CASE REPORT

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Successfully physical therapy program for functional respiratory rehabilitation after lung transplant surgery – case report

DIANA-LIDIA TACHE-CODREANU[1)], IULIANA DAVID[2)], CRISTIANA GABRIELA POPP[3)], LUCIAN BOBOCEA[1)], MAGDALENA RODICA TRĂISTARU[4)]

[1)]*Department of Rehabilitation, Colentina University Hospital, Bucharest, Romania*

[2)]*Research Core from Department of Rehabilitation, Colentina University Hospital, Bucharest, Romania*

[3)]*Department of Pathology, Colentina University Hospital, Bucharest, Romania*

[4)]*Department of Physiotherapy, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

The first lung transplant (LT) was made in Romania in 2018 at a 36-year-old male patient with chronic obstructive pulmonary disease (COPD). The study follows the first LT rehabilitation by describing the physical therapy program (PTP), the measurements of body mass and appendicular skeletal muscle mass (ASM) by bio-impedancemetry analysis (BIA) and the functional capacity assessment realized by the six-minute walk test (6MWT) and by the functional respiratory tests (FRTs) in order to evaluate the effectiveness of functional respiratory rehabilitation in this case during a period of one year. In parallel, repeated transbronchial biopsies were performed after six weeks, three months, six months and one year since the transplant. Only the first biopsies showed injuries suggesting an acute rejection, all the rest revealing mild, unspecific lesions. The patient followed 15 sessions of respiratory exercises, joints mobilizations and progressive global muscle strength started one month after LT surgery and was also instructed to perform the exercises at home, using a tablet given at discharge and under monthly guidance through telemedicine. All the measurements were performed before and after the rehabilitation cure, and it was repeated at three different evaluations for one year. The results showed that at the end of follow-up, the 6MWT was significantly increased from 59% of predicted distance at the intake in post-acute hospitalization to 166% at one year after LT, without desaturation that represent a very good evolution; the FRTs increased to normal, and the body weight increased with 18 kg (from severe underweight to normal weight) with constant increasement of skeletal muscle mass. The use of PTP after LT surgery significantly improves functional capacity and increases body mass and skeletal muscle mass.

Keywords: lung transplant rehabilitation, acute rejection, physical therapy, respiratory rehabilitation, six-minute walk test.

Introduction

The *International Society for Heart and Lung Transplantation* (ISHLT) administrates a worldwide registry that contains data from more than 50 000 adult lung transplants (LTs) performed since 1985 [1]. The *ISHLT* has developed a recipient selection guideline for appropriate identification and selection of LT candidates [2]. Therefore, a pretransplant evaluation is recommended for candidate identification and to avoid the exposure at the risk of the transplant surgery of a patient until other viable treatment options are considered. Current indications for LT are age <65 years, severe disability despite maximal drug therapy, lack of other associated conditions, such as liver or kidney disease. There are three specific diseases indicated for LT: chronic obstructive pulmonary disease (COPD), interstitial lung disease and cystic fibrosis [1].

COPD is a major cause of death and mortality worldwide [3]. According to *World Health Organization* (WHO) predictions, by 2030, COPD will become, worldwide, the third leading cause of death. COPD is also a common indication for LT and represents 26.1% to 40% of all surgeries for LT [2, 4]. The characteristics of COPD are expiratory limitation that is not fully reversible, deregulated chronic inflammation, and emphysematous destruction of lungs [5]. *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) classified COPD in four stages depending on the severity. Several clinical features comprise COPDs, such as chronic bronchitis, destruction of small airways and enlargement/disorganization of alveoli and loss of alveolar tissue [5]. Data from population-based studies show that cigarettes smoking as a risk factor may only be attributed to half of COPD case [6]. However, some studies show that patients who stopped smoking cigarettes at second stage of life presents better function of the lungs [3].

The aim of the rehabilitation program (RP) in COPD is to maintain healthy activity of daily living skills, improve pulmonary capacity and reduce effort induced dyspnea [6]. A program of exercises training of the muscles of ambulation is recommended as a mandatory component of RP for patients with COPD [7]. Also, RP reduces the hospitalization period [3].

For the LT candidate, the RP has benefits in both cases: before and after surgery [4]. Before LT, RP helped to increase physical functioning [8] and survival rate [9]. After LT, the recovery strategies recommend RP to stabilize the

This is an open-access article distributed under the terms of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Public License, which permits unrestricted use, adaptation, distribution and reproduction in any medium, non-commercially, provided the new creations are licensed under identical terms as the original work and the original work is properly cited.

symptoms and to prevent the complications in order to change behavior according to the new status and to improve quality of life (QoL) [10]. Exercise training is one of the main components of RP and it has a key role in improving physical tolerance, increasing oxidative capacity in skeletal muscle, and reducing perceived dyspnea during daily activities [4].

Aim

In the present, there is not enough data to establish the impact of exercises training and/or physical activities on transplant rejection and survival and the appropriate parameters of the frequency, intensity, and duration in physical training. So, we performed an RP, based on exercise training, for a patient with LT. The studied parameters permitted us to establish the positive effect of rehabilitation on lung function, performing daily activities and physical performance [six-minute walk test (6MWT)]. Moreover, each assessed moment included histopathological (HP) evaluation, to follow-up if some adaptive modification appeared.

Case presentation

We present the case of a 36-year-old man from an urban area, known with sequential bilateral LT performed on April 2018 in Bucharest for COPD, which was the first case of LT in Romania. Informed patient's consent was given for the data presented. This study was made retrospectively, without influencing patients' treatment or management and the work respects the *World Medical Association* (WMA) Declaration of Helsinki. The research was approved by Colentina University Hospital Research Ethics Committee.

Evaluation and rehabilitation

The pre-LT phase

The patient with 174 cm height, 46 kg weight, smoker in the past for 15 years, 20 cigarettes a day, had right lung pulmonary tuberculosis in 2010 associated with bilateral pulmonary emphysema for which a right lower lobectomy was performed in 2011. Starting with that year, the patient was known to have COPD stage IV GOLD. In 2016, the patient had five episodes of spontaneous left pneumothorax. He completed a pretransplant rehabilitation in the Department of Pulmonology (DP), Colentina University Hospital, Bucharest, Romania, in several hospitalizations before the LT.

The diagnosis of pre-LT phase was COPD stage IV GOLD, with chronic respiratory insufficiency and bilateral central and pan-lobular pulmonary emphysema. Right lower lobectomy; recurrent left pneumothorax; severe mixed ventilatory dysfunction; cachexia; candidate for LT.

According to the diagnosis, the patient followed hygienic and dietary treatment (hypercaloric diet), counseling for improvement of dyspnea and also followed pharmacological treatments prescribed by the Pulmonology Team. The specific physical therapy program (PTP) made in the pre-LT phase by the rehabilitation team is described below.

For the pre-LT phase, the patient made, at each hospitalization in DP, Colentina University Hospital, daily respiratory rehabilitation (RR) sessions using progressive intensity and duration exercises according to oxygen saturation, heart rate and dyspnea and leg fatigue symptoms. He performed physical exercises for inferior and superior limbs (twice per day), and once per day training at ergometric bicycle with progressive loading under oxygen therapy for maintaining a level of 90–92% oxygen saturation and heart rate less than 120 beats/min. The exercises program was followed by the patient at home. The last intake in hospital was three months before LT.

The post-LT phase

After the sequential bilateral LT followed by the intake in Intensive Care Unit (ICU) in St. Mary Hospital, Bucharest, the patient was hospitalized in Colentina University Hospital for four times during a period of one year in order to establish the RR program to follow in hospital and after discharge. Thus, at one month after LT, the patient was discharged from ICU and he was transferred in DP in Colentina Clinical Department, in a dedicated area strictly supervised by pulmonology team who indicated a complex assessment of clinical, functional, and HP evaluations combined with biological and imagistic tests.

