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Research Article

Pulmonary Alveolar Proteinosis Long-Term Outcome After Bronchopulmonary Lavage

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Abstract

Introduction: Pulmonary alveolar proteinosis (PAP) is a rare disease characterised by accumulation of surfactant-like material within alveolar spaces. Broncho pulmonary Lavage (BPL) under extra corporal membrane oxygenation (ECMO) is the mainstay treatment in PAP patients.

Objective: To determine the long-term outcome of pulmonary alveolar proteinosis in patients who underwent BPL.

Method: 11 patients with PAP hospitalized from January 1, 2005 to January 1, 2015 and underwent BPL with ECMO were enrolled in this prospective study. Patients were regularly visited at Pediatric Pulmonary clinic and if they were admitted to hospital, all their labs were extracted from their file recorded in system.

Results: Total 11 patients were enrolled in the study and were followed up for 10 years. Dyspnea was the most common symptoms and alveolar infiltration was the most common CT scan diagnostic features among patients. Hypoxia was the most common feature in ABG in these patients. Three of 11 patients with PAP (27.7%) underwent one single BPL, 8 (72.3%) underwent multiple BPL. During the 10-year follow-up period, 3 patients (27%) in one BPL group died of severe respiratory insufficiency. Only one (9%) patients who underwent a single BPL remained in remission for whole 10 years. All 7 (63%) had relapse and remission course during the follow-up period. Survival rate was 100% in multiple BPL group and 33% in one BPL group.

Conclusion: BPL is currently the mainstay therapy for severe PAP that could significantly improve patients for several years. Patients with relapse-remission course could undergo multiple BPL without severe side effects and decrease mortality.

Keywords: *Pulmonary; Proteinosis; Lavage*

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease characterised by impaired surfactant metabolism that leads to accumulation of surfactant-like material in macrophages within the alveolar spaces and distal bronchioles. Usually, it appears as a "crazy-paving" pattern on high-resolution computed tomography (CT) [1]. The typical image along with the characteristic bronchoalveolar lavage examination with presence of Periodic Acid Schiff positive substance is sufficient for establishing diagnosis [2]. The molecular pathogenesis in over 90% of cases involves the disruption of GM-CSF signaling [3].

The course of the disease is variable and the prognosis is often good. However, progressive disease in some patients can cause respiratory dysfunction and can be life threatening. Patients with minimal symptoms are managed conservatively, whereas patients with hypoxemia require aggressive therapy [4]. The standard of care for treatment of PAP remains Broncho pulmonary Lavage (BPL), which is required in patient with respiratory dysfunction [5]. BPL is the most effective treatment modality for symptomatic pulmonary alveolar proteinosis and could be performed under extra corporal membrane oxygenation (ECMO).

During BPL, one lung is irrigated and drained in 500 to 1000-mL aliquots through one side of a double lumen tube (DLT) under general anesthesia up to 20 L [6]. It is then performed on the contralateral lung during anesthesia. Since the introduction of BPL the prognosis of PAP has greatly improved. However, various studies reported different outcomes and survival rates for PAP patients who undergo BPL.

Objective

To determine the long-term outcome of pulmonary alveolar proteinosis in patients who underwent BPL.

Method

Ethics Declaration

The study was reviewed and approved by the Shahid Beheshti University of Medical Sciences Ethics Committee and been performed in accordance. Information about the study was given comprehensively both orally and in written form to all patients or their accompanying adult. They gave their informed written consents prior to their inclusion in the study.

Study population

Patients with characteristic suggestive radiologic features and confirmed histologic findings in the BALF (amorphous PAS-positive material) or biopsy specimens were included in the study [7,8]. Patients with confirmed secondary conditions such as silicosis and other inhalational syndromes, autoimmune diseases, malignancies, and hematopoietic disorders were excluded.

In total, 11 patients with PAP hospitalized from January 1, 2005 to January 1, 2015 and underwent BPL in Masih Daneshvari hospital were enrolled in this prospective study. Patients' information was recorded from their medical file and records. Patients were regularly visited at Pediatric Pulmonary clinic and if they were admitted to hospital, all their labs were extracted from their file recorded in system. For analysis patients were divided to the group who had 1 BPL and group who had multiple BPL during 10 years' follow-up.

All patients had thorough immunologic survey and laboratory test to detect any accompanying cellular or humoral immunodeficiency syndroms.

Broncho pulmonary Lavage

The patient was in the supine position during the procedure. To improve the effectiveness of the lavage, ventilation with FIO_2 100% for a few minutes was initiated after induction to de-nitrogenate both lungs. Patients under 20 kg underwent BPL under ECMO. In patients, higher than 30 kg BPL was performed under one lung ventilation (OLV). A disposable irrigation and drainage system was used to instill approximately 1 L of warm normal saline (37°C) into the lavage lung. Thereafter, the saline was rapidly drained by gravity into a container positioned 60 cm below or with the assistance of a small level of suction (< 20 cm H_2O). This process was repeated as needed until the effluent fluid was clear. Chest physiotherapy-mainly percussion, vibration, and pressure- was applied during the filling and the drainage phases. Procedure was interrupted if hydrothorax was suspected.

