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Whole lung lavage: our experience in pulmonary alveolar proteinosis and in type B Niemann Pick disease

Lavaggio polmonare totale: la nostra esperienza nella proteinosi alveolare polmonare e nella malattia di Niemann Pick di tipo B

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Summary

Whole lung lavage (WLL) is an invasive and safe procedure used for pulmonary alveolar proteinosis (PAP). Despite the scientific progress achieved in terms of therapy, WLL remains the gold standard in PAP and could be also applied in other diseases. Here we present a retrospective data collection of 5 patients who underwent to WLL, four suffered from PAP and one suffered from type B Niemann-Pick disease.

Key words: pulmonary alveolar proteinosis, whole lung lavage, type B Niemann-Pick disease

Riassunto

Il lavaggio polmonare totale è una procedura terapeutica sicura e invasiva utilizzata nella proteinosi alveolare polmonare (PAP). Nonostante il progresso scientifico abbia portato a nuove terapie, il lavaggio polmonare totale rimane il gold standard nella PAP con possibilità di applicazione in altre condizioni patologiche. In questo lavoro presentiamo una raccolta dati retrospettiva di 5 pazienti sottoposti a lavaggio polmonare totale di cui quattro affetti da PAP e uno affetto dalla malattia di Niemann-Pick di tipo B.

***Parole chiave**: proteinosi alveolare polmonare, lavaggio polmonare totale, malattia di Niemann-Pick tipo B*

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Conflict of interest statement
The Authors declare no conflict of interest.

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Introduction

Whole lung lavage (WLL) is a technique designed in 1963 by Dr. Riviera for patients with pulmonary alveolar proteinosis (PAP) [1]. PAP is a rare disease in which an impairment of surfactant homeostasis and production leads to the accumulation of lipoproteins in the alveoli. This could bring to an impaired oxygen delivery with a restrictive respiratory pattern and reduction of diffusing capacity of the lung for carbon monoxide ($D_{L_{CO}}$) and an increased alveolar arterial oxygen gradient in the blood gas analyses ($P_{(A-a)}O_2$). Characteristic is a milky appearance of broncoalveolar lavage fluid (BAL-F) and the

presence of acellular globules positive to periodic acid-Schiff staining [2].

Therefore, the rationale of whole lung lavage is based on washing away the accumulation of lipoproteinaceous material in the alveolar space in order to improve the gas exchange and symptoms of respiratory distress in more severe form of PAP.

Over the years the technique has undergone some changes but to date there is no standardized method for its execution. Discrepancy from different centres includes: the first lung to be subject to lavage, position and the use of chest percussion, timing of extubation, lavage method for pediatric patients and total volume instilled for lung [1-3]. There is a general agreement on the WLL execution in PAP when there is a worsening of: function/gas exchange (100% of centers), radiological imagines (79%) and symptoms (42%) [1]. The most common complication are: fever (18%), hypoxemia (14%), wheezing (6%), pneumonia (5%), fluid leakage (4%), pleural effusion (3,1%) and pneumothorax (0,8%) [1]. WLL has been also applied in other alveolar filling disorders with value of rescue therapy in some extreme cases. In this study we want to describe our experience regarding the execution of the WLL and the results obtained in the treatment of pulmonary alveolar proteinosis and type B Niemann-Pick Disease (type B NPD).

Material and methods

This is a retrospective study that includes patients who underwent to WLL at GB Morgagni Hospital in Forlì from 2019 to 2020. Patient's data have been extracted from hospital database and they include information taken before and after the procedure such us: age, sex, initial symptoms, medical history, diagnostic methods,