After the functional assessment, the PTP was created by the rehabilitation team led by the specialist rehabilitation doctor. They established the PTP program based on functional tests results, and they monitored the recovery evolution during the hospitalization. The PTP program was made up of 15 daily sessions and it was realized by the subject under the direct guidance of the physical therapist. At the discharge, it was made another functional assessment which was the basis for establishing a home adapted PTP program for the patient to follow upon leaving the hospital. To monitor the RR evolution of the patient, another three short hospitalizations were made in DP: at three months, at six months and at one year after LT and the same tests were made as the first hospitalization. After each short hospitalization, the Rehabilitation Team adapted the PTP to follow by the patient at home.

The diagnosis at the time of the post-acute LT intake was status post bilateral sequential LT for COPD stage IV GOLD with chronic respiratory insufficiency and bilateral central and axillary pulmonary emphysema.

This clinical diagnosis is completed with the functional alteration: physical and cardiovascular deconditioning, resistive breathing from airflow limitation, skeletal muscle abnormality with decreased skeletal muscle mass.

At the assessment of the neuro-arthro-kinematic system of the body was found deconditioning syndrome; hyperinflation of the thoracic cage – typical for a COPD patient; generalized muscle atrophy; walking – possible without support.

The patient continued the hygienic and dietary treatment (hypercaloric diet) started in pre-LT phased adjusted for this time and also pharmaceutical treatments prescribed by the pulmonology team. The specific PTP made by the rehabilitation team is described below.

The PTP in the post-LT phase

The PTP in the post-LT phase includes aims and used methods.

The following aims of PTP were developed according with clinical and functional assessments: increase of the respiratory volume; improvement of the diaphragm mobility;

increase muscles strength and effort endurance; maintaining the alignment of the body and posture; maintaining joints mobility and muscles spine tone; recovery of functional mobility; increase of body mass, according to body mass index (BMI) evaluation; reintegration in family life and work life.

For the above described objectives, we used the following methods:

Kinesiotherapy used exercises for the topics: respiratory exercises which train accessory muscles and diaphragm mobility for abdominal breathing, joints mobilizations and progressive increasing the global muscle strength for rib cage, vertebral column and for the upper and lower limbs using the ergometric bicycle with progressive loading. The training program was performed once a day for three weeks, was one hour long and also included longer outside walks monitored with a phone application. Cycling leads to less exercise-induced desaturation and lower dyspnea levels, while walking is a functional training that is important for gait training and activities of daily life.

A combination of endurance training and strength training, at a moderate intensity (60–70% of the maximum tolerated), was used. Symptoms (10-point Borg Respiratory Scale) and hemodynamic parameters were closely monitored, and supplemental oxygen was available, although never necessary.

Special attention was given to strength exercises of upper limbs in the early phase of minimal invasive LT as it is mentioned in Table 1.

Breathing exercises included: cough training, pursed lips breathing, dyspnea induced breathing, diaphragmatic breathing, and coordination of breathing with movement.

Massage – therapeutic tonic massage for the limbs and sedative massage for the paravertebral muscle of the vertebral column.

Table 1 – ***Special mentions/limitations in exercises training for post-LT***

Timeline post-LT	Limitations
1–2 weeks	No stretch or traction to the scar tissue (*pectoralis major* and *serratus anterior* muscles). Carry loads less than 5 kg.
3–6 weeks	Maximum 90° flexion and abduction in the shoulder joint.
After six weeks	Carry loads over 5 kg.
After three months	Range of motion and load capacity fully restored.

LT: Lung transplant.

The patient was also instructed to perform the exercises at home, using a tablet given at discharge and under monthly guidance through telemedicine.

At the discharge after the first hospitalization that followed the PTP, the patient was given the dismissal recommendations to continue the learned PTP, targets: oxygen saturation 98%, spontaneous, blood pressure 115/70 mmHg, heart rate 100 beats/min, afebrile.

The patient followed the same recommendations after each phase of future assessments (at one month, three months, six months and one year after LT).

Evaluated parameters

The focus of this case study was to analyze the post-acute LT rehabilitation phase and the evolution on short, medium, and long term from the point of view of the functional status. Thus, it was analyzed the same parameters for each assessment that was made: at the intake in DP (made at one month after LT), at the discharge from DP (after 15 days of hospitalization with daily sessions of PTP), at three months, at six months and at one year after LT.

The analyzed parameters were mentioned in Tables 2–4.

Table 2 – ***Weight parameters***

Weight parameters	Three months pre-LT	Intake 17.05.2018 One month after LT	Discharge 07.06.2018	July 2018 Three months after LT	October 2018 Six months after LT	April 2019 One year after LT
Body weight [kg]	46	47	50	53	58	65
BMI [kg/m^2]	15.2 (severe underweight)	15.52 (severe underweight)	16.51 (underweight)	17.51 (underweight)	19.2 (normal)	21.46 (normal)
ASM [kg]	23.1	23.3	23.9	25.5	26.7	27.8
ASMI [kg/m^2]	7.62	7.69	7.89	8.42	8.81	9.18

ASM: Appendicular skeletal muscle mass measured by bio-impedancemetry analysis (BIA); ASMI: Appendicular skeletal muscle mass index (ASM/square of height) for better correlations with predictor factors; BMI: Body mass index (weight/square of height); LT: Lung transplant.

Table 3 – ***6MWT, hemodynamic parameters***

Hemodynamic parameters		Intake 17.05.2018 One month after LT	Discharge 07.06.2018	July 2018 Three months after LT	October 2018 Six months after LT	April 2019 One year after LT
Date of measurement		21.05.2018	06.06.2018	10.07.2018	23.10.2018	12.04.2018
6MWT	Distance achieved [m]	435	528	660	628	1000
	Percent of distance predicted	59%	72%	90.5%	87%	166%
Oxygen saturation (initial value)		96%	97%	97%	98%	97%
Oxygen saturation (final value)		97%	98%	97%	98%	98%
Heart rate [beats/min] (initial value)		118	110	108	103	107
Heart rate [beats/min] (final value)		139	130	126	109	116
Borg Respiratory Scale (initial value)		2	0	0	0	0
Borg Respiratory Scale (final value)		3	1	1	0.5	1
Borg Feet Fatigue Scale (initial value)		0	0	0	0	0
Borg Feet Fatigue Scale (final value)		3	3	3	1	0.5

6MWT: Six-minute walk test; LT: Lung transplant.

Table 4 – ***Functional respiratory tests parameters***

Functional respiratory tests parameters	Intake 17.05.2018 One month after LT	Discharge 07.06.2018	July 2018 Three months after LT	October 2018 Six months after LT	April 2019 One year after LT
Date of measurement	21.05.2018	07.06.2023	10.07.2018	23.10.2018	2.04.2019
FEV1 [L]	2.98 (75%)	3.58 (89%)	4.15 (106)	4.77 (101%)	3.94 (100%)
FVC [L]	3.2 (67%)	3.73 (77%)	4.44 (94%)	4.74 (95%)	4.88 (103%)
FEV1/FVC ratio	93%	96%	93.7%	99%	80.7%
DLCOc [mL/min/mmHg]	27.75 (85%)	26.71 (82%)	29.18 (91%)	26.85 (83%)	27.30 (91%)
DLCO per unit of alveolar volume [mL/min/mmHg/L]	4.50 (94%)	3.87 (81%)	4.43 (93%)	3.87 (81%)	4.01 (84%)
TLC during DLCO [L]	6.21 (91%)	6.94 (102%)	6.66 (98%)	6.99 (102%)	6.65 (97%)
RV during DLCO [L]	3.36 (183%)	3.35 (182%)	2.98 (139%)	2.63 (141%)	1.77 (95%)
$RV_{(DLCO)}/TLC_{(DLCO)}$ ratio	54.2 (194%)	48.4 (173%)	44.75 (137%)	37.62 (133%)	15.03 (94%)

DLCO: Diffusing capacity of the lungs for carbon monoxide; DLCOc: DLCO corrected for hemoglobin; FEV1: Forced expiratory volume in one second; FVC: forced vital capacity; RV: Residual volume; TLC: Total lung capacity.