At the end of the procedure the lavaged lung was thoroughly suctioned. A dose of furosemide (10 mg) was administered to increase diuresis of absorbed saline. If there was a persistent large alveolar-arterial oxygen gradient the procedure was terminated at this stage. After the procedure, after re-intubation with a single-lumen tracheal tube, inspection with fiberoptic bronchoscopy was performed for suctioning. Mechanical ventilation was continued, usually for less than 2 hours and patients were observed in the intensive care unit for 24 hours.

Statistical analysis

Statistical calculations were conducted using SPSS 22 (Chicago, IL, USA). Quantitative variables are expressed as the mean value and standard deviation (SD) or the median value and interquartile range (IQR). The Kolmogorov-Smirnov test was used to test the normal distribution of quantitative variables. Qualitative variables are summarized as counts and percentages. Cox regression analysis was used to distinguish patients with the need for repeated BPL survival rate.

Results

Total 11 patients were enrolled in the study and were followed up for 10 years. Details of demographic variables at the time of diagnosis are described in Table1. Age of diagnosis, sex and having relative parents was not significantly different between two groups of one BPL and multiple BPL ($p > 0.05$). None of patients had any family history of PAP. None of patients had any immunologic tests abnormality and all immunologic lab data were completely normal in all patients.

Demographic variables	One BPL (n=4)	Multiple BPL (n=7)	p-value
Age at the time of diagnosis	6.6 ± 4.7	6.1 ± 3.7	0.37
Sex Male Female	1 (9%) 3 (27%)	5 (45) 2	0.13
Relative Parents	3 (27%)	4 (36%)	0.35
Family history of Proteinosis	0	0	NA
Immunodeficiency	0	0	NA

Table 1*: Demographic variables in PAP patients.*

PAP: Pulmonary alveolar proteinosis; BPL: Bronchopulmonary lavage; NA: not applicable

Diagnostic Methods

In this study, the median time from the onset of symptoms to diagnosis was 8.5 months. Trans Bronchial lung biopsy (TBLB) analysis was the most frequently applied diagnostic method in 9 (81.5%) patients; in 2 (18.5%) patient's diagnosis was made by BALF.

Frequency of the most common symptoms is listed in Table 2. The most common CT scan diagnostic features among patients are depicted in Figure 1; besides the frequency of arterial blood gas (ABG) findings at the time of BPL are depicted in Figure 1.

Symptoms	Number (%)
Dyspnea	11 (100%)
Cough	10 (90%)
Cyanosis	5 (45%)
Crackle	5 (45%)
Sputum	3 (27%)
Tachypnea	2 (18%)
Clubbing	2 (18%)

Table 2: *Symptoms of patients at the time of admissions to hospital.*

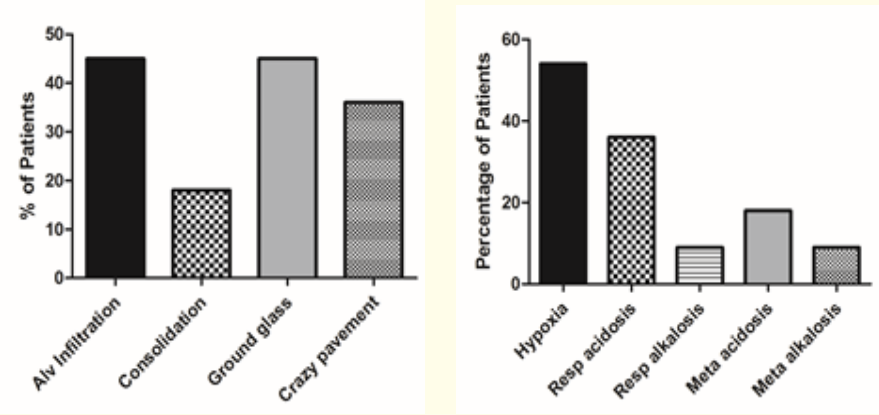

Figure 1: *Frequency of the most common CT scan finding and arterial blood gas (ABG) variables prior to BPL in PAP patients.*

Bronchopulmonary Lavage (BPL)

All BPL were performed at the first admission to the hospital. From 11 patients, 4 had 1 BPL and 7 had multiple BPL. In 1 BPL group, 3 patients died and only 1 patient remained symptom free during 10 years' follow-up. 7 patients required multiple BPL during 10 years' follow-up, from 3 patients had 2 BPL, 2 patients had 3 courses of BPL and 2 patients had 5 courses of BPL during 10 years' follow-up. In total, 3 patients died of lung infection or respiratory insufficiency during 10 years follow up and all 3 patients had 1 BPL. None of patients in multiple BPL group died during 10 years.

