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An eleven-year retrospective cross-sectional study on pulmonary alveolar proteinosis

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Abstract

Introduction: Pulmonary alveolar proteinosis (PAP) is a rare disease in the field of pulmonary medicine. The efficacy of whole-lung lavage (WLL) as the treatment of PAP had never been evaluated in the Iranian population. Therefore, there is a real need to investigate the characteristics of PAP and also to evaluate the efficacy of WLL in this rare disease. The study aimed to investigate demographic features, clinical presentation and treatment outcomes of the disease in Iranian PAP patients.
Material and methods: Data of 45 patients with definite diagnosis of PAP, who had regular follow-ups from March 2004 to March 2015 at an Iranian referral respiratory hospital, were collected. Whole-lung lavages (WLL) efficacy was assessed by comparing spirometric, arterial blood gas parameters and six-minute walk test (6MWT) results before and after all lavages.
Results: Mean age at diagnosis of disease was 30.33 ± 14.56 years. Four patients (8.8%) reported non-massive hemoptysis and three subjects (6.6%) had concomitant pulmonary tuberculosis. In 71.1% of cases, transbronchial lung biopsy and bronchoalveolar lavage were sufficient for diagnosis. Spirometric results and arterial blood gas parameters and 6MWD improved significantly after all the lavages. Four patients (8.8%) died because of respiratory failure. The only variable capable of predicting treatment failure was the history of hemoptysis.
Conclusion: The study revealed sufficiency of WLL as the PAP patients' treatment. Also hemoptysis was found to be the independent factor that can predict treatment failure.

Key words: bronchoalveolar lavage (D018893), pulmonary alveolar proteinosis (D011649), whole-lung lavage
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Introduction

Pulmonary alveolar proteinosis (PAP), which was first described by Rosen *et al.*, in 1958 [1], is a rare and complex disorder caused by the excessive accumulation of lipoproteins within alveolar spaces [2]. Basing on pathological aspect, the disease is divided into the three following forms: "congenital PAP" — with prevalence of 2% of total cases, "secondary PAP" — with prevalence of less than 10% of all cases, and "idiopathic or acquired PAP" — constituting 90% of total cases [2, 3]. Congenital PAP is the result of genetic mutation in surfactant protein, granulocyte macrophage colony-stimulating factor (GM-CSF) receptor or ATP-Binding Cassette A3 (ABCA3) [4]. Secondary

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PAP occurs due to the functional impairment or reduction in the number of alveolar macrophages being exposed to toxic substances, infections, hematologic malignancies and allogeneic stem cell transplantation [2, 5]. IPAP, which is also called "acquired PAP", occurs as an autoimmune disease with neutralizing antibody of immunoglobulin G isotype against GM-CSF [6].

Whole-lung lavage (WLL), which is known as the gold standard treatment [7–12] for PAP, was used for the first time among Iranian PAP patients in the present study. Since 1958, more than 500 cases of PAP have been reported worldwide [1]. Western and Asian countries have published reports including data on epidemiology, clinical features and treatment outcomes of PAP patients [3, 7, 13–16]. One of the largest studies to date is a meta-analysis by Seymur et al. reporting on 410 patients from 241 publications [3]. Another one is the largest single center cohort study on PAP which was conducted by Bonella *et al.* [13], and which described epidemiologic and different characteristics of PAP patients in Germany. Inoue *et al.* [15] released data on features of 166 Japanese patients with PAP [15], furthermore, Xu *et al.* [14], reviewed clinical qualities of 241 patients over time, and Byun *et al.* [17], reviewed features of IPAP in the Korean population. Nevertheless, reports on characteristics of the disease in Middle East are limited. Accordingly, the study by Ben-Dov et al. is one of the reports on PAP patients in Middle East [18], on the other hand, one brief paper by Parsa *et al.* [19], and two case reports concerning Iranian patients by Radpay *et al.* [20, 21] are available as well. WLL had never been used as the treatment in Iranian PAP patients before the present study.

In this research, it was decided to describe demographic, epidemiological and clinical features, as well as treatment outcomes of Iranian PAP patients during eleven years.

Material and methods

Study design

The study was conducted as a retrospective cross-sectional study at the Iranian referral respiratory hospital. Forty-five PAP patients (21 females and 24 males), i.e. 42 cases from the "adult group" and three cases under 14 years of age from the "pediatric group" were included in the study on the basis of definitive diagnosis of PAP after bronchoalveolar lavage (BAL) or transbronchial lung biopsy (TBLB) between March 2004 and March 2015. Mean age ± SD at diagnosis was 30.33 ± 14.56 years.