For comparison with the pre-LT phase, it was presented the measured walking distance until 85% oxygen desaturation (because the subject could not walk for six minutes) and also the most important values of functional respiratory tests (FRTs) measured three months before LT.

In addition to the analysis of respiratory capacity, the post-LT transbronchial biopsies images made at each stage of evaluation were studied in order to observe the possible correlations between the results of HP exams and functional parameters.

During his post-LT surveillance, the patient underwent transbronchial lung biopsies *via* flexible bronchoscopy after six weeks, three months, six months and one year since the transplant. All tissue fragments were immediately immersed in 10% neutral buffered formalin, fixed for six hours, washed with water, and then routinely processed using an automatic tissue processor for paraffin embedding. From every paraffin block, there were obtained at least two sections of 2.5 μm from three different levels for routine Hematoxylin–Eosin (HE) staining and supplemental sections for special staining [Periodic Acid–Schiff (PAS), Giemsa, Ziehl–Neelsen and Grocott] and immunohistochemical (IHC) assays for cytomegalovirus (CMV) and *Pneumocystis jirovecii*. Every biopsy was evaluated by two independent pathologists, one with special training in post-LT lesions, then discussed and a final diagnosis was formulated.

We respected current recommendations – the diagnosis of acute and chronic rejection of a LT was made on HE-stained sections [11]. We didn't use complement 4d (C4d) immunostaining because its role for antibody-mediated rejection in the lung remains controversial [12].

We carefully screened every slide for opportunistic infections: fungi, CMV, and *P. jirovecii*, all frequently involved in infections after LT [13]. Although these infections can be asymptomatic or have misleading symptoms, they usually have negative influences on postoperative outcomes after LT and increase the occurrence of chronic lung allograft dysfunction [14–17].

In order to facilitate the analysis and the interpretation of data, we present the measured parameters in Tables 2–4 containing comparative values of each evaluation.

On the first biopsy there were identified multiple lesions leading to the diagnosis of acute cellular rejection, as is the consensus statement by the *Lung Rejection Study Group* (LRSG): multiple dense, nodular, perivascular mononuclear infiltrates, areas of ischemic necrosis of alveolar septa, areas of interstitial hemorrhage (Figure 1, A and B; Figure 2, A and B).

A very interesting observation is the fact that these lesions were significant only in the sections from the first level. On the second level, the inflammatory infiltrate fades away (Figure 3, A and B) to almost disappear on the third level, leaving an area of nodular, dense, hyaline fibrosis (Figure 4).

This aspect emphasizes the importance of multiple sections from lung biopsies in LT receivers, since the lesions can be very small and multifocal. No microorganisms were found on the examined tissue. Also, no bronchiolitis was identified. The final diagnosis was acute cellular mediated allograft rejection, A3B0 grading, with accompanying reperfusion lesions (Table 5).

Table 5 – ***Revised working formulation for classification and grading of pulmonary allograft rejection [16]***

A. Perivascular inflammation (acute rejection)	B. Airway inflammation	C. Chronic airway rejection	D. Chronic vascular rejection
Grade 0: none	Grade 0: none	0: absent obliterative bronchiolitis	0: absent accelerated graft vascular sclerosis
Grade 1: minimal	Grade 1R*: low grade	1: present obliterative bronchiolitis	1: present accelerated graft vascular sclerosis
Grade 2: mild	Grade 2R*: high grade		
Grade 3: moderate			
Grade 4: severe			
AX: ungradable	BX: ungradable	CX: ungradable	DX: ungradable

*R denotes new revised stage.

Since the patient was clinically asymptomatic and HP findings did not correlate with his performance status, this diagnosis offered him the possibility to perform an adapted RP.

The second transbronchial lung biopsy was performed approximately three months after the LT.

On three different levels, only two nodular lymph cells infiltrates, comprising 15–20 cells (resolving rejection) were found. Also, the HP examination revealed small areas of atelectasis, inconspicuous *corpora amylacea*, small interstitial accumulations of anthracotic pigment and minimal interstitial fibrosis (Figure 5, A and B; Figure 6, A and B; Figure 7, A and B). No vascular or bronchial lesions were identified. Special stains (PAS, Giemsa, Ziehl–Neelsen and Grocott) did not reveal microorganisms. IHC stains for CMV and *P. jirovecii* were negative.

After six months from the LT, the patient underwent another biopsy, during his routine hospitalization. The microscopic examination revealed a quasi-normal lung tissue, with inconspicuous lymph cells in alveolar interstitium, areas of atelectasis and emphysema and minimal interstitial fibrosis (Figure 8, A and B). Special stains (PAS, Giemsa, Ziehl–Neelsen and Grocott) did not reveal microorganisms. IHC stains for CMV and *P. jirovecii* were negative.

Finally, after one year from the transplant, another transbronchial lung biopsy was performed. The HP examination revealed areas of emphysema, significant areas of lambertosis – replacement of alveolar lining cells with bronchiolar epithelium, inconspicuous foamy macrophages in alveolar spaces and small interstitial accumulations of anthracotic pigment. No interstitial fibrosis or bronchiolar lesions are seen. Special stains (PAS, Giemsa, Ziehl–Neelsen and Grocott) did not reveal microorganisms.

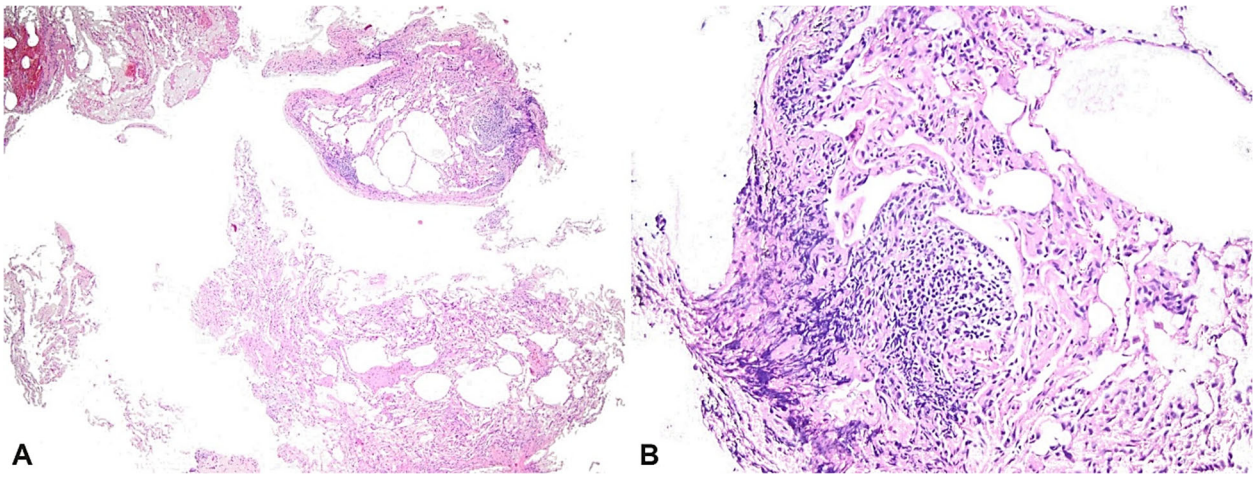

Figure 1 – ***Left lung biopsy six weeks after transplantation. First level of the first biopsy: (A) Irregular inflated alveoli with prominent nodular inflammatory infiltrate surrounding concentrically a small blood vessel and infiltrating adjacent alveolar interstitium; no endothelialitis or bronchiolitis; (B) Detail of the previous image highlighting the nodular inflammatory infiltrate comprising lymph cells, plasma cells and monocytes; no eosinophils are seen. HE staining: (A) ×40; (B) ×200. HE: Hematoxylin–Eosin.***