Table I. Table shows the demografic data, the onset symptoms, the comorbidities, the diagnosed illness, and the employed methods, the parameters taken into account to start treating patients with WLL (worsened PFT, symptoms or imaging) and whether it was necessary to repeat the procedure.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	65	62	49	44	42
Sex	M	F	M	F	M
Smoke	40 p/y	NO	30 p/y	NO	ex 27 p/y
Initial symptoms	Fiver, dyspnea, acute hypoxemic respiratory failure	No symptoms	Dyspnea, dry cough, acute hypoxemic respiratory failure	Dyspnea, dry cough, acute hypoxemic respiratory failure	Dyspnea, acute hypoxemic respiratory failure
Medical history	Hypertension, OSAS, obesity	Surgery for uterine polyps	Hypertension, horseshoe kidney	Idiopathic segmental dystonia, idiopathic CD4 lymphocytopenia, lymphedema and septicaemia due to Parvovirus B19, Pneumocystis jiroveci pneumonia, acute cardiac failure	Factor VII deficiency, orchiectomy for necrotizing orchitis, knee hemartrosis, thalamic hemorrhage, piastrinopenia, lymphocytopenia, splenomegaly
Diagnostic methods	VATS	Bronchoscopy with BAL	Bronchoscopy with BAL	Bronchoscopy with BAL	Cryobiopsy + bone marrow biopsy
Diagnosis	A-PAP	A-PAP	A-PAP	S-PAP	NPD type B
GM-CSF Antibodies	Positive	Positive	Positive	Negative	Negative
Indication WLL	PFTs	Thorax CT	Symptoms, thorax CT, hypoxemic respiratory failure	Thorax CT	Symptoms, thorax CT, hypoxemic respiratory failure
Time between diagnosis-WLL	1y	1y	10 days	6 months	10 days
Interval WLL-R-L lungs	Unperformed for better PFTs	1 month	Boths lung one session	3 weeks	2 months

PFT: pulmonary function test; R: right; L: left; A-PAP: autoimmune PAP; S-PAP: secondary PAP.

Table II. Table shows the follow up data just after the WLL and at a distance of time in terms of respiratory symptoms, imaging and blood gas parameters.

	Case 1	Case 2	Case 3	Case 4	Case 5
Complications post WLL	Hypoxemia, mild pleural effusion, fever	Hypoxemia, fever	Hypoxemia, mild pleural effusion	Hypoxemia	Hypoxemia
Days in IT	1 day	Few hours	Few hours	Few hours	1 day
Post WLL chest RX	Improved	Unchanged	Improved	Improved	Improved
Prior PFTs vs PFTs post WLL	Improved	Not available	Not available	Not available	Unchanged, not available D_{LCO}
Respiratory symptoms post WLL	Improved	Improved	Improved	Improved	Improved
Thorax CT follow up	Improved (after 6 months)	Not available	Worsened (after 2 months)	Improved (after 1 month)	Improved after first WLL, worsened after the second
Blood gas	None	None	Improved	None	Improved

IT: intensive therapy

Table III. Table shows the improvement of arterial blood gas analysis values before and after WLL.

	Before first WLL	After first WLL	After second WLL
pH	7.37	7.40	7.38
pO_2	57.3	59.3	70.6
pCO_2	29.4	31.6	28
HCO3-	16.8	19.5	18.7
FiO_2	24%	21%	21%

radiological imaging, pulmonary function test, arterial blood gas and complications. Mentioned data are summarized in Tables I-III. A total of five patients have been treated by WLL. Most of patients suffered from PAP while one suffered from type B NPD.

An alveolar storage disease was suspected on the basis of clinical and radiological data.

Symptoms like exertional dyspnea and cough are common in both diseases, while there is a different pattern on high resolution computed tomography (HRTC) of the chest. As it also happens to our cases, interlobular septal thickening associated with patchy ground glass knows as "crazy pavig" is characteristic in PAP [2]. "Crazy paving" pattern is less frequent in type B NPD where a smooth interlobular septal thickening and focal or diffuse ground-glass opacities predominantly in the lower lobes have been most commonly reported [4]. Most of time, the diagnosis has been confirmed through the identification of pathognomonic features on BAL-F such as acellular globules positive to PAS staining for PAP and foamy histiocyte for type B NPD [2-5].

