tests were sent to Cincinnati Children's Hospital. At that time, the patient's SpO_2 was around 95% while on 20-hour oxygen support of

2 L/minute with parenteral corticosteroid therapy, salbutamol and ipratropium inhalations, prophylactic antibiotics, and hydroxychloroquine therapy. By September 2011, the presence of anti GM-CSF antibodies was confirmed (57–66 μg/mL) and the final diagnosis of an autoimmune subtype of PAP (aPAP) was established. At that time, the patient's SpO_2 was around 90% while on oxygen therapy with evident dilatation of the right ventricle and slight regurgitation of the tricuspid valve.

After the diagnosis of aPAP, a council of physicians deliberated on all possible therapeutic approaches. Whole lung lavage (WLL) was dismissed as a possible therapy because the patient was in poor general condition and there was a high possibility of a fatal outcome during such an invasive procedure. Therefore, a therapy with the inhaled GM-CSF sargramostim (Leukine) was initiated in October 2011. In spite of this introduced therapy, the patient's condition was continuously deteriorating, so a pre-lung transplantation protocol was started in collaboration with the Allgemeines Krankhaus der Stadt Wien (a hospital in Vienna) and Clinic for Lung Diseases Jordanovac (a hospital in Croatia). By March 2012, the patient had received seven cycles of sargramostim therapy. In April 2012, the patient was hospitalized in Wien due to respiratory insufficiency, and while waiting for a donor organ. In June 2012, a bilateral LTx was performed. Although the transplantation was complicated with *Klebsiella* sepsis, post-operative renal failure, and a mild form of rejection indicated on initial post-transplantation lung biopsy, the patient recovered and was discharged three weeks later. In August 2012, after revealing ground-glass opacities lesion in the left lung on control chest x-ray, an high-resolution (HR) CT indicated multiple solid lesions of the lungs. Analysis of the lung biopsy confirmed the diagnosis of monomorphic post-transplant lymphoproliferative disease (PTLD) associated with Epstein Barr virus infection. Therefore, immunosuppressive therapy was reduced and treatment with rituximab was initiated. After receiving seven cycles of rituximab therapy, a PET scan showed a remaining thoracic lesion. A new R-CHOP chemotherapy protocol was introduced. Four days after receiving the first cycle of R-CHOP, the patient experienced intense jaw pain and generalized bone pain followed by a generalized seizure. An MR scan revealed signs of posterior reversible encephalopathy syndrome (PRES). Due to the described reaction, which was considered to be an adverse reaction to vincristine, a modified R-CHOP (without vincristine) was administered.

Repeated lung biopsies showed no signs of organ rejection. Lung function tests revealed a constant improvement. By April 2013, the patient had received 10 cycles of rituximab and six cycles of modified R-CHOP therapy. A control PET scan showed a decrease of the known lesion, but detected a new lesion in the right upper lobe, which proved to be organized pneumonia. By April 2012, the patient's PTLD was considered to be in remission. In August 2013, 14 months after his transplantation, the patient was in good clinical condition with no signs of rejection, and a control PET scan confirmed remission of PTLD.

Discussion

The diagnosis of aPAP is based on HRCT, PAS-positive stain of BALF, or PAS-positive material in the alveoli on histopathological analysis of lung tissue and the presence of anti GM-CSF antibodies in serum or BALF. In our patient, the HRCT showed a pattern of diffused ground glass opacities typical for PAP, and the diagnosis was confirmed by intra-alveolar PAS-positive staining of lung biopsy material and GM-CSF autoantibodies in serum.

Literature describes a few therapeutic approaches in treatment of patients with PAP. Although the whole lung lavage (WLL) has been a therapeutic option since early 1960s [1], the success of WLL was confirmed in adults and adolescents with response rate of 60–84% [2–4]. However, for infants and children, information regarding its efficacy is limited, and it is difficult to perform and not well tolerated by children [1,5]. Both subcutaneous [6–9] and inhaled GM-CSF [10–12] therapy was been proven to be effective in a number of studies. Inhaled GM-CSF was used in a pediatric population by Price et al. [13] to treat a 13-year-old girl after the failure of WLL, and by Yamamoto et al. [14] to treat a 9-year-old girl. However, WLL was not an adequate therapy for our patient due to his poor clinical condition. As our patient was deteriorating rapidly in spite of GM-CSF, the only remaining therapeutic option was LTx.

LTx is a therapeutic option in non-responsive patients. Huddleston et al. [15] have reported that 6.3% of all LTx in a 12-year period were performed in PAP patients. In the 2014 annual report of the ISHLT Registry, 7% of all performed LTx in a 24-year period were due "to other causes" (including PAP) [16]. However, there is no consensus regarding indications for LTx in patients with different PAP subtypes. A literature search revealed a number of reports regarding LTx in infants and in patients with surfactant deficiency. However, reports of LTx in patients with an autoimmune and secondary PAP subtype are rare. Reports suggest that the long-term outcomes after infant LTx for SP-B-deficient infants are similar to those of infants transplanted for other indications [17,18].

Parker and Novotny reported a case of recurrence of PAP after LTx [19], and a few case reports describe occurrence of PAP as a complication after a LTx in non-PAP patients. Our patient underwent successful bilateral LTx without signs of organ rejection and was in excellent clinical condition 17 months after transplantation.

However, in the first month after LTx, our patient developed PTLD, which was treated with modified R-CHOP

therapy. The occurrence of PTLD was reported to be 13% by Huddleston et al. [15]. Cohen et al. [20] reported PTLD to be the most common malignancy in the pediatric LTx population. The primary risk factor is EBV infection, and, as children are more commonly EBV seronegative in comparison with adults, they are at increased risk. As was the case with our patient, PTLD usually occurs in the first year after LTx.

Along with plasmapheresis, rituximab is described as an effective agent in a few cases of PAP patients [21]. Borie et al. [22] administered rituximab to a patient who refused WLL, with dyspnea improvement evident nine months after the treatment, and Amital et al. [23] administered rituximab to a patient who was deteriorating after WLL and GM-CSF therapy; the patient's DLCO, chest x-ray, and CT scan improved after the therapy. For our patient, rituximab therapy due to PTLD could be a contributable factor to the successful control of the patient's autoimmune disease after transplantation.

The latest modality of treatment being investigated is pulmonary macrophage transplantation therapy, which shows promising results as a curative treatment option for PAP [24,25].

Conclusions

We report a case of a 12-year-old boy diagnosed with an aPAP, who underwent successful bilateral LTx after failure of GM-CSF therapy. Due to the development of PTLD, the patient was treated with rituximab and R-CHOP, and developed an adverse reaction in the form of PRES to vincristine application. In spite of rapidly progressive PAP, unresponsiveness to therapy, and post-transplantation malignancy development, our patient is now a teenager in excellent clinical condition. Since literature describes cases of recurrence of PAP [19,26] in patients with newly transplanted organs, our patient will remain supervised and screened both for signs of organ rejection and signs of recurrence of pulmonary alveolar proteinosis.

PAP is a rare and life-threatening disorder with limited treatment options, so we believe that our case report of successful treatment will be beneficial for physicians who encounter patients with the same disorder.

Acknowledgments

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Disclosure

Authors would like to disclose that there were no conflicts of interest.

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