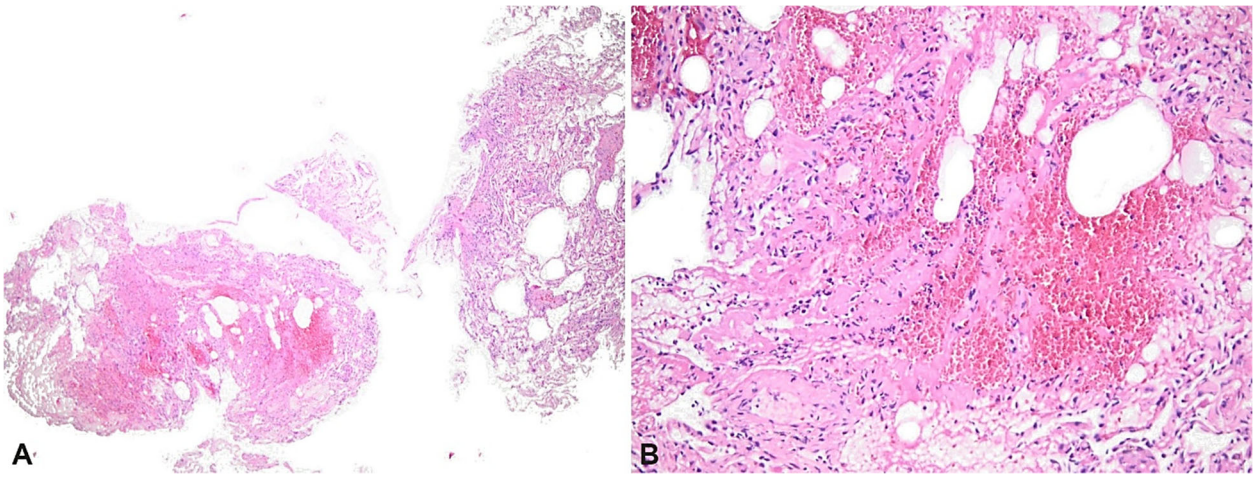

Figure 2 – ***Left lung biopsy six weeks after transplantation. First level of the first biopsy: (A) Partially inflated alveoli with large area of interstitial hemorrhage and coagulative necrosis alternating with fibrosis composed of thin strains of collagen; areas of reactive alveolar epithelial hyperplasia; no bronchiolitis in the visible bronchia; (B) Detail of the previous image highlighting the area of ischemic necrosis and fibrosis of alveolar walls and interstitial hemorrhage; no endothelialitis. HE staining: (A) ×40; (B) ×200.***

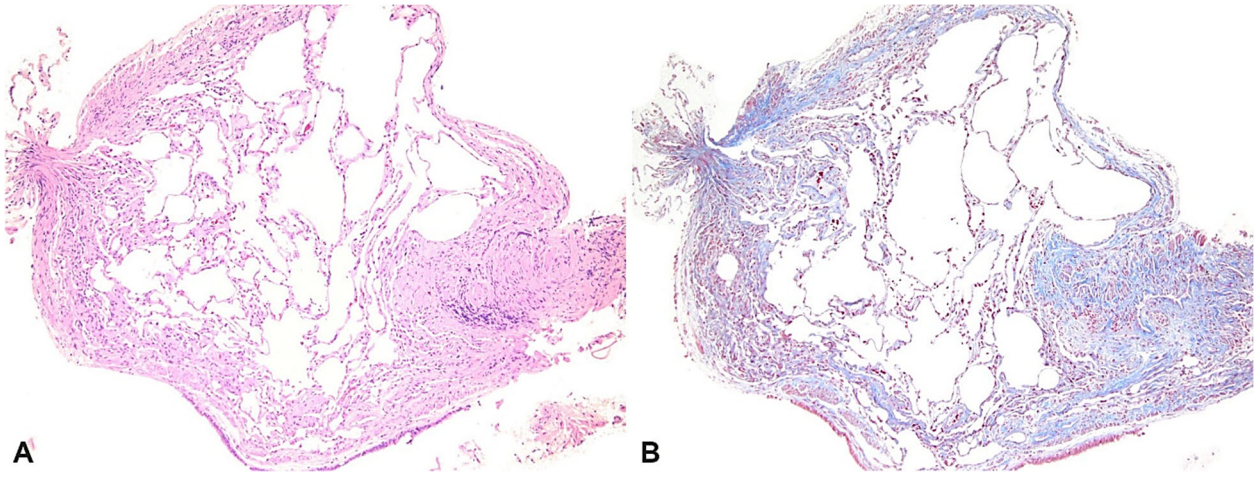

Figure 3 – ***Left lung biopsy six weeks after transplantation. Second level of the first biopsy: (A) Note on the second level (approximately at 90 µm distance) the lighter infiltrate on the same fragment as the one in Figure 1; (B) MT staining reveals fibrosis (blue) in alveolar walls. HE staining: (A) ×100. MT staining: (B) ×100. MT: Masson's trichrome.***

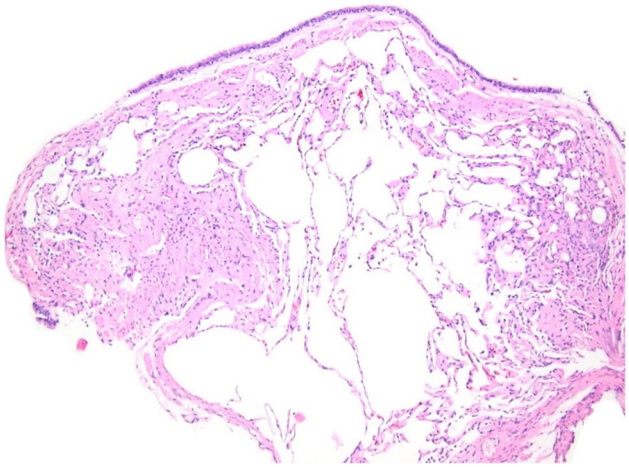

Figure 4 – ***Left lung biopsy six weeks after transplantation. Third level of the first biopsy. The third level (approximately at 200 µm distance from the first one) shows only fibrosis with inconspicuous lymph cells. No bronchiolitis is seen. HE staining, ×100.***