The patients were contacted by phone in order to ascertain their participation every two weeks for at least 12 months (mean ± SD = 10.00 ± 3.64).

The study was approved by the ethics committee of the hospital. Moreover, written consent was obtained from all patients before their participation in the study.

Diagnostic and treatment methods

The diagnosis of PAP was based on three criteria, which were different in each case, i.e. radiographic findings on HRCT in some cases, pathological/cytological outcomes and positive result of GM-CSF autoantibody [22] in others; but definitive diagnosis of PAP was confirmed by bronchoalveolar lavage or lung biopsy (transbronchial or open).

All patients had been treated for TB about six months with isoniazid and rifampicin before conducting the first WLL. We made sure that all patients had been cured completely, not only of TB but also of other infections.

It was the first time that WLL, which is often chosen as the first option of PAP disease treatment [7], was performed in the Iranian population.

Whole lung lavage

The procedure was conducted by an experienced lavage team including an interventional pulmonologist, anesthesiologist, nurse and respiratory therapist. WLL was carried out under general anesthesia. The lungs were ventilated with FiO_2 of 1.0 for 15 minutes. Then degassing was performed at a rate of up to 125 ml/min for 10–15 minutes. Warm saline (to 37^0C) flowed into the lung slowly. The filling continued up to the estimated functional residual capacity volume of the lung and then suction was done. Repeated cycles of lung filling with warmed saline (500–1000 cc) continued for 2 minutes with chest percussion therapy. Lavages had been continued under control until the returned fluid was clear. Lavage is the main treatment of PAP. In our study, all patients received whole lung lavage as the treatment but we did not perform lavages of both lungs at the same time. The number of lavages varied from one to 12, basing on O_2 saturation, medical state and CT findings of each patient.

Bronchoalveolar lavage

BAL was performed in accordance with the standard protocol confirmed by the Department of Pulmonary Medicine. Through a two-way syringe, 20 ml of sterile saline (0.9%) was inserted in the suction port, after that, the fluid was pulled back

Table 1. Spirometry, arterial blood gases analyses, six-minute walking distance results before and after whole-lung lavages

Index	Before treatment	After treatment	p-value
DLCO%	52.66 ± 13.41	63.34 ± 13.30	< 0.0001*
FEV_1%	58.46 ± 9.60	68.20 ± 7.410	< 0.0001*
FVC%	59.28 ± 8.70	68.70 ± 8.50	< 0.0001*
O_2 Sat%	81.30 ± 3.70	92.00 ± 2.30	< 0.0001*
O_2 Pressure, mm Hg	58.30 ± 2.20	70.30 ± 7.00	< 0.0001*
CO_2 Pressure, mm Hg	35.40 ± 2.30	40.52 ± 1.15	< 0.0001*
6MWD, meter	381.40 ± 61.90	476.80 ± 39.50	< 0.0001*

Data are presented as the mean ± SD for 45 patients; asterisk indicates significant ($p < 0.05$); DLCO — diffusing capacity of the lungs for carbon monoxide; FEV_1 — forced expiratory volume in one second; FVC — forced vital capacity; O_2 sat — oxygen saturation; 6MWD — 6 min walking distance

immediately by the use of 50–100 mm Hg negative pressure suction. The lavage and suction process was repeated up to four times. The collected fluid was clinically analyzed.

Transbronchial lung biopsy

TBLB was performed by experienced pulmonologist under conscious sedation. Six-eight tissue specimens were obtained from the right middle lobe and lower lobe of all cases with standard biopsy forceps (sample size ~ 3 mm).

Data collection

Demographic and historical data, signs and symptoms, radiologic features, diagnostic modalities and the number of conducted WLL were recorded. Efficiency of WLL was assessed by comparing spirometric parameters, arterial blood gas analysis (PaO_2, $PaCO_2$ and O_2 saturation) and six-minute walk test (6MWT). The lung function tests were performed before and after all the lavages, and the data, which are presented in Table 1, were collected before performing WLL and after all the lavages.

Statistical analysis

Variables were reported as frequency and percentage for qualitative data, and the quantitative variables were described as means ± standard deviation. The normality distribution was performed using the Kolmogorov Smirnov (KS) test. Spirometry, arterial blood gas analysis, six-minute walk test results before and after whole-lung lavages were compared using T-test for parametric data and the Mann-Whitney U test for nonparametric data.

