ramr
Revista Americana de Medicina Respiratoria
American Review of Respiratory Medicine

REVIEW ARTICLE

ISSN 1852 - 236X

Whole Lung Lavage Protocol at Hospital Santa Clara of Bogotá: Presentation of a Patient with Resistant Pulmonary Alveolar Proteinosis

Protocolo de lavado pulmonar total del Hospital Santa Clara de Bogotá, a propósito de una paciente con proteinosis alveolar pulmonar resistente

Osejo-Betancourt, Miguel[1]; Moreno-Ramírez, Carlos Ernesto[2]; Chaparro-Mutiz, Pedro[3]

Received: 12/20/2021
Accepted: 8/5/2022

Correspondence
Miguel Osejo Betancourt.
E-mail: mosejob@unbosque.edu.co

ABSTRACT

Pulmonary alveolar proteinosis is a clinical entity characterized by the accumulation of proteinaceous material, rich in surfactant, mediated by reduced clearance by alveolar macrophages. In adult patients, it is commonly associated with autoimmune phenomena resulting in a deficiency of the granulocyte-macrophage colony stimulating factor, which implies alterations in cell maturation and dysfunction, causing a decrease in surfactant degradation and its accumulation in the alveolar space. Its diagnosis poses a challenge to the clinician, based on the findings of pulmonary function tests and the crazy paving pattern of the high-resolution computed tomography of the chest, and is confirmed by obtaining the proteinaceous material in the bronchoalveolar lavage. Given its rarity, the ideal treatment remains to be elucidated, with whole lung lavage currently being the cornerstone of treatment. We report an anecdotal case of a 41-year-old female patient suffering from pulmonary alveolar proteinosis since 2011, who has required multiple whole lung lavages, with poor response to these, with persistent dyspnea and supplemental oxygen requirement even though she has performed the procedure, but with a progressive tendency towards improvement in the last 2 years. The lavage technique is not completely standardized and its use in Latin America is still limited, which is why we publish the protocol used in the Hospital Santa Clara of Bogotá, Colombia.

Key words: Pulmonary alveolar proteinosis; Pulmonology; Protocol; Whole lung lavage; Rare diseases

RESUMEN

La proteinosis alveolar pulmonar es una entidad clínica caracterizada por la acumulación de material proteinaceo, con alta riqueza en surfactante, mediado por una menor aclaración por parte de los macrófagos alveolares. En pacientes adultos, comúnmente se asocia a fenómenos autoinmunes que tienen como resultado una deficiencia del factor estimulante de colonias de granulocitos y macrófagos, lo que implica alteracio-

Rev Am Med Resp 2022;22:354-364
https://doi.org./10.56538/ramr.FPKS7802

[1] Specialist in Internal Medicine, Universidad Nacional Autónoma de Honduras, and in Pulmonology, Hospital Santa Clara, Bogotá, Colombia.
[2] Specialist in Epidemiology and Resident in Internal Medicine, Hospital Santa Clara, Bogotá, Colombia
[3] Specialist in Internal Medicine and Pulmonology, Hospital Santa Clara, Bogotá, Colombia.

nes en la maduración y disfunción celular, lo que provoca disminución de la degradación del surfactante y su acumulación en el espacio alveolar. Su diagnóstico corresponde a un reto para el clínico, sobre la base de los hallazgos en pruebas de función pulmonar, el patrón en "empedrado" (*crazy paving*) en la tomografía computarizada de tórax de alta resolución y que se confirma al obtener el material proteínico en el lavado broncoalveolar. Dada su rareza, el tratamiento ideal permanece por ser elucidado y en la actualidad el pilar del tratamiento es el lavado pulmonar total. Reportamos un caso anecdótico de una paciente de 41 años con proteinosis alveolar pulmonar desde 2011, que ha requerido múltiples lavados pulmonares totales, con pobre respuesta a estos, persistencia de disnea y necesidad de oxígeno suplementario a pesar de realizar el procedimiento, pero con tendencia progresiva a la mejoría en los últimos 2 años. La técnica del lavado no está completamente estandarizada y su uso en América Latina es aún limitado, por lo que publicamos el protocolo utilizado en el Hospital Santa Clara de Bogotá, Colombia..

Palabras clave: Proteinosis alveolar pulmonar; Neumología, Protocolo; Lavado pulmonar total; Enfermedades raras

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a pulmonary disease caused by the accumulation of surfactant in the alveolar space mediated by a reduced clearance by alveolar macrophages. It was first described in 1958 by Rosen et al.[1, 2]

The altered macrophage function is the effect of the reduced availability of the granulocyte-macrophage colony stimulating factor (GM-CSF) mediated by the production of autoantibodies against this protein in up to 90% of adult patients. Other causes include mutations in the GM-CSF receptors, hematologic disorders, infections, drugs and exposure factors (silica, cellulose, heavy metals and some organic materials).[1]

PAP symptoms are non-specific, with progressive dyspnea as the main symptom. Lung function tests show reduced diffusing capacity of the lungs for carbon monoxide (DLCO), and the spirometry might show a restrictive pattern.[3] The high-resolution chest tomography (HRCT) shows the crazy paving pattern, with ground glass opacities superimposed on interlobular septal thickening that is characteristic of this condition, though it may also be present in other diseases, and in the cases of autoimmune etiology, the presence of antibodies against GM-CSF confirms the diagnosis.[4-6]