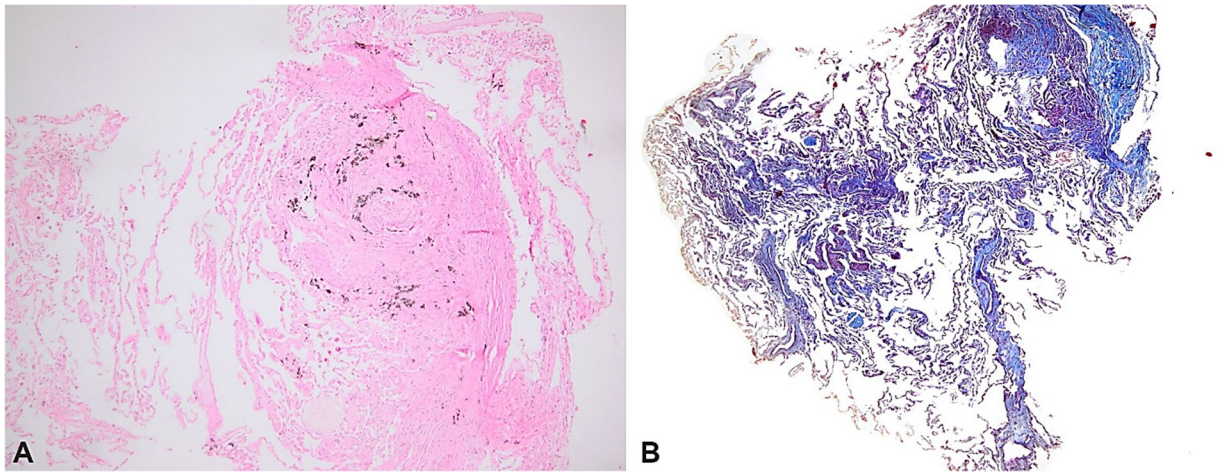

Figure 5 – ***Left lung biopsy three months after transplantation. First level of the second biopsy: (A) Interstitial fibrosis and some extracellular accumulations of black, granular, anthracotic pigment; (B) MT staining highlighting interstitial fibrosis. HE staining: (A) ×200. MT staining: (B) ×40.***

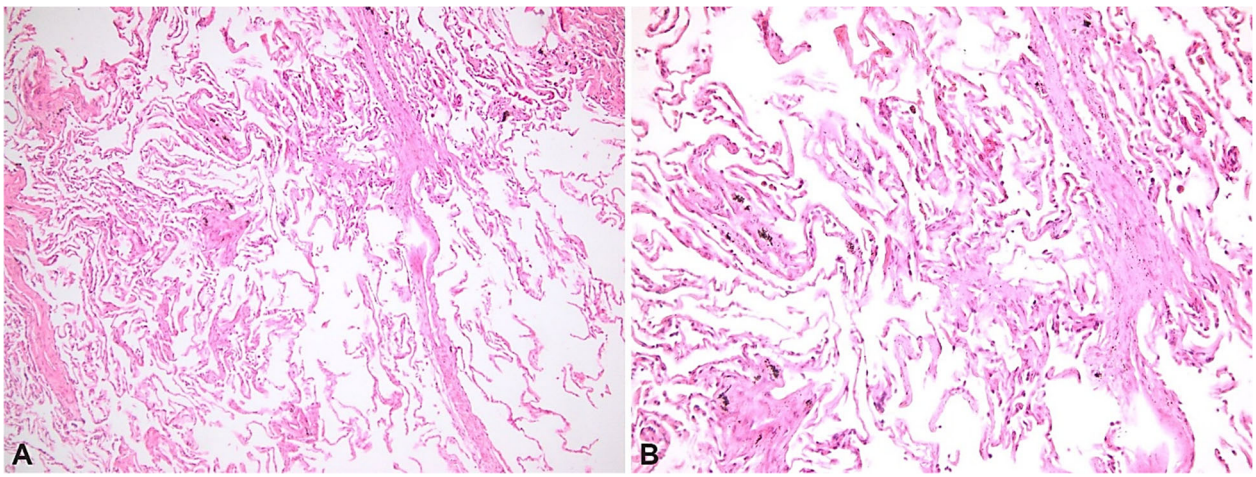

Figure 6 – ***Left lung biopsy three months after transplantation. Second level of the second biopsy: (A) Atelectasis and small anthracotic deposits in alveolar walls; (B) Detail of the previous area; no signs of reperfusion injuries or graft reject are visible. HE staining: (A) ×100; (B) ×200.***

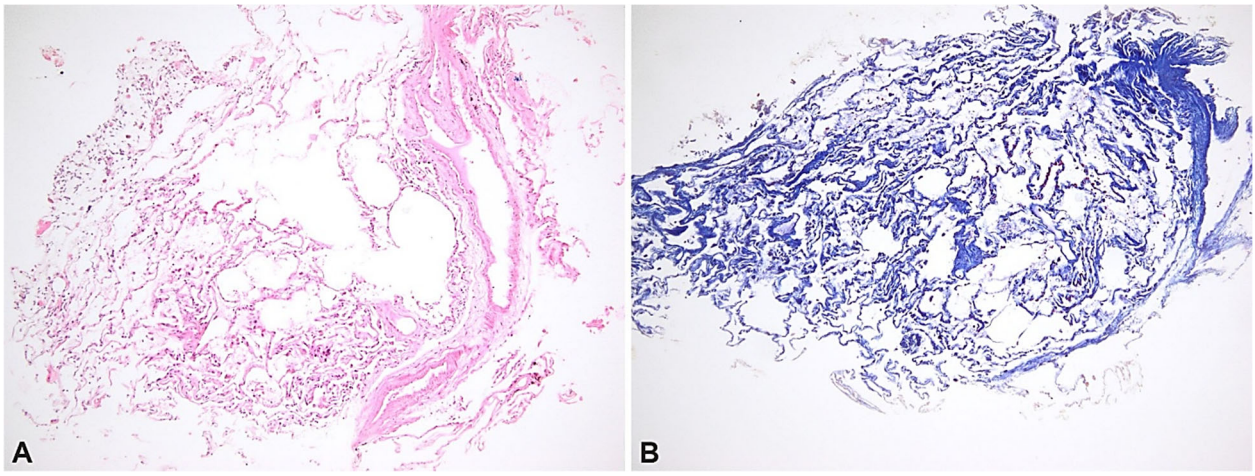

Figure 7 – ***Left lung biopsy three months after transplantation. Second level of the second biopsy: (A) Alveolar spaces, some dilated, with fragmented walls (emphysema) and others with atelectasis; (B) Same area revealing minimal fibrosis in alveolar walls. HE staining: (A) ×100. MT staining: (B) ×100.***

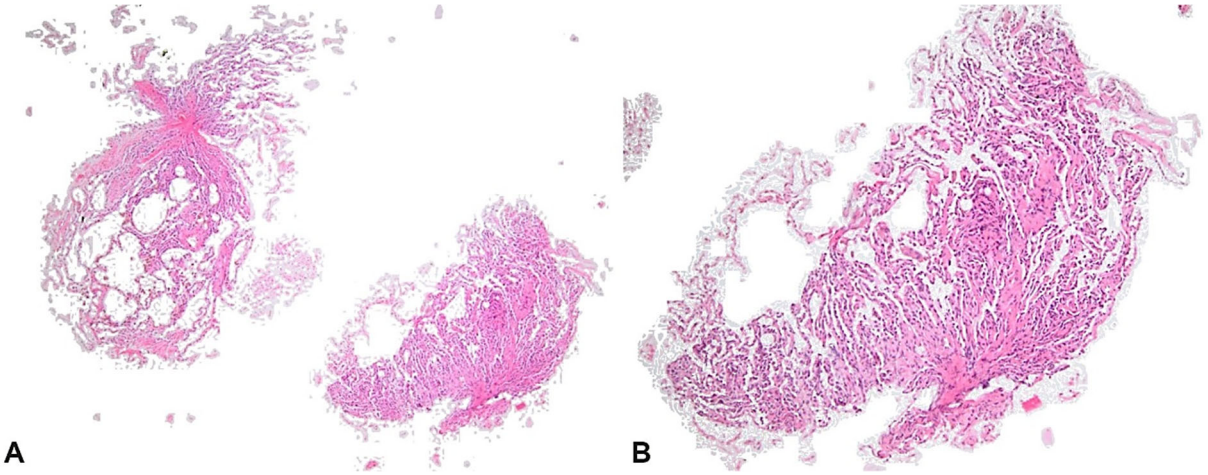

Figure 8 – ***Left lung biopsy six months after transplantation. Second level of the third biopsy: (A) Lung tissue with areas of emphysema alternating with atelectasis; (B) Detail of one fragment from the previous image, revealing areas of lambertosis accompanying the atelectatic lesions; also, an area of emphysema is clearly visible. HE staining: (A) ×40; (B) ×100.***

Discussions

The PTP used

Based on the evidence that patients prior to LT tolerate exercise training very well [18] and that dynamic hyperinflation reduces as a consequence of an increased oxidative capacity in skeletal muscle and delayed lactic acidosis [19], the exercise training was one of the key components of the treatment prior and post-LT.