Demographic data, clinical manifestation including symptoms, diagnostic methods, comorbid diseases, spirometry and 6MWT result and arterial blood gas analysis were compared between "the treatment failure group" and "treatment responders group" using chi-square test for qualitative data and parametric paired t-test and nonparametric Mann Whitney U test for continuous variables. Logistic regression was applied for predicting the treatment failure based on some predictor variables. Data were analyzed by using statistical software (SPSS 22) and the level of statistical significance was set at $p < 0.05$.

Results

Forty-five patients who were diagnosed with PAP between March 2004 and March 2015 and had regular follow-ups were included in the study.

Results before and after WLL are shown in Table 1. FVC%, FEV_1, DLCO%,O_2sat, O_2 pressure, CO_2 pressure and 6MWD increased significantly after WWL.

Demographic and historical data: The study group consisted of 21 (46.7%) females and 24 (53.3%) males. Beside three cases under 14 years of age who were classified as the "pediatric group", the mean age at diagnosis was 30.33±14.56 years. Male to female ratio was 1.1 among adults (Table 2). Active pulmonary tuberculosis and hypothyroidism were identified as comorbidities. The patients had been investigated regarding occupational exposure. The types of dusts the patients had been exposed to included as follows: silica, aluminum oxide and a variety of dusts and fumes (Table 2).

Clinical manifestation: Dyspnea was the most common symptom found among the patients; cough was the second most frequent ma-

Table 2. Patients' demographic data and clinical manifestation

Index			Adult	Children
Sex	Male		21 (50%)	3 (100%)
	Female		21 (50%)	–
Symptoms	Dyspnea		43 (95.5%)	
	Pain		40 (88.8%)	
	Cough		25 (55.5%)	
	Weakness		15 (33.3%)	
	Fever		10 (22.2%)	
	Lose weight		6 (13.3%)	
	Non massive hemoptysis		4 (8.8%)	
	Sweats		0	
Diagnostic methods	Bronchoalveolar lavage staining		32 (71.1%)	
	Transbronchial lung biopsy		13 (28.8%)	
	Open lung biopsy		10 (23.8%)	3 (100%)
Comorbidities	Pulmonary tuberculosis		3 (7.1%)	–
	Hypothyroidism		3 (7.1%)	–
Environmental risk factor exposure	Smoking	Current smokers	14 (33.3%)	–
		Passive smokers	24 (57.1%)	–
	Occupational Dust Exposure	Silica	6 (14.2%)	–
		Aluminum oxide	2 (4.8%)	–
		Fumes	1(2.4%)	–

nifestation, non-massive hemoptysis was reported in less than 10% of the patients (Table 2).

Diagnostic method: BAL and TBLB were used as a diagnostic tool in more than 70% of patients. Open lung biopsy was required only in cases in whom BAL or TBLB were non-diagnostic.

The median time from diagnosis of PAP to performing WLL was 3-24 months in both pediatric and adult groups. Beside the pediatric group in which the time between the symptoms onset and diagnosis was under 6 months, the majority (95%) of adults were diagnosed with PAP between 3-24 months from the first manifestation of symptoms. All patients had been hospitalized between 1-4 weeks in the hospital.

Treatment method: All patients received WLL as the treatment. The number of lavages was different in each case — from one to 12 lavages (mean ± SD for WLL: 6.91 ± 3.31), according to the patient's state and O_2 saturation. Mean spirometric, arterial blood gas parameters and the results of 6MWD improved significantly after lavages (p-value < 0.0001) (Table 1).

Disease course: All patients had follow-up at least 12 months after diagnosis (mean ± SD: 10.00 ± 3.64). Three pediatric patients died during this period as a result of respiratory failure. One adult who has presented with hemoptysis and dyspnea died within five months after WLL, and seven other patients (15.6%) developed respiratory failure during the follow-up period. According to these results, relapses were seen in 11 patients (24.4%). Other patients did not show any relapses or adverse effects during observation time.

The patients who died or developed respiratory failure (11 patients, 24.4%) were categorized into the "treatment failure group" while the remaining 34 patients were classified as "treatment responders". Demographic, historical and clinical characteristics of treatment failure and treatment responders groups were compared.