In order to distinguish an autoimmune PAP form from secondary one, granulocyte macrophage colony stimulating factor (GM-CSF) antibodies has been researched in all patients with PAP. The serum GM-CSF antibodies test has been performed in translational pulmonary science laboratory at Cincinnati Children's Hospital medical center by enzyme-linked immunosorbent assay (ELISA) method.

Lung function tests have been performed according to current American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations [6,7].

The time between the diagnosis of the pathology and the execution of the procedure has depended on the severity of the symptoms, respiratory function tests, the radiological imagines and blood gas parameters.

WLL has been performed by a team of expert pneumologists and anesthesiologists. In all patients a central venous catheter and radial arterial catheter have been placed in order to monitor pressure values and blood gas parameters. A general anaestesia with propofol and fenthanil was induced [8]. One lung ventilation was carried out by the use of Robertshaw double lumen tube (37-36 size for female and 39 size for male) in order to isolate the no target lung from liquid instillation and maintain its ventilation [9]. The correct position was confirmed by pediatric bronchoscope. The first lung gone under the WLL was the worst according to radiological

images. The main position of the body was the lateral decubitus at 45°C inclination with lavage lung up. If the target lung is the right, the patient is placed on the left side, and vice versa.
The two ends of DLT tube were connected on one side to the ventilator and on the other to a y connector. The y connector is in communication on one side with the saline solution to be installed in the lung and on the other with the collection container [10].
The y connector was clamped during the instillation of one liter of saline solution warmed to 41°C (Fig. 1A). After each liter all patients were subjected to a mechanical percussion of 10-12 hz for 5 minutes (Fig. 1B). The patient in fact wore a vest connected by two tubes to a pulsed air generator that inflated and deflated the vest in order to compress and release the chest wall (Fig. 1C). This process improves the mobilization of secretions from the airways (the vest™ Model 104-airway clearance system-Hill Rom).
Subsequently the circuit was opened allowing the drainage of the liquid according to gravity.
At first, in PAP patients the fluid was milky and the instillation and drainage cycle continued until the fluid became cleaner. From 7 to a maximum of 8 liters were instilled with a close monitoring. A maximum loss of 0,60 l was registered.
The washing of the left and right lung was usually carried out in two different sessions whit a period of distance between the two procedures of minimum three weeks and maximum one year. In only one case we did both lungs in same session lasting after 7 hours.
We measured how the patient responded to the treatment through symptom presence, respiratory function test and radiological imaging at the follow up.

Results

A total of five patients were treated by WLL. Four patients suffered from alveolar proteinosis while one suffered from type B NPD. The median age was 52 years, 3 patients were male and 2 were female. Two of them were smokers, two no-smokers and one was a former smoker. Dyspnea and dry cough were the most common symptoms. In 4 cases the clinical onset was more severe because of the presence of hypoxemic respiratory failure, in case 5 hospitalization in intensive care unit was necessary; in only one case the patient was asymptomatic. In four patients the diagnosis was PAP, three with the autoimmune form and one with secondary form related to GATA 2 deficiency (already published) [11].
In three cases the diagnosis of PAP was confirmed by