Due to the loss of cough reflex and denervation of the transplanted lung [20] an important role in airway clearance has the special cough techniques (huffing, autogenic drainage) of which the patient was instructed.

The therapeutic massage used in tonic technique helped to increase blood circulation and for trophic effect on the muscle from inferior and superior limbs, and in sedative technique on muscles from cervical, dorsal, and lumbar regions to facilitate the reducing of the contractures made by prolonged immobilization [21].

The measured values of the evaluated parameters

From the point of view of **body weight**, the patient has severe underweight before and one month after LT; however, he gained 4 kg at the discharge at the first hospitalization after LT. But, three months after LT, he gained 7 kg, and he was still underweight. Six months after LT, he gained 12 kg, and he was healthy weight. Also, he gained another 7 kg one year after transplant (normal weight).

From the point of view of **skeletal muscle mass**, the patient had under normal values at all bio-impedancemetry analysis (BIA) examinations, but at one year after LT, it was nearest to normal (27.8 kg), considering a normal value around 33 kg. For appendicular skeletal muscle mass index (ASMI), the values increased constantly from 7.62 kg/m^2 at each evaluation until 9.18 kg/m^2 at one year after LT. The reducing under 7.23 kg/m^2 of ASMI values at men is known as sarcopenia and is correlated with increased morbidity, premature mortality [22] and also with poor QoL [23]. The constantly increased values of BIA of appendicular skeletal muscle mass (ASM) and ASMI and the fact that the patient developed no sarcopenia according to the measurements, represent a predictor for a good evolution of the post-LT status of the patient.

Analyzing **6MWT** data, it can easily be observed that the distance achieved and the percent of distance predicted grew from 435 m, respectively 59% at the intake in post-acute hospitalization to 528 m, respectively 72% at the discharge, and to 660 m, respectively 90.5% at three months after LT, with a little decrease in value at six months after LT at 628 m, respectively 87% but with a grow to 1000 m, respectively 166% at one year after LT that represent a very good evolution. The 6MWT proceeded in all measurements without oxygen desaturation until the finish and with a mild tachycardia at the end proving a good tolerance at the effort. The dyspnea measured with Borg Respiratory Scale [24] has an initial value of 2 at the intake in post-acute hospitalization and 0 at all other measurements and grows with only 1 unit after each test. Regarding Borg Feet Fatigue Scale, the initial values were 0 at all measurements and the final values were constantly 3 at the intake, at the discharge and three months after the LT but at six months after LT the final value was 1 and at one year was 0.5 that prove also a very good evolution and permanent increasing of effort toleration.

Analyzing the **FRTs** data, it can be notice that in July 2018 (three months after LT) the volumes and pulmonary flows were improved to normal [forced vital capacity (FVC), forced expiratory volume in one second (FEV1)/FVC ratio], the capillary diffusion factor was normal too [diffusing capacity of the lungs for carbon monoxide (DLCO), DLCO corrected for hemoglobin (DLCOc), total lung capacity (TLC), residual volume (RV), RV/TLC] and the RV decreased. In October 2018 (six months after LT), it was maintained the same trends and normal values were obtained measuring lung volumes. Also, in April 2019 (one year after LT), the evolution was favorable, with normal values at functional parameters (FVC, FEV1/FVC ratio, DLCO, DLCOc, TLC, RV, RV/TLC).

Although, in the lack of symptoms and objective signs, the patient had HP lesions of acute graft reject, he successfully continued his RR program. Certainly, if our patient would have A4 grading (severe acute rejection – diffuse perivascular, interstitial, and alveolar infiltrates of mononuclear inflammatory cells; prominent pneumocyte damage and endothelialitis; intra-alveolar necrotic epithelial cells, hyaline membranes, hemorrhage) with grade B cellular rejection, his functional reserve would be significantly limited and the PRP couldn't be performed [25, 26].

Moreover, the FEV1/FVC ratio parameter had a favorable evolution at discharge. So, our patient did not a chronic lung allograft dysfunction, which is characterized through irreversible graft loss, 20% decrease in FEV1 [27].

Acute cellular rejection is frequent in LT recipients, various studies recording its incidence as ranging between 21% [25] and 64% [28], and many patients are asymptomatic and have a good evolution [29]. Class A lesions are more frequent in asymptomatic patients, with good outcome, while class B infiltrates have an unfortunate prognosis, being a very strong risk factor for chronic rejection [30]. Lack of airway inflammation on all biopsies explains why our patient had an optimal evolution, without chronic rejection.

The second and the third biopsies revealed only fibrous scars with anthracosis and some interstitial fibrosis in alveolar walls, with no inflammatory infiltrates or microorganisms. The chronic rejection microscopic aspects (nonspecific large airway fibrosis, constrictive bronchiolitis, fibrotic bronchiolar stenosis nonrelated to transplant) were not observed in our pathological examination [31].

The third and fourth biopsies revealed an increasing emphysema, correlated with better functional status of patient. This aspect is similar to other studies. It is known that an emphysematous pattern of fibrosis was associated with a better survival, whereas fibrinous exudates were associated with a worse survival [32].

Surveillance through multiple transbronchial lung biopsies is the best method for an early diagnosis and an adequate treatment with best results concerning the outcome of the first year post-LT [33]. The fact the lesions were limited and confined on the first level emphasizes the importance of harvesting multiple tissue fragments and of a thorough HP evaluation. Although, sometimes, HP data are not correlated with clinical signs and functional tests, performing lung biopsies at each admission is the key for diagnosis and treatment of early rejection [33].

The significance of various injurious patterns by HP examination and microscopic changes associated with poor clinical outcomes are still studied worldwide, in order to find the exact aspects that need therapeutical intervention [34]. In 2022, it was proposed "lung allograft standardized histological analysis" (LASHA) template. Its three aims are (*i*) to identify key morphological features to be assessed, (*ii*) to select consistent and reproducible terminology for each histological feature, and (*iii*) to provide standardized definitions for pathological assessment and grading [35]. Using of this tool is now mandatory for research purposes, as well as for routine surveillance of LT patients. In our case, only the first two biopsies fulfill the criteria for specimen adequacy (the last two did not have at least five fragments). Excepting C4d staining recommended in this template, although considered an insensitive, but specific marker for immunological insults, this patient HP evaluation can be translated in this new template. Although this template is reproducible and easily applicable, it does not yet provide a useful scoring system for standardized quantification [35]. This emphasizes the need to report even individual cases and short series with complete clinical, HP, and functional evaluation and data concerning their outcome.

Our results are in accordance with literature data. In 2022, Wu *et al.* [36] have mentioned that for LT recipients, early extubation combined with a PTP is scientific, safe, and feasible. The postoperative recovery of LT patients reduces the length of hospitalization, helps patients improve their lung function and ability to engage in activities of daily living.