The diagnosis must be confirmed through bronchoalveolar lavage collecting whitish, milky proteinaceous material with precipitating amorphous *detritus*; the microscopy showing oval, acellular bodies, basophilic in May-Grünwald-Giemsa Stain and positive for PAS (Periodic acid Schiff) staining.[1, 7]

The treatment includes smoking cessation and vaccination against influenza and pneumococcus for the prevention of respiratory infections. The cornerstone of treatment for symptomatic patients with reduced vital forced capacity (VFC), reduced DLCO or hypoxemia is whole lung lavage. At present there are other treatments such as inhaled or subcutaneous GM-CSF, and for treatment-refractory patients, additional interventions may be used, such as the use of rituximab, plasmapheresis or lung transplantation, with studies of highly variable results.[1, 8-10]

Since it is a rare disease, there aren't any randomized clinical studies that standardize the whole lung lavage technique; there are some descriptions in languages other than Spanish and modifications in accordance with the Center's experience, without any established protocols in Latin America. Taking that into consideration, the objective of this review was to describe the protocol for the whole lung lavage procedure that has been followed in the Hospital Santa Clara of Bogota, which has been used for the treatment of several PAP patients in that institution; and in comparison with the techniques described in the literature review, we will briefly describe the experience of one case that was refractory to treatment.

CASE REPORT

Female patient, 41 years old, who presented to the institution in 2011 with chronic dyspnea. Chest tomography showed crazy paving pattern (Figure 1). A bronchoscopy was performed and proteinaceous material was collected. Gram, Ziehl Neelsen and Grocott stains were performed, as well as cultures for bacteria, mycobacteria and fungi, all with negative results but with PAS-positive staining. PAP diagnosis was confirmed through clinical symptoms, tomography, lavage findings, and PAS-positive staining, without the need to perform a biopsy. The patient proceeded with the whole lung lavage in the Pulmonology Department, with unsatisfactory evolution, even though she had performed multiple procedures. The patient showed a partial response, and required lung lavages every 6 months on average, 26 lung lavages in total (13 right, 13 left) since she was first treated at the institution; and the protocol described in Table 1 was followed at all times. No complications occurred during the procedure; during the postoperative period, she only had some isolated fever spikes. The patient presented pulmonary hypertension, with a 2018 echocardiogram showing calculated pulmonary artery systolic pressure (PASP) of 70 mmHg. In September 2020, she went to the emergency department with exacerbation of respiratory symptoms, no fever, oxygen saturation of 65% on admission, and the last lung lavage having been done in August 2019. Once SARS-CoV-2 infection was discarded, a new lung lavage was scheduled. During the lung lavage, a thick, yellowish proteinaceous material was obtained (Figure 2), and then washed with 25 L. As there were no complications, a new lavage was scheduled for the following week, and was also performed without complications. The patient was discharged with clinical improvement, saturation 90% on supplemental oxygen. She reported significant improvement with a few symptoms. New control echocardiogram in April 2021; PSAP of 20 mmHg reported with normal systolic function. The dyspnea improved and as regards the functional limitation, she no longer required oxygen for daily activities (it was necessary only at night). She was admitted on November 2021 with dyspnea class 2 according to the mMRC (Modified Medical Research Council) scale, saturation 88% on room air. Control chest X-ray (Figure 3) showing bibasilar alveolar opacities with significant improvement compared to previous tests. New whole lung lavage scheduled. Lavage performed in two sessions; the second one, with 20 L. Fluid cleared completely (Figure 4)

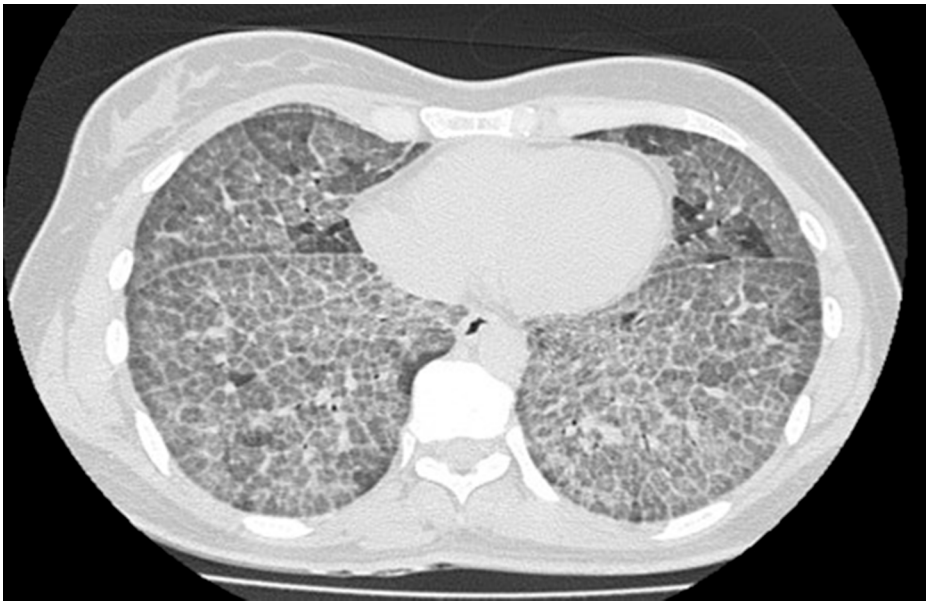

Figura 1. TACAR inicial: Antes del primer lavado; se observa el patrón de «empedrado» de opacidades en «vidrio esmerilado» sobrepuestas a un engrosamiento septal interlobulillar.