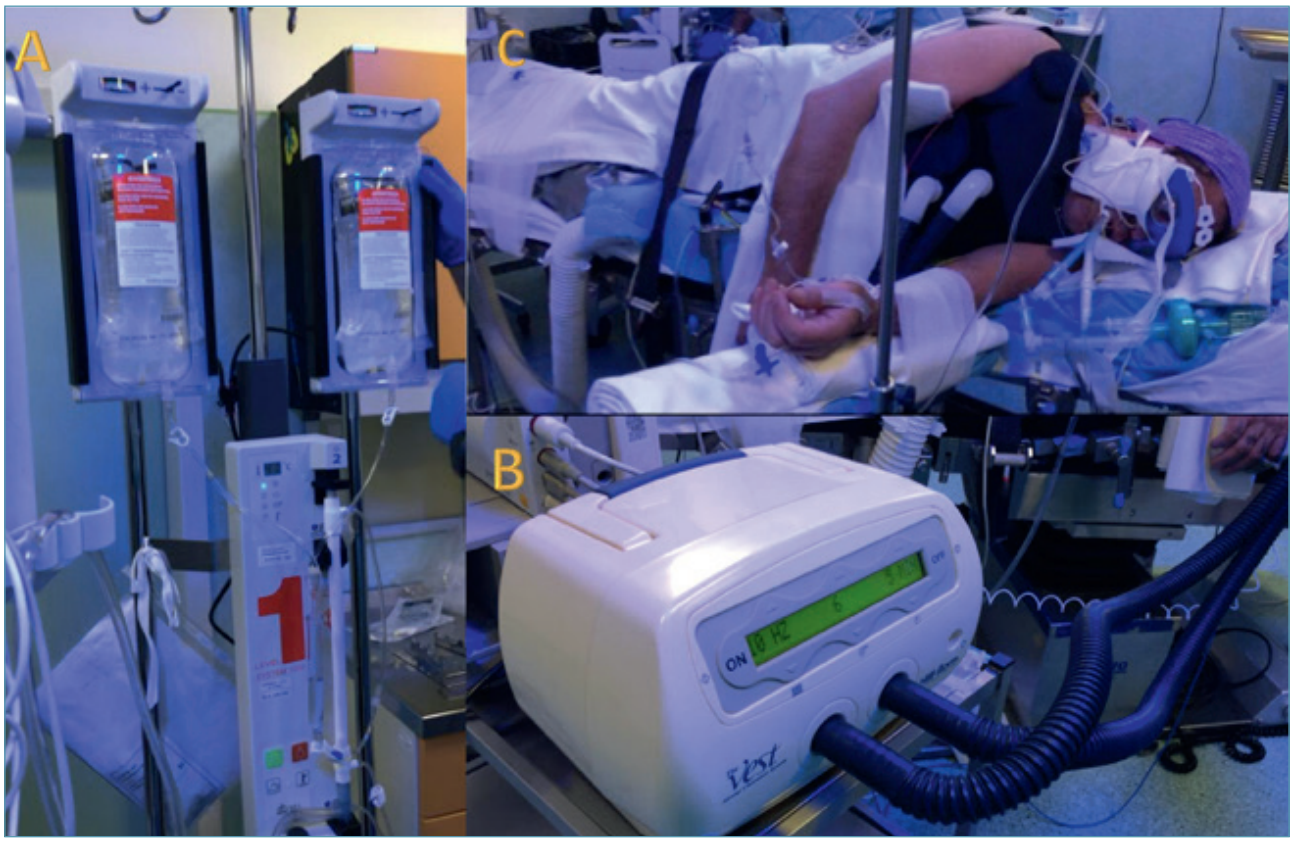

Figure 1. A) bags of saline solution warmed to 41°C. B) mechanical chest compressor. C) vest.