Previous to perform RP, for each LT patient must be established the standardization of HP diagnosis and grading of rejection (acute cellular rejection, antibody-mediated rejection, and chronic lung allograft dysfunction) [16]. In the last years, several statements and guidelines has been achieved through consensus supporting the importance of a multidisciplinary approach for the best outcome of these patients [37, 38].

Conclusions

In this case, can be observed the discordance between the diagnosis of suspicion of graft rejection suggested by repeated biopsies and the favorable clinical and functional evolution. Correlation of clinical and histological data, as well as the multidisciplinary management of LT patients are allowing these patients to have the best possible care, in order to achieve bold functional goals. The use of PTP in LT case significantly improves functional capacity and increases body mass and skeletal muscle mass for short, medium, and long term. It remains to be established if these results influence only the QoL of these patients or even their lifespan.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Gloeckl R, Schneeberger T, Jarosch I, Kenn K. Transplantation. In: Clini E, Holland AE, Pitta F, Troosters T (eds). Textbook of pulmonary rehabilitation. 1st edition, Springer, Cham, Switzerland, 2018, 337–348. https://doi.org/10.1007/978-3-319-65888-9_25 https://link.springer.com/chapter/10.1007/978-3-319-65888-9_25

[2] Weill D. Lung transplantation: indications and contraindications. J Thorac Dis, 2018, 10(7):4574–4587. https://doi.org/10.21037/jtd.2018.06.141 PMID: 30174910 PMCID: PMC6105990

[3] Loscalzo J. Harrison's pulmonary and critical care medicine. 1st edition, McGraw–Hill Medical, New York, NY, USA, 2010, 178–189. https://search.worldcat.org/title/458577961

[4] Abidi Y, Kovats Z, Bohacs A, Fekete M, Naas S, Madurka I, Torok K, Bogyo L, Varga JT. Lung transplant rehabilitation – a review. Life (Basel), 2023, 13(2):506. https://doi.org/10.3390/life13020506 PMID: 36836863 PMCID: PMC9962622

[5] Bagdonas E, Raudoniute J, Bruzauskaite I, Aldonyte R. Novel aspects of pathogenesis and regeneration mechanisms in COPD. Int J Chron Obstruct Pulmon Dis, 2015, 10:995–1013. https://doi.org/10.2147/COPD.S82518 PMID: 26082624 PMCID: PMC4459624

[6] Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DMG, López Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA, Agusti A. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. Eur Respir J, 2017, 49(3):1700214. https://doi.org/10.1183/13993003.00214-2017. Erratum in: Eur Respir J, 2017, 49(6):1750214. PMID: 28182564

[7] Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, Zuwallack R, Herrerias C. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest, 2007, 131(5 Suppl): 4S–42S. https://doi.org/10.1378/chest.06-2418 PMID: 17494825

[8] da Fontoura FF, Berton DC, Watte G, Florian J, Schio SM, Camargo JJP, Teixeira PJZ, Moreira JS. Pulmonary rehabilitation in patients with advanced idiopathic pulmonary fibrosis referred for lung transplantation. J Cardiopulm Rehabil Prev, 2018, 38(2):131–134. https://doi.org/10.1097/HCR.0000000000000315 PMID: 29465499

[9] Florian J, Watte G, Teixeira PJZ, Altmayer S, Schio SM, Sanchez LB, Nascimento DZ, Camargo SM, Perin FA, Camargo JJ, Felicetti JC, Moreira JS. Pulmonary rehabilitation improves survival in patients with idiopathic pulmonary fibrosis undergoing lung transplantation. Sci Rep, 2019, 9(1):9347. https://doi.org/10.1038/s41598-019-45828-2 PMID: 31249363 PMCID: PMC6597536

[10] Pontee N, Cuenant L, Brunworth K. Pulmonary rehabilitation before and after pulmonary transplantation. PM&R Knowledge NOW®, American Academy of Physical Medicine and Rehabilitation, Rosemont, IL, USA, 2024. https://now.aapmr.org/pulmonary-rehabilitation-before-and-after-pulmonary-transplantation/

[11] Stewart S, Fishbein MC, Snell GI, Berry GJ, Boehler A, Burke MM, Glanville A, Gould FK, Magro C, Marboe CC, McNeil KD, Reed EF, Reinsmoen NL, Scott JP, Studer SM, Tazelaar HD, Wallwork JL, Westall G, Zamora MR, Zeevi A, Yousem SA. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant, 2007, 26(12):1229–1242. https://doi.org/10.1016/j.healun.2007.10.017 PMID: 18096473

[12] Aguilar PR, Carpenter D, Ritter J, Yusen RD, Witt CA, Byers DE, Mohanakumar T, Kreisel D, Trulock EP, Hachem RR. The role of C4d deposition in the diagnosis of antibody-mediated rejection after lung transplantation. Am J Transplant, 2018, 18(4): 936–944. https://doi.org/10.1111/ajt.14534 PMID: 28992372 PMCID: PMC5878693

[13] Nosotti M, Tarsia P, Morlacchi LC. Infections after lung transplantation. J Thorac Dis, 2018, 10(6):3849–3868. https://doi.org/10.21037/jtd.2018.05.204 PMID: 30069386 PMCID: PMC6051843

[14] Wulff SM, Perch M, Helweg-Larsen J, Bredahl P, Arendrup MC, Lundgren J, Helleberg M, Crone CG. Associations between invasive aspergillosis and cytomegalovirus in lung transplant recipients: a nationwide cohort study. APMIS, 2023, 131(11): 574–583. https://doi.org/10.1111/apm.13317 PMID: 37022293

[15] Melendez Rivera JG, Ciofoaia GA. *Pneumocystis jirovecii* prophylaxis, 2023 Aug 8. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL, USA, 2024 Jan–. PMID: 32809365

[16] Yousem SA, Berry GJ, Cagle PT, Chamberlain D, Husain AN, Hruban RH, Marchevsky A, Ohori NP, Ritter J, Stewart S, Tazelaar HD. Revision of the 1990 working formulation for the

classification of pulmonary allograft rejection: Lung Rejection Study Group. J Heart Lung Transplant, 1996, 15(1 Pt 1):1–15. PMID: 8820078

[17] Gelman AE, Fisher AJ, Huang HJ, Baz MA, Shaver CM, Egan TM, Mulligan MS. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part III: Mechanisms: a 2016 Consensus Group Statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant, 2017, 36(10):1114–1120. https://doi.org/10.1016/j.healun.2017.07.014 PMID: 28818404 PMCID: PMC5724959

[18] Wallen MP, Skinner TL, Pavey TG, Hall A, Macdonald GA, Coombes JS. Safety, adherence and efficacy of exercise training in solid-organ transplant candidates: a systematic review. Transplant Rev (Orlando), 2016, 30(4):218–226. https://doi.org/10.1016/j.trre.2016.07.004 PMID: 27496067

[19] Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest, 2005, 128(4):2025–2034. https://doi.org/10.1378/chest.128.4.2025 PMID: 16236851

[20] Dolovich M, Rossman C, Chambers C, Grossman RF, Newhouse M, Maurer JM. Mucociliary function in patients following single lung or lung/heart transplantation. Am Rev Respir Dis, 1987, 135(7):A363. https://scholar.google.com/scholar_lookup?title=Muco-ciliary%20function%20in%20patients%20following%20single%20lung%20or%20lungheart%20transplantation&publication_year=1987&author=M%20Dolovich&author=C%20Rossman&author=C%20Chambers