After analysis, the four following variables were shown to be different between the two groups: 1 — hemoptysis, 2 — concomitant tuberculosis, 3 — six-minute walk test (6MWT) distances, 4 — oxygen saturation after lavages. Logistic regression analysis was conducted afterwards, considering these variables, which were shown to be different between the two

groups, in order to determine independent predictors of treatment failure. Among the four variables, i.e. hemoptysis, concomitant tuberculosis, six-minute walk test distance and oxygen saturation after lavages, hemoptysis was the only variable capable of significantly predicting treatment failure (p-value = 0.03 odds ratio: 23).

No significant relationship was observed between the number of lavages and patients' outcome using the Mann Whitney U test (p-value = 0.9). No significant difference was observed between smoking cigarette and the number of performed lavages using the Pearson's correlation coefficient (r). $P < 0.05$ was considered statistically significant ($r = 0.207$; $p = 0.177$).

CT findings: The "crazy-paving" pattern (ground glass opacity [GGO] and reticular bilateral upper zone) was the most common finding of computed tomography (CT) — it was seen in 28 patients (62.2%). Bilateral upper zone GGO was the second common feature which was found in the CT scans of 12 patients (26.7%). Nodular or reticular radiographic features in the lower zone were totally seen in five patients (11.11%).

Discussion

Although some studies from different countries have described demographic features, clinical characteristics, diagnostic modalities and treatment outcomes of PAP patients worldwide [3, 14, 15, 18], this study is the first report on the Iranian population.

WLL was found as the sufficient treatment for PAP patients due to significant improvement of spirometric parameters, oxygen saturation, arterial blood gas analysis and 6MWD after WLL (p-value < 0.0001). This confirmed previous findings indicating that WLL is the sufficient treatment for PAP [3, 11, 13–15].

The sufficiency of BAL and TBLB as diagnostic methods were consistent with the results of Inoue et al., Xu *et al.* and Bonella *et al.* studies [13–15] but were different from Seymur's meta -analysis [3].

Mean age at diagnosis among adult PAP patients was lower in the Iranian population in comparison to the Japanese [15], German [13], Chinese [14] and Korean populations [17], but it was comparable to the Israeli population [18]. This could raise the possibility that geographic or ethnic factors play a role in determining the manifestation age of PAP. This probability requires further investigation.

Regarding gender distribution, there was no predominance of males, and male to female ratio was 1.1, similarly to studies conducted in Germany and Israel [18, 23], and in contrast to the majority of previous studies that reported a 2-fold predominance of males [3, 14, 15].

Nine patients (20%) had history of dust exposure similar to the report in the Inoue's study [15] but lower than it was documented in the paper by Bonella *et al.* [13]. An overall number of 11 patients (24.4%) had an underlying comorbidity (active tuberculosis) or dust exposure. Those patients who had active tuberculosis or dust exposure might have had secondary PAP, however, we could not definitely distinguish primary from secondary PAP due to lack of access to laboratory facilities for measuring anti-GM-CSF autoantibody. This is one of the limitations of the present study.

The study also analyzed different variables in order to investigate their contribution to treatment failure. The four variables, i.e. hemoptysis, concomitant tuberculosis, 6MWD and oxygen saturation after lavages were significantly different in the treatment failure and treatment responder groups. Given the fact that tuberculosis — the disease which is a frequent cause of hemoptysis — is endemic to our country — and since hemoptysis has been an independent predictor of treatment failure in our patients, considering concomitant tuberculosis in PAP patients and proper treatment of tuberculosis may improve outcome in PAP patients. Larger studies are warranted to investigate the exact relationship between tuberculosis treatment and prognosis of PAP patients.

Lack of significant association between smoking cigarette and the number of performed lavages is in contrast to the results obtained by Bonella *et al.* [13], according to whom, smokers needed twice as many lavages as non-smokers.

To the best of our knowledge, no study has reported the status of passive smoking in PAP patients. Although a noticeable number of passive smokers had been seen among patients, a true causative relationship between PAP and passive smoking is not clear yet. Therefore, more investigation is needed in this area.

Conclusion

To conclude, regarding the significant improvement in spirometry result, ABG gas analysis and 6MWD after all lavages, our study revealed sufficiency of WLL as the PAP patients' treatment.

Hemoptysis was the only independent factor that could predict treatment failure, therefore in Iran, where tuberculosis is endemic, proper treatment of tuberculosis may improve outcome in PAP patients.

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