TABLE 1. Whole lung lavage protocol

1. Preparation:
   a. Determine which of the lungs has the larger lesion through chest X-ray.
   b. Prepare from 20 to 40 aliquots of normal saline solution in 1000 ml bags heated at 37°C.
   c. Prepare suction stand 50 cm above the patient to place the aliquots.
   d. Prepare percussion or kinesiotherapy machine.
   e. Prepare the Y-shaped connector device.
   f. Keep the patient in supine position.
2. Selective lung intubation:
   a. Intubation with left double-lumen orotracheal tube (35 Fr for females and 37 Fr for males).
   b. Perform bronchoscopy to confirm tube position.
   c. Check ventilation of each lung separately in search of leaks and resistance.
   d. Measure lung compliance separately to determine which is the most affected lung and, together with radiological findings, decide which one will be treated first.
3. Lung lavage:
   a. Denitrogenation: Ventilate and oxygenate both lungs with 100% FiO_2 for 5-15 minutes.
   b. Begin lavage in the lung that has the lowest compliance.
   c. Allow gravity flow of aliquots: at first it is slow, but then pressures are levelled and the solution no longer enters through the Y-shaped connector.
   d. Allow gravity drainage while chest percussion is being performed (only during drainage), and check that all (or almost all) the instilled liquid of the first aliquot is out. During the following lavage, suction can be used in order to avoid the collapse of the drainage tubes.
   e. Repeat filling cycles with heated aliquots of 1000 ml on average (until the flow stops), followed by gravity drainage and suction concomitant with chest percussion.
   f. Monitor entry and exit of saline solution continuously, drips of more than 1000 ml may indicate leakage towards the contralateral lung or pleural space.
   g. Watch liquid exit through the contralateral lung lumen in search of leaks.
   h. Continue with lavage until a clear liquid is obtained (average of 25-30 L).
   i. When the procedure has finished, aspirate remaining liquid from the lung.
   j. Ventilate and recruit both lungs.
   k. Perform recruitment maneuver in washed lung and aspirate again.
   l. Taking into account the patient's conditions, consider extubation or reintubation with single-lumen orotracheal tube for transfer to ICU.
   m. Perform control chest X-ray after the procedure.
   n. Perform contralateral lung lavage 3-7 days after the first lavage.
   o. The use of loop diuretics may be considered after the procedure, especially on suspicion of instilled liquid leak towards the pleural space or contralateral lung.

Own preparation. ICU: Intensive Care Unit; FiO_2: fraction of inspired O_2.

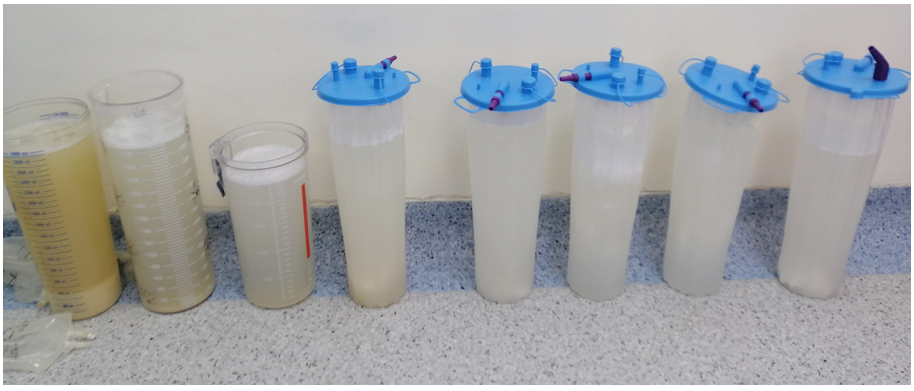

Figure 2. 2020 lung lavage: thick, yellowish proteinaceous material, which cleared during the procedure.

for the first time in this patient. PAS staining requested (Figure 5) in the last lavage. There weren't any complications and the patient was discharged without symptoms, with saturation 91% without supplemental oxygen. She had a follow-up plan for external consultation, with tomographic control and new echocardiogram to confirm previous findings.