[21] Van Pelt DW, Lawrence MM, Miller BF, Butterfield TA, Dupont-Versteegden EE. Massage as a mechanotherapy for skeletal muscle. Exerc Sport Sci Rev, 2021, 49(2):107–114. https://doi.org/10.1249/JES.0000000000000244 PMID: 33720912 PMCID: PMC8320327

[22] Lee MM, Jebb SA, Oke J, Piernas C. Reference values for skeletal muscle mass and fat mass measured by bioelectrical impedance in 390 565 UK adults. J Cachexia Sarcopenia Muscle, 2020, 11(2):487–496. https://doi.org/10.1002/jcsm.12523. Erratum in: J Cachexia Sarcopenia Muscle, 2020, 11(3):859. PMID: 31943835 PMCID: PMC7113534

[23] Moon JJ, Park SG, Ryu SM, Park CH. New skeletal muscle mass index in diagnosis of sarcopenia. J Bone Metab, 2018, 25(1):15–21. https://doi.org/10.11005/jbm.2018.25.1.15 PMID: 29564302 PMCID: PMC5854819

[24] Wickerson L, Rozenberg D, Janaudis-Ferreira T, Deliva R, Lo V, Beauchamp G, Helm D, Gottesman C, Mendes P, Vieira L, Herridge M, Singer LG, Mathur S. Physical rehabilitation for lung transplant candidates and recipients: an evidence-informed clinical approach. World J Transplant, 2016, 6(3):517–531. https://doi.org/10.5500/wjt.v6.i3.517 PMID: 27683630 PMCID: PMC5036121

[25] Chambers DC, Cherikh WS, Goldfarb SB, Hayes D Jr, Kucheryavaya AY, Toll AE, Khush KK, Levvey BJ, Meiser B, Rossano JW, Stehlik J; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult lung and heart-lung transplant report-2018; Focus theme: multiorgan transplantation. J Heart Lung Transplant, 2018, 37(10):1169–1183. https://doi.org/10.1016/j.healun.2018.07.020 PMID: 30293613

[26] Manyeruke F, Pennel T, Roberts R, Calligaro GL. Acute cellular rejection in lung transplantation. Afr J Thorac Crit Care Med, 2019, 25(2):10.7196/AJTCCM.2019.v25i2.010. https://doi.org/10.7196/AJTCCM.2019.v25i2.010 PMID: 34286249 PMCID: PMC8278989

[27] Fu A, Vasileva A, Hanafi N, Belousova N, Wu J, Rajyam SS, Ryan CM, Hantos Z, Chow CW. Characterization of chronic lung allograft dysfunction phenotypes using spectral and intra-breath oscillometry. Front Physiol, 2022, 13:980942. https://doi.org/10.3389/fphys.2022.980942 PMID: 36277208 PMCID: PMC9582781

[28] Hachem RR, Kamoun M, Budev MM, Askar M, Ahya VN, Lee JC, Levine DJ, Pollack MS, Dhillon GS, Weill D, Schechtman KB, Leard LE, Golden JA, Baxter-Lowe L, Mohanakumar T, Tyan DB, Yusen RD. Human leukocyte antigens antibodies after lung transplantation: primary results of the HALT study. Am J Transplant, 2018, 18(9):2285–2294. https://doi.org/10.1111/ajt.14893 PMID: 29687961 PMCID: PMC6117197

[29] Subramani MV, Pandit S, Gadre SK. Acute rejection and post lung transplant surveillance. Indian J Thorac Cardiovasc Surg, 2022, 38(Suppl 2):271–279. https://doi.org/10.1007/s12055-021-01320-z PMID: 35340687 PMCID: PMC8938213

[30] Martinu T, Pavlisko EN, Chen DF, Palmer SM. Acute allograft rejection: cellular and humoral processes. Clin Chest Med, 2011, 32(2):295–310. https://doi.org/10.1016/j.ccm.2011.02.008 PMID: 21511091 PMCID: PMC3089893

[31] Tabarelli W, Bonatti H, Tabarelli D, Eller M, Müller L, Ruttmann E, Lass-Flörl C, Larcher C, Geltner C. Long term complications following 54 consecutive lung transplants. J Thorac Dis, 2016, 8(6):1234–1244. https://doi.org/10.21037/jtd.2016.05.03 PMID: 27293842 PMCID: PMC4885970

[32] von der Thüsen JH, Vandermeulen E, Vos R, Weynand B, Verbeken EK, Verleden SE. The histomorphological spectrum of restrictive chronic lung allograft dysfunction and implications for prognosis. Mod Pathol, 2018, 31(5):780–790. https://doi.org/10.1038/modpathol.2017.180 PMID: 29327719

[33] Tosi D, Carrinola R, Morlacchi LC, Tarsia P, Rossetti V, Mendogni P, Rosso L, Righi I, Damarco F, Nosotti M. Surveillance transbronchial biopsy program to evaluate acute rejection after lung transplantation: a single institution experience. Transplant Proc, 2019, 51(1):198-201. https://doi.org/10.1016/j.transproceed.2018.04.073 PMID: 30655138

[34] Roux A, Levine DJ, Zeevi A, Hachem R, Halloran K, Halloran PF, Gibault L, Taupin JL, Neil DAH, Loupy A, Adam BA, Mengel M, Hwang DM, Calabrese F, Berry G, Pavlisko EN. Banff Lung Report: current knowledge and future research perspectives for diagnosis and treatment of pulmonary antibody-mediated rejection (AMR). Am J Transplant, 2019, 19(1):21–31. https://doi.org/10.1111/ajt.14990 PMID: 29956477

[35] Calabrese F, Roden AC, Pavlisko E, Lunardi F, Neil D, Adam B, Hwang D, Goddard M, Berry GJ, Ivanovic M, Thüsen JV, Gibault L, Lin CY, Wassilew K, Glass C, Westall G, Zeevi A, Levine DJ, Roux A. Lung allograft standardized histological analysis (LASHA) template: a research consensus proposal. J Heart Lung Transplant, 2022, 41(10):1487–1500. https://doi.org/10.1016/j.healun.2022.06.021 PMID: 35931644

[36] Wu T, Zhou S, Wu B, Chen J, Zhu X, Cai Y. The effect of early tracheal extubation combined with physical training on pulmonary rehabilitation of patients after lung transplantation: a randomized controlled trial. J Thorac Dis, 2022, 14(4):1120–1129. https://doi.org/10.21037/jtd-22-119 PMID: 35572910 PMCID: PMC9096297

[37] Glanville AR, Verleden GM, Todd JL, Benden C, Calabrese F, Gottlieb J, Hachem RR, Levine D, Meloni F, Palmer SM, Roman A, Sato M, Singer LG, Tokman S, Verleden SE, von der Thüsen J, Vos R, Snell G. Chronic lung allograft dysfunction: definition and update of restrictive allograft syndrome – a consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant, 2019, 38(5):483–492. https://doi.org/10.1016/j.healun.2019.03.008 PMID: 31027539

[38] Verleden GM, Glanville AR, Lease ED, Fisher AJ, Calabrese F, Corris PA, Ensor CR, Gottlieb J, Hachem RR, Lama V, Martinu T, Neil DAH, Singer LG, Snell G, Vos R. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment – a consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant, 2019, 38(5):493–503. https://doi.org/10.1016/j.healun.2019.03.009 PMID: 30962148

Corresponding author

Cristiana Gabriela Popp, MD, Department of Pathology, Colentina University Hospital, 19–21 Ştefan cel Mare Highroad, Sector 2, 020125 Bucharest, Romania; Phone/Fax +4021–210 22 40, Mobile +40721–298 871, e-mail: brigaela@yahoo.com

Received: January 22, 2024 *Accepted: May 10, 2024*