Patients' outcomes

According to therapeutic criteria, 4 (36.5%) of 11 patients with PAP underwent only one BPL,and 7 (63.5%) underwent multiple BPL. None of the 11 patients developed severe complications after BPL. During 10-year follow-up period, 1 patient among those who underwent 1 BPL died of severe respiratory depression 4 years after her first BPL. Two other one patient died 5 and 6 years after single BPL. 7 (63%) patients survived during the follow-up period and all of them had period of relapse and remission and multiple BPL.

Survival plot show PAP patients who underwent BPL during 10 years' follow-up time (Figure2), 3 patients died in one BPL group. None of patients in multiple BPL group died during 10 years' follow-up. The survival proportion was 100% in patients who had 5 times BPL, and 33% in 1 BPL group (Figure 2).

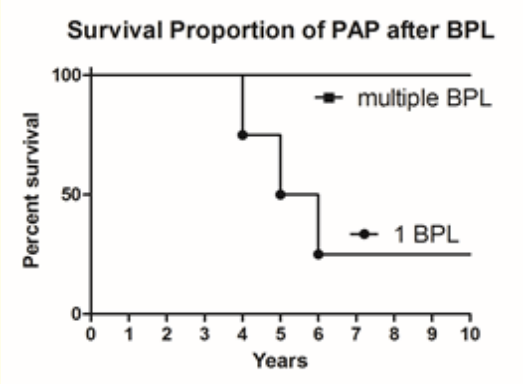

Figure 2: *Survival plot show PAP patients who underwent BPL during 10 years' follow-up time. The survival proportion was 100% in patients who had multiple BPL, and 33% in 1 BPL group.*

Discussion

Here in this study, we report course of the disease of 11 PAP patients who underwent BPL and their 10 years follow up time. The clinical findings of dyspnea or dyspnea on exertion and persistent dry cough are the most common findings in these patients. Radiographic findings of alveolar infiltration, ground glass and crazy paving appearance in high-resolution CT are suggestive of PAP.

Survival proportion was 100% in patients who had multiple BPL, and 33% in1 BPL group. This demonstrates that multiple BPL improves survival rate.s Only one patient had complete remission after first time BPL, and 63% of patients needed multiple BPL. Interestingly, all patients who had multiple BPL course did not died during 10 years follow up. In another report, they showed that in four patients with severe course of PAP, BPL was performed with significant improvement in 3 (75%) of them [9].

In our patients with severe course of PAP, BPL was performed with significant functional and radiological improvement in 8 (72%) of them and 3 patients died after 1 BPL (27%). In a meta-analysis, totally, 206 PAP patients who received BPL were recruited in the 12 cohort studies [10]. It showed that BPL can evidently improve the diffusing capacity, forced expiratory volume, forced vital capacity, and arterial partial pressure of oxygen of patients with PAP. Our results along with others depicted that BPL is an effective treatment of PAP even if performed in multiple times in patients with relapsing-remitting course of PAP. Some patients require lavage every few months, whereas others remain in remission for years [11]. Therefore, BPL is the optimal treatment method for PAP and provides remarkable improvements for affected patients [12]. In a case report, patient showed marked clinical and radiological improvement after sequential BPL [13].

We did not observe any significant side effects of BPL in our patients. BPL for PAP is currently a safe procedure in an experienced setting, and provides long-lasting benefits in the majority of patients [14]. On the other hand, other modalities have not been accompanied with high success rate. Corticosteroid therapy may worsen disease severity score (DSS) of PAP, increasing the risk for infections [15]. If patient has severe global respiratory insufficiency, patient could not undergo the classic BPL using a double-lumen tube and one lung ventilation. In such cases, BPL could be performed with the support of extracorporeal membrane oxygenation (ECMO) [16].

One important aspect of our study was the thorough immunologic survey in our cases. None of cases had any sort of immunodeficiency or immune system abnormality. Previous reports on autoimmune disorders in PAP have been controversial. Autoimmune PAP, a rare, antibody-mediated disease, is causes by IgG autoantibodies that block GM-CSF effect and macrophage maturation. Macrophages dysfunction plays a crucial role in the development of the disease and causes immunodeficiency [17]. Further, idiopathic PAP patients and GM-CSF-deficient mice have similar defects in neutrophil functions including adhesion, phagocytosis, and microbial killing [18].

In conclusion, BPL is currently the mainstay therapy for severe PAP that could significantly improve patients for years without relapse. Patients with relapse-remission course could undergo multiple BPL without severe side effects.

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