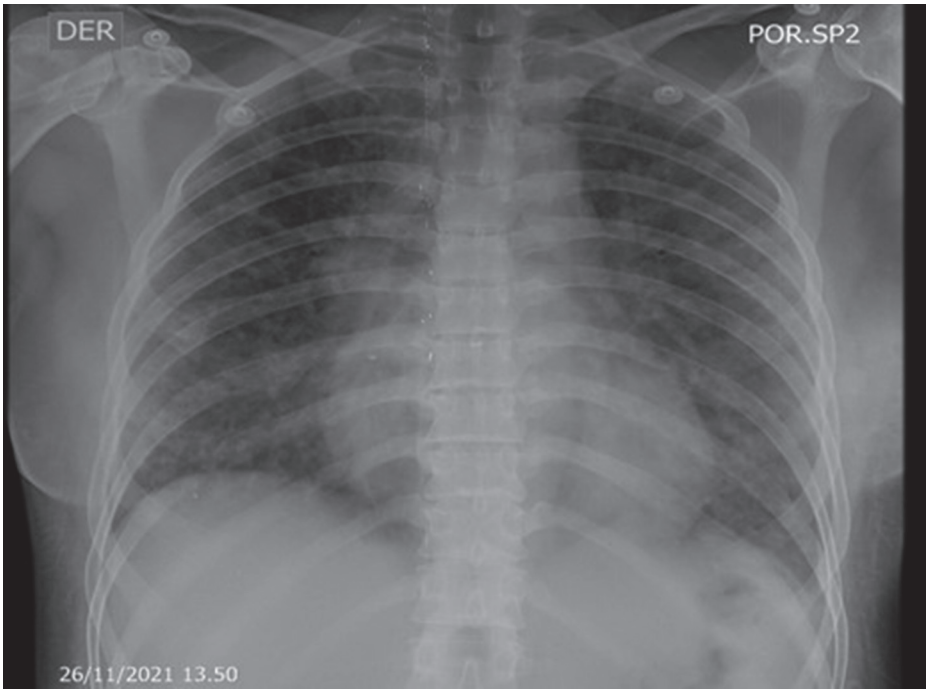

Figure 1. Initial HRCT: before the first lavage; crazy paving pattern with ground glass opacities superimposed on interlobular septal thickening.

Figure 4. 2021 lung lavage: slightly pink proteinaceous material that cleared completely at the end of the procedure.

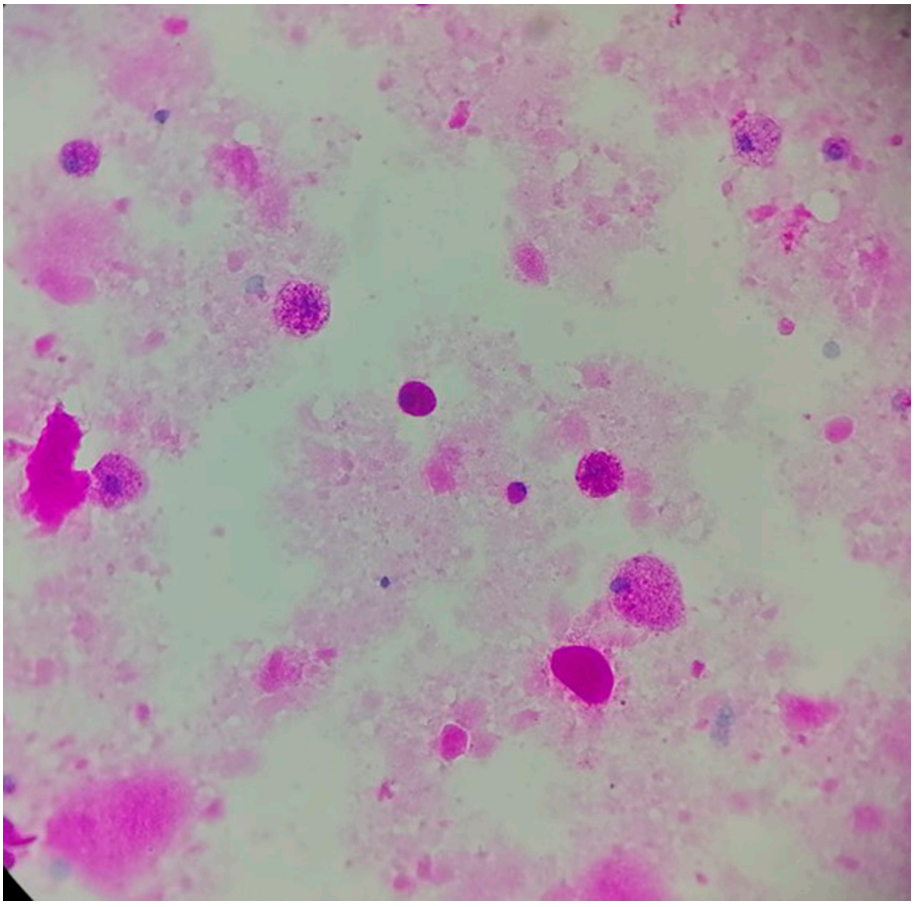

Figure 5. PAS staining: photography taken with the microscope with 100x magnification. Amorphous material observed that stained pink. Courtesy of Dr. Constanza Franco and Dr. Diana Caballero, Pathology Service, Hospital Santa Clara.

METHODOLOGY

A narrative review was performed of the bibliography using the PubMed, Google Scholar and ScienceDirect databases between January 1st, 2014 and September 30th, 2021. Also, the search of relevant bibliography was complemented with the review of the references of articles selected by the authors. For the bibliography search we used the MeSH Terms and selected the following as key words: «whole lung lavage» and «pulmonary alveolar proteinosis» and their combinations, using AND and OR as Boolean operators.

RESULTS

When searching and writing the summary of the bibliography, articles were selected according to the preferences of the topic to be discussed, including review articles, case reports, guidelines and protocols, observational studies and clinical trials.