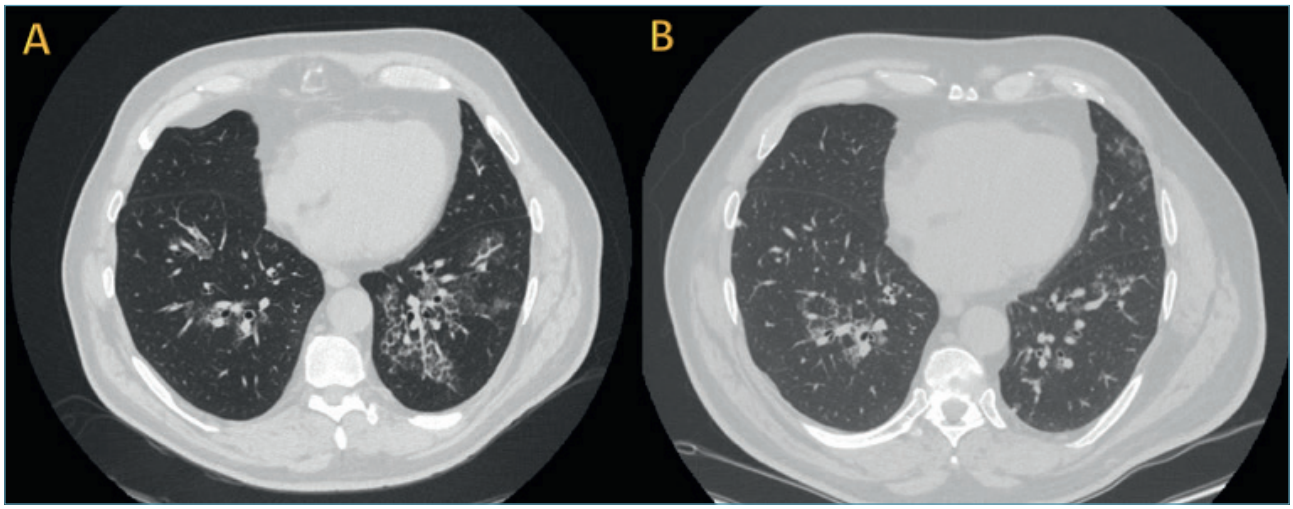

Figure 2. A) Thorax HRCT shows ground glass opacities in the right lower lobe and interlobular septal thickening in region of ground glass opacities representing "crazy paving" in the left lower lobe. B) Note the reduction of opacities specially in the left lower lobe after treatment.

flexible bronchoscopy with the presence on the BAL of periodic acid Schiff (PAS) positive lipoproteinaceous substance [12-14]. Surgical lung biopsy was performed in only one case. The BAL-F of the case 5 showed foamy macrophages and macrophages with sea blue pigmented granules in the cytoplasm at May Grunwald-Giemsa technique [5]. The diagnosis of type B Niemann-Pick Disease was confirmed by cryobiopsy [15] and bone marrow biopsy. The time elapsed between the diagnosis of the pathology and the execution of the procedure was between a minimum of 10 days to a maximum of one year. Only two patients were subjected to procedure ten days after diagnosis for hypoxemic respiratory failure.

All patients were admitted to intensive care unit after WLL for at least one day (Tab. II). In three patients extubation was possible in the same day of the procedure. Two patients were maintained on mechanical ventilation one more day and were successful extubated when the ratio of the partial pressure of oxygen in arterial blood (PaO_2) to the inspired oxygen fraction (FiO_2) (PaO_2/FiO_2 ratio) was 190 for the case 1 and 300 for the case 5. No extubation failure was registered, all patients restarted spontaneous breathing whit low flow oxygen supply.

Fever and mild pleural effusion were reported in only two patients after the procedure and then they were resolved respectively with furosemide and paracetamol.

The longest follow up period available is 18 months old in Case1. In this case the disease began with acute respiratory failure treated at another Center. When the patient presented to our center, he was stable with value of forced vital capacity (FVC) and DL_{CO} equal to respectively 98% and 70% of predicted. At first we made observation alone and performed a WLL after 1 year for worsening lung function: FVC 69% and D_{LCO} 60% of predicted.

We observed an improvement of FVC 85% and D_{LCO} 87% of predicted with a return to its normal value in five days after WLL's left lung . These values remained stable for other six months and were confirmed by the improvement of the left lung on the thorax HRCT and the reduced dyspnea (Fig. 2A-B). For better clinical conditions we did not carry out a sequential WLL.

In Case 2, patient reported an improvement of respiratory symptoms after the first WLL but, no other follow up data are available.

In Case 3 symptoms and analytical blood gas parameters got better just after WLL of both lungs.

At the 2 months follow up the thorax HRCT showed an increase of crazy paving pattern areas with continuing dyspnea, so we decided to perform a right WLL. After this, patient reported decrease of symptoms confirmed by further improvement of blood gas parameters (Tab. III) and value of FVC and D_{LCO} respectively equal to 92% and 40%.

In Case 4, we do not have any valid respiratory function test. The compliance of the execution test was difficult because of neurological dysfunctions caused by idiopathic segmental dystonia. After a month, the follow up thorax HRCT was better and the patient had less dyspnea [10] (Fig. 3 A-B).

