

Whole Pulmonary Lavage: Treating Pulmonary Alveolar Proteinosis At The Time of COVID Pandemic

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Abstract

Pulmonary alveolar proteinosis (PAP) is a rare syndrome due to increased production or decreased clearance of surfactant in alveoli and terminal bronchi that cause hypoxemic respiratory insufficiency. Here we present a patient with past medical history of PAP whose disease was exacerbated by superimposed COVID-19 pneumonia. He underwent whole pulmonary lavage (WPL). Evaluation of the viral count of the first and the last lavage of the left lung showed viral load in the alveolar space dropped by approximately 10-folds, however the magnitude of the viral load was substantial in both lavage samples. Whole pulmonary lavage may be used as a treatment option on patients with COVID pneumonia superimposed on a pulmonary alveolar proteinosis (PAP) exacerbation.

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a rare syndrome due to increased production or decreased clearance of surfactant in alveoli and terminal bronchi that cause hypoxemic respiratory insufficiency. Here we present a patient with past medical history of PAP whose disease was exacerbated by superimposed COVID-19 pneumonia. He underwent whole pulmonary lavage (WPL). Evaluation of the viral count of the first and the last lavage of the left lung showed viral load in the alveolar space dropped by approximately 10-folds, however the magnitude of the viral load was substantial in both lavage samples. Whole pulmonary lavage may be used as a treatment option on patients with COVID pneumonia superimposed on a pulmonary alveolar proteinosis (PAP) exacerbation.

Background

PAP is a rare syndrome characterized by abnormal accumulation of surfactant in alveoli and terminal airways resulting in hypoxemic respiratory insufficiency [1,2], and defects in alveolar macrophage- and neutrophil-mediated host defense [3]. It is divided into disorders of surfactant production or surfactant clearance [4]. Disorders of production include pulmonary surfactant metabolic dysfunction disorders caused by mutations in genes encoding surfactant proteins or genes encoding proteins involved in production of surfactant. Disorders in clearance can be further divided into primary PAP caused by disruption of granulocyte/macrophage colony-stimulating factor (GM-CSF) signaling and secondary PAP caused by another condition that disrupts alveolar macrophage surfactant clearance.

Case presentation

The patient is a 29-year-old man with a past medical history of PAP diagnosed in 2018. He had no other medical problems and endorsed working in construction for 12 years, mainly brick work with some exposure to cement and dust.

In 2018, he presented with complain of 15-days of lip/ear cyanosis, shortness of breath (SOB), cough productive of yellow sputum, and maculopapular rash on his back and neck. He was found to be hypoxic to 72% on room air and admitted to the medical intensive care unit. CT scan on admission was concerning for PAP with grand glass opacities with inter-septal thickening. Two months prior to his admission, he had been hospitalized at another hospital and underwent a lung biopsy that confirmed PAP. There, he received a right lung lavage with 18L normal saline, which was aborted as he developed hypoxemia.

Extensive work up was negative for HIV, acid fast bacilli (AFB) and various fungal infections. His ANA, P-ANCA, C-ANCA were negative. GM-CSF autoantibody was positive and STAT5 phosphorylation index test was abnormal.

During his stay, he underwent a left lung lavage with 24L of saline, followed by a right lung lavage with 25L of saline 7 days later. He was discharged on room air, with inhaled GM-CSF for 12 weeks. He was instructed to return to pulmonary clinic for serial pulmonary function tests (PFT), as well as genetics and rheumatology to