DISCUSSION

In 1953, Dr. Benjamin Castle described a patient with alveolar filling of proteinaceous material stained with PAS staining, and in the following 5 years accumulated 27 patients with the same findings, making the first report about this new disease which subsequently received the name of pulmonary alveolar proteinosis. It is a progressive, fatal disease with no suitable treatment, for which many therapies have been tested with unfavorable results.[11] In 1963, Dr. José Ramírez Rivera used a transtracheal catheter placed in one lung at a time and instilled 100 ml saline solution aliquots at 50-60 drops per minute, four times a day, 2 to 3 times a week which, despite being a stressful

and long process, improved the opacities in the radiological images, the oxygenation and DLCO.[11] In 1964, he used a double lumen tube to instill 3 L of saline solution to an isolated lung together with heparin or N-acetylcysteine and showed that the instillation of large volumes is a safe procedure. During the following decades, the procedure has been perfected and the whole lung lavage as we know it today was first described in 1994.[12]

Indications and contraindications

The main indication is considered to be dyspnea with functional limitation, worsening of radiological images and hypoxemia.[9, 11] The use of other clinical and paraclinical parameters to define whether or not a lavage should be performed is variable according to the experience of each center, and other causes of hypoxemia should be discarded, for example pulmonary embolism or infection.[12]

The main contraindications to the procedure include severe heart disease, findings of pulmonary fibrosis or sepsis.[13] It is not recommended for patients with untreated coagulopathy, especially in cases of thrombocytopenia with platelet count below 50 000 /mm^3 or an INR (International Normalized Ratio) of more than 1.5; however, given the rarity of this condition, there aren't any randomized studies that guide the procedure, thus explaining the high variability of the different institutions.[11]

In most centers, lung lavage is preferably carried out in two sessions (one for each lung), with 1-3 weeks in-between sessions; however, cases have been reported of bilateral lung lavages performed in only one session.[11] Most patients will require separate lung lavages, and even a considerable number of patients will require only one procedure to reach spontaneous remission; that is why it is preferred as first-line treatment in contrast to the administration of GM-CSF, which is more expensive and not easily available in most Latin American countries.[9, 12]

The objective of lung lavage is to remove as much proteinaceous material as possible, having instilled the least amount of solution, while reducing complications related to anesthesia and post-procedure hospitalization.

Preparation

We suggest a suitable preanesthetic assessment including pulmonary function tests and radiographic control, and during the visit, advice should be given on the management of the airway and of the double-lumen endotracheal tube.[9, 12]

For the induction and maintenance of anesthesia use endovenous anesthetic agents to avoid leakage during the lavage and contamination of the area, with fluid restriction to avoid fluid overload, continuous hemodynamic monitoring, arterial gasometry and a patient warming device so as to prevent hypothermia, especially in patients with unstable cardiovascular disease.[14, 15] In patients with significant polycythemia, a phlebotomy could be considered before the procedure to reduce the risk of thromboembolic complications.[12]

Protocol description

The procedure is carried out in the operating room by trained staff including a pulmonologist, respiratory therapy and an anaesthesiologist.[11, 12] It is done with general anesthesia with neuromuscular blockade, using a left double-lumen tube (because the placement of the right tube is more complicated and might obstruct the bronchus of the upper lobe). There must be an air column at both ends, and generally the anesthesiologist does resistance tests to verify the position of the tube, which is then confirmed with the bronchoscopy; this step is fundamental for the procedure.[8, 11, 12, 14, 16]

The procedure is carried out in supine position because it is more comfortable and to prevent the double-lumen tube from moving out of its place, a common complication of this procedure. Some authors report cases of the procedure being performed with the patient lying on a side, in the direction of the lung to be washed, to reduce the probability of leakage towards the contralateral lung.[11, 12]

The lung to be washed is selected with the support of radiological images and confirmed during the procedure with the evaluation of lung compliance: the most affected lung is the least compliant. After the intubation, denitrogenation of both lungs is carried out to avoid the formation of bubbles during the procedure through the administration of a fraction of inspired oxygen (FiO_2) of 100% for 5-15 min. During that time, the saline solution is heated to 37 °C to reduce hypothermia, and approximately 20 L - 40 L are prepared for the procedure.[8, 11, 12, 14, 16] A closed system is prepared with the Y-shaped connector, with one end connected to the saline solution bags and the other

one to the double-lumen tube towards the side of the lung to be washed, and the other one, to the drainage system.[14] When it is ready, the instillation of the first aliquot begins slowly to avoid the formation of bubbles and barotrauma, until the pressures are equal and no more liquid enters the system.[14] The inlet valve is closed and the drain valve is opened (it may or may not be connected to a suction system). The drain valve can be opened immediately after finishing the instillation of the solution, because it seems to be as effective as keeping it for a few minutes, and apparently it reduces absorption to the systemic circulation and secondary hypervolemia.[12]

Once the drainage has begun, chest percussion is carried out to facilitate the mixture of the proteinaceous material with the instilled solution. Percussion can be carried out with kinesiotherapy or percussion equipment, like the one we use in our center, but it can also be administered manually. If done manually, it is exhausting for the staff and the patient complains of more pain after the procedure.[11, 12] The first drained material will be whitish and milky, or from yellowish to reddish if there are microhemorrhages, and will clear while aliquots are instilled.