For Case 5 there was an improvement of radiological imaging and arterial O_2 tension (PaO_2) after the first WLL (Fig. 4 A-B-C). Prior and post FVC was stable at 55% of predicted, D_{LCO} was not available. The HRTC of the thorax made after two months and after the second WLL got worst. Its follow up is still ongoing.

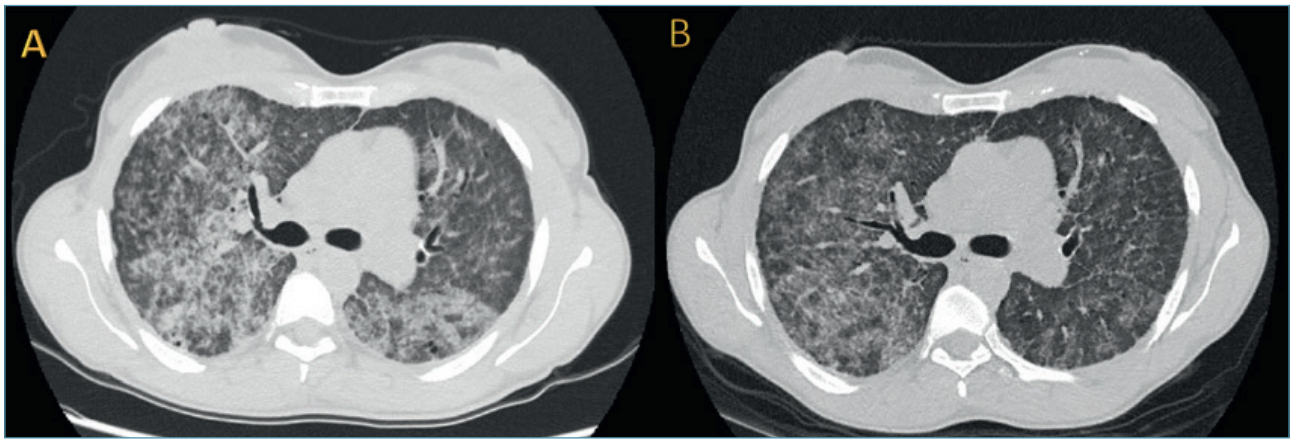

Figure 3. A) Thorax HRCT shows bilateral "crazy paving" pattern with small pulmonary consolidation opacities. B) Thorax HRCT after bilateral whole lung lavage treatment: note the reduction of "crazy paving" pattern and consolidation area.

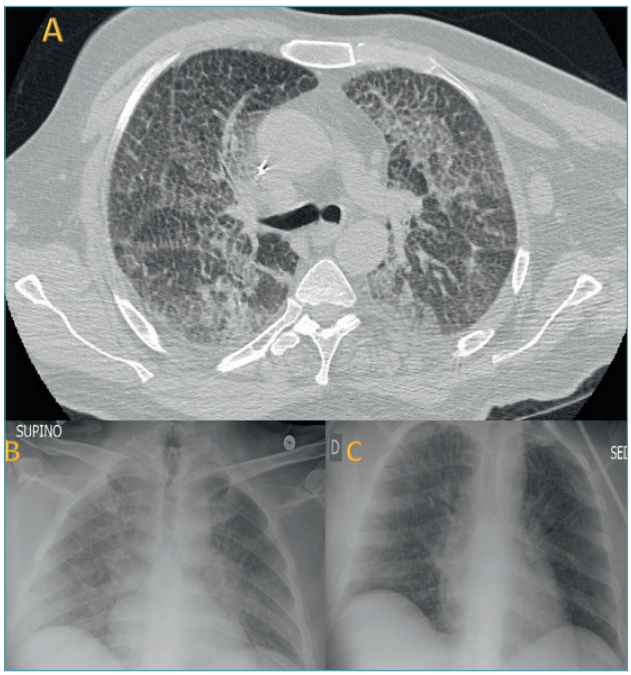

Figure 4. A) Thorax HRCT shows the radiological findings in type B Niemann-Pick Disease: bilateral smooth intra- and inter-lobular septal thickening and ground-glass opacities with crazy-paving pattern in the apical segment of the right lower lobe and in the left upper lobe. B) Chest radiographs before the WLL shows radiopacities areas with reticular thickening predominantly in the right lung. Note the improvement in C) after the first lavage.

Discussion

WLL is the main therapeutic approach for pulmonary alveolar proteinosis [1], a rare respiratory disease characterized by the accumulation of surfactant inside the alveoli leading to worsening of the gaseous exchanges [16]. According to etiopathogenesis, PAP could be classified in 3 forms: primary (autoimmune, hereditary), secondary and congenital [16].

The autoimmune form is the most common and occurs in about 90% of cases. It is characterized by the presence of antibodies against GM-CSF which is a pivotal cytokine mediating differentiation of alveolar macrophages involved in the catabolism of surfactant [2]. The discovery of the GM-CSF role in PAP has resulted in different emerging therapies such as a supplement of GM-CSF in subcutaneous or aerosolic form [16,17]. If GM-CSF treatment may be considered in patients with moderate disease and could induce remission [18], it is not enough in the severe form and must be associated to WLL. Ohkouchi et al. reported that in patients with autoimmune PAP, the GM-CSF inhalation after WLL improved clinical, radiological and laboratory parameters compared to GM-CSF inhalation before WLL particularly in severe form [19].

Beccaria et al. reported the long-benefit of WLL measured in terms of respiratory function, effort tolerance, arterial blood gas analyses and disease recurrence.

In a three-year follow up all registered parameters got better. FVC was improved after only one week. $D_{L_{CO}}$, PaO_2, $P_{(A-a)}O_2$ got better more slowly without a complete recovery. In more than 70% of patients there was a lack of worsening of respiratory symptoms without the need for other treatments such as repeated lavage [20].

Although WLL remains the gold standard therapy in primary and in some causes of secondary PAP; it could be also applied in other disease such as exogenous lipoid pneumonia, silicosis, silicoproteinosis, alveolar hemorrhage, cryptogenic fibrosing alveolitis [1-21].

WLL is also one of the few possible treatments for lung involvement in Type B NPD in addition to bone marrow transplantation [22,23]. Type B NPD is a subtype of lysosomal storage disorder in which the sphingomyelinase mutation determines the accumulation of sphingomy-

elin in endothelial reticulum cells of various organs. It is characterized by hepatosplenomegaly, thrombocytopenia, few or no neurological symptoms and quite frequently pulmonary involvement. The accumulation of lipid laden macrophages in the alveolar septa, bronchial walls and pleura brings to respiratory failure with poor prognosis [24]. WLL in type B NPD was reported in only three cases in literature: one in adult, one in child e one in an adult patient in which A-PAP and type B NPD coexisted [25-27]. The problem in the use of the WLL in the NPD is that it is not always successful and when it happens reduces only the symptoms not altering the course of the disease [26]. WLL brings more lasting benefits to patients with PAP. PAP may undergo remission and it has been reported that most patients who went into remission were subjected to one more than one WLL [16].

Conclusions

In this study we reported a series of 5 patients who underwent to WLL. The major limitation of this study is the lack of different lung function test follow-up because of the limitation of spirometry exam in COVID-19 pandemic. Overall WLL gives some benefits to patients in terms of improved symptoms, blood gas analysis, respiratory function test and radiological imaging. Although, WLL is an invasive procedure, it remains a viable and safe option [1] *and as such could be applied in more centers than the current ones.*

Treatment with supplement of GM-CSF will be proposed in patient with autoimmune PAP and particularly in severe form. More difficult seems the response to WLL in the case of NPD in which the procedure gives only a temporary improvement. Dramatically as opposed to PAP there are not many other therapeutic changes for NPD.

A longer observation is necessary to elucidate the duration of benefits.

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