The procedure is repeated with aliquots of 1000 ml on average, the flow rate being determined by the infusion system, and performing the percussion only during drainage. The amount of fluid entering and leaving the system must be strictly calculated and monitored; drips of more than 1000 ml might indicate system leakage towards the contralateral lung or the pleural space .[8, 14] This could occur if the double-lumen tube moves out of its place, and it could be necessary to replace it and confirm with a new bronchoscopy; that is why it is important to pay attention to bubbles going out from the contralateral lumen.[8, 14]

Cycles will be repeated until the fluid drainage is as clear as possible. On average, most patients need 20 L per procedure and may require up to 40 L.[17]

Physiological changes during whole lung lavage

During the filling phase, blood is physiologically sent from the non-ventilated lung to the ventilated one due to hypoxic pulmonary vasoconstriction and pressure changes induced by the instillation of the solution. This change in the physiological shunt results in higher oxygenation, since the hemoglobin saturation increases and, once drainage is completed, oxygen saturation decreases again as a consequence of airway pressure drop and pulmonary perfusion towards the non-instilled lung.[17] In addition, fluid overload during the filling phase might increase pulmonary vascular resistance, thus causing right ventricular overload, especially in patients with pulmonary hypertension or left ventricular dysfunction.[14]

Post-procedure care

Once the procedure is completed, the remaining liquid is absorbed from the lung. Then, ventilation and recruitment of both lungs are carried out. If liquid is observed coming out from the tube, it is absorbed. Subsequently, the lung that has been washed is recruited and liquid is absorbed as needed.[12, 14, 16]

It is important to remember that drained proteinaceous material is pulmonary surfactant lost during lavage, even the amount necessary to maintain surface tension is lost, thus facilitating alveolar collapse; that is why post-lavage recruitment is routinely done.[11, 12]

Taking into account the patient's conditions, extubation can be an option and transferring the patient to the Intensive Care Unit to be surveilled during 12 to 24 hours. Patients with severely compromised oxygenation or hemodynamic instability are recommended to replace the double-lumen tube with a conventional orotracheal tube after the procedure and continue postoperative management in the Intensive Care Unit with protective mechanical ventilation, with or without loop diuretics, using the therapeutic strategies indicated for other causes of pulmonary edema.[12]

Technique variations

Some centers report the use of the bilateral procedure, which starts with the most affected lung and once the liquid is clear, continues with the other. It is a much longer procedure, which lasts up to 8 hours, then the orotracheal tube is replaced with a conventional one and the patient is subsequently managed in the Intensive Care Unit.[11] The advantage of this method is that it reduces hospital costs and the time until the patient is discharged, enhancing patient comfort earlier. Silva et al published in 2014 a series of 3 cases of bilateral lung lavage, in accordance with their specific protocol.[16]

There are also some reports of PAP patients with respiratory failure who didn't tolerate single-

lung ventilation, so in those cases the procedure was performed with extracorporeal membrane oxygenation.[9, 11, 15, 16]

Microbiological studies of drained material can be conducted to study *Nocardia, Actinomyces*, mycobacteria and fungi, such as *Aspergillus* and *Cryptococcus*, because, given the dysfunction of alveolar macrophages, there is predisposition towards these infections.[17]

The use of dynamic ultrasound imaging has also been reported to guide the procedure and observe the way in which lung echogenicity changes, from being ventilated to achieving a consolidation pattern after the solution has been instilled or evidencing complete atelectasis after drainage. Echocardiographic guideline could reduce pulmonary stress and help prevent volutrauma and barotrauma, and also check for fluid leaks.[18]

Since 1988, Bingisser et al described the use of manual ventilation during the procedure, and in 2012, Bonella et al added intermittent percussion (both for instillation and drainage) as a strategy to recruit a larger amount of proteinaceous material during the procedure with the least amount of solution.[19] In 2021, Grutters et al modified the Bonella technique and performed manual hyperinflation every 3 aliquots, with intermittent percussion. So, they found that the amount of solution necessary for performing the lavage was reduced, with an average of 15 L with the largest amount of drained material (91%) after 3 cycles with this maneuver.[19]

The work of Akasaka et al in 2014 designed a mathematical model to predict the number of proteins that were going to be removed during lung lavage, for the purpose of predicting or modifying filling and drainage times. However, the calculation didn't modify the number of cycles or liquid retention time, compared to the standard treatment, and the measurements of different proteins would increase procedure costs.[20]

There is a report of a patient with a bad response to lavage, similar to our patient, that used treatment combination, lung lavage with cycles of inhaled GM-CSF after the procedure for up to 6 months, showing evident improvement; but this pharmacological intervention isn't easily available and its cost limits its administration significantly, like in the case reported in this article.[21]

Segmental lavages are also performed through flexible bronchoscopy in patients who don't tolerate single lung ventilation or pediatric patients, but with lower fluid volumes and reduced efficacy.[13, 22]

Follow-up and efficacy

Given the heterogeneous condition of this disease, improvement of the various clinical parameters is different and variable. In 2015, a retrospective study was carried out of 120 PAP adult patients in China, 80 of which required lung lavage; they were followed-up for 8 years and after the procedure, the oxygen arterial pressure (PaO_2), FVC, total lung capacity, DLCO and distance travelled in the 6-Minute Walk Test (6MWT) all improved: the most significant changes occurred in the DLCO, with an average increase of 10 points, and in the 6MWT, with an average of 100 m, without any dead patients in the follow-up period.[23]

In 2016, a meta-analysis was published evaluating the efficacy of the lavage; it included twelve studies and reported significant improvement in the DLCO, FVC, PaO_2 and forced expiratory volume on the first second (FEV1), with no changes in the arterial pressure of the carbon dioxide or the arterial oxygen saturation.[24]

Another 2020 report of 10 patients in India showed clear improvement in oxygenation, but only stabilization or mild improvement in the other parameters of lung function.[25] Another report of fifty lung lavages conducted in a reference center in Thailand showed improvement in oxygenation, DLCO, and radiographic findings, with 42% of patients showing partial improvement and 47% complete improvement after the procedure.[26]

It has also been found that smoking alters the efficacy of the procedure, that is why in smokers more lavages were necessary to achieve disease remission or stabilization.[17] Survival after the procedure ranges from 63% to 94%, so it is part of the cornerstone of treatment of PAP patients.[17, 26]

Complications

The most frequently reported complications are: fever (18%), hypoxemia (14%), sibilance (6%), pneumonia (5%), fluid leakage (4%), pleural effusion (3.1%) and pneumothorax (0.8%).[9, 11, 13, 27] Hypoxemia is particularly relevant, and is related to hospital readmission within 30 days following the procedure in up to 5% of the cases, with patients requiring treatment with high FiO_2 and recruitment with positive end-expiratory pressure (PEEP),

trying to avoid barotrauma (pneumothorax).[11, 28] Exacerbation of the symptoms was also reported within the first 30 days following the procedure, together with respiratory infections, though there was no association with opportunistic infections.[17, 28] Bad positioning of the double-lumen tube may cause fluid leakage towards the other lung, but this rarely occurs with highly-trained professionals and after confirmation with bronchoscopy. The rapid instillation of large volumes might cause barotrauma with hydropneumothorax or significant pleural effusion, which could require management with chest tube or thoracentesis .[8, 11]

Another important effect is hypothermia. Body temperature should be monitored using physical media and the aliquots should be heated before instillation, thus avoiding the appearance of intraoperative arrhythmia and other hypothermia-derived complications.[8]

It has been reported that up to 10% of patients resist whole lung lavage, with no significant improvement, and require more lavages plus other treatments.[23] Our patient is included in that group, though she has shown evident clinical improvement in the last 2 years of treatment.

CONCLUSIONS

Pulmonary alveolar proteinosis is a rare disease, generally unknown to primary care physicians. This situation could delay the diagnosis and, even though there are several treatment alternatives, these are expensive and not easily available for most Latin American countries. Cases have been reported of patients who respond to treatment with stimulating factors, but whole lung lavage is still the treatment standard and although the procedure is expensive, it is cost-effective, given the rapid improvement of the patient and long-term maintenance. However, the procedure remains largely unknown, and many physicians are afraid to use it due to the already mentioned implications, and the need for specific supplies, such as the double-lumen tube, and of staff trained in the procedure and perioperative management; this indicates that it is necessary to standardize some therapeutic strategies. For that reason, we decided to write this protocol for the purpose of simplifying the available information, with an approach that can be easily replicated in most of the Latin American territory.

Conflicts of interest

The authors have no conflict of interest to declare in relation to writing or publishing this article.

REFERENCES

1. Kumar A, Abdelmalak B, Inoue Y, Culver DA. Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. Lancet Respir Med [Internet]. 2018;6:554–65. https://doi.org/10.1016/S2213-2600(18)30043-2
2. Rosen SH, Castleman B, Liebow AA, Enzinger FM, Hunt RTN. Pulmonary Alveolar Proteinosis. N Engl J Med [Internet]. 1958:258:1123–42. https://doi.org/10.1056/NEJM195806052582301
3. Inoue Y, Trapnell BC, Tazawa R, et al. Characteristics of a Large Cohort of Patients with Autoimmune Pulmonary Alveolar Proteinosis in Japan. Am J Respir Crit Care Med [Internet]. 2008;177:752–62. https://doi.org/10.1164/rccm.200708-1271OC
4. Ishii H, Trapnell BC, Tazawa R, et al. Comparative Study of High-Resolution CT Findings Between Autoimmune and Secondary Pulmonary Alveolar Proteinosis. CHEST [Internet]. 2009;136:1348–55. https://doi.org/10.1378/chest.09-0097
5. Villar A, Rojo R. Alveolar Proteinosis: The Role of Anti-GM-CSF Antibodies. Arch Bronconeumol [Internet]. 2018;54:601–2. https://doi.org/10.1016/j.arbres.2018.03.017
6. Fisser C, Hamer OW, Eiber R, Pfeifer M, Lerzer C. Pflastersteine in der Lunge [Crazy Paving Pattern of the Lung]. Pneumologie [Internet]. 2019;73:49-53. https://doi.org/10.1055/a-0767-7960
7. Burkhalter A, Silverman JF, Hopkins III MB, Geisinger KR. Bronchoalveolar Lavage Cytology in Pulmonary Alveolar Proteinosis. Am J Clin Pathol [Internet]. 1996;106:504–10. https://doi.org/10.1093/ajcp/106.4.504
8. Misra S, Das PK, Bal SK, et al. Therapeutic Whole Lung Lavage for Alveolar Proteinosis. J Cardiothorac Vasc Anesth [Internet]. 2020;34:250-7. Available from: https://doi.org/10.1053/j.jvca.2019.07.001
9. Iftikhar H, Nair GB, Kumar A. Update on Diagnosis and Treatment of Adult Pulmonary Alveolar Proteinosis. Ther Clin Risk Manag [Internet]. 2021;17:701-10. https://doi.org/10.2147/TCRM.S193884
10. Soyez B, Borie R, Menard C, et al. Rituximab for autoimmune alveolar proteinosis, a real life cohort study. Respir Res [Internet]. 2018;19:74. https://doi.org/10.1186/s12931-018-0780-5
11. Awab A, Khan MS, Youness HA. Whole lung lavage-technical details, challenges and management of complications. J Thorac Dis [Internet]. 2017;9:1697–706. https://jtd.amegroups.com/article/view/13803/11597
12. Abdelmalak BB, Khanna AK, Culver DA, Popovich MJ. Therapeutic Whole-Lung Lavage for Pulmonary Alveolar Proteinosis: A Procedural Update. J Bronchology Interv Pulmonol [Internet]. 2015;22. https://doi.org/10.1097/LBR.0000000000000180
13. Campo I, Luisetti M, Griese M, et al. Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures. Orphanet J Rare Dis [Internet]. 2016;11:115. Available from: https://doi.org/10.1186/s13023-016-0497-9
14. Mata-Suarez SM, Castro-Lalín A, Mc Loughlin S, de Domini J, Bianco JC. Whole-Lung Lavage- a Narrative Review

of Anesthetic Management. J Cardiothorac Vasc Anesth [Internet]. 2022;36:587–93. https://doi.org/10.1053/j.jvca.2020.12.002
15. Tempe DK, Sharma A. Insights into Anesthetic Challenges of Whole Lung Lavage. J Cardiothorac Vasc Anesth [Internet]. 2019;33:2462–4. https://doi.org/10.1053/j.jvca.2019.04.033
16. Silva A, Moreto A, Pinho C, Magalhães A, Morais A, Fiuza C. Bilateral whole lung lavage in pulmonary alveolar proteinosis – A retrospective study. Rev Port Pneumol [Internet]. 2014;20:254–9. https://doi.org/10.1016/j.rppneu.2014.04.004
17. Jouneau S, Ménard C, Lederlin M. Pulmonary alveolar proteinosis. Respirology [Internet]. 2020;25:816–26. https://doi.org/10.1111/resp.13831
18. Sigakis MJG, de Cardenas JL. Lung Ultrasound Scans During Whole Lung Lavage. CHEST [Internet]. 2021;159:e433–6. https://doi.org/10.1016/j.chest.2020.06.089
19. Grutters LA, Smith EC, Casteleijn CW, et al. Increased Efficacy of Whole Lung Lavage Treatment in Alveolar Proteinosis Using a New Modified Lavage Technique. J Bronchology Interv Pulmonol [Internet]. 2021;28(3). https://doi.org/10.1097/LBR.0000000000000741
20. Akasaka K, Tanaka T, Maruyama T, et al. A mathematical model to predict protein wash out kinetics during whole-lung lavage in autoimmune pulmonary alveolar proteinosis. Am J Physiol - Lung Cell Mol Physiol [Internet]. 2014;308:L105–17. https://doi.org/10.1152/ajplung.00239.2014
21. Yu HY, Sun XF, Wang YX, Xu ZJ, Huang H. Whole lung lavage combined with Granulocyte-macrophage colony stimulating factor inhalation for an adult case of refractory pulmonary alveolar proteinosis. BMC Pulm med [Internet]. 2014;14:87. https://doi.org/10.1186/1471-2466-14-87
22. Gay P, Wallaert B, Nowak S, et al. Efficacy of Whole-Lung Lavage in Pulmonary Alveolar Proteinosis: A Multicenter International Study of GELF. Respiration [Internet]. 2017;93:198-206. https://doi.org/10.1159/000455179
23. Zhao YY, Huang H, Liu YZ, Song XY, Li S, Xu ZJ. Whole Lung Lavage Treatment of Chinese Patients with Autoimmune Pulmonary Alveolar Proteinosis: A Retrospective Long-term Follow-up Study. Chin Med J (Engl) [Internet]. 2015;128:2714-9. https://doi.org/10.4103/0366-6999.167295
24. Zhang HT, Wang C, Wang CY, Fang SC, Xu B, Zhang YM. Efficacy of Whole-Lung Lavage in Treatment of Pulmonary Alveolar Proteinosis. Am J Ther [Internet]. 2016;23:e1671-9. https://doi.org/10.1097/MJT.0000000000000239.
25. Marwah V, Katoch CDS, Singh S, et al. Management of primary pulmonary alveolar proteinosis: A multicentric experience. Lung India [Internet]. 2020;37:304-9. https://doi.org/10.4103/lungindia.lungindia_401_19.
26. Kaenmuang P, Navasakulpong A. Efficacy of whole lung lavage in pulmonary alveolar proteinosis: a 20-year experience at a reference center in Thailand. J Thorac Dis [Internet]. 2021;13:3539-48. https://doi.org/10.21037/jtd-20-3308
27. Hunter Guevara LR, Gillespie SM, Klompas AM, Torres NE, Barbara DW. Whole-lung lavage in a patient with pulmonary alveolar proteinosis. Ann Card Anaesth [Internet]. 2018;21:215-7. https://doi.org/10.4103/aca.ACA_184_17.
28. Smith BB, Torres NE, Hyder JA, et al. Whole-lung Lavage and Pulmonary Alveolar Proteinosis: Review of Clinical and Patient-centered Outcomes. J Cardiothorac Vasc Anesth [Internet]. 2019;33:2453–61. https://doi.org/10.1053/j.jvca.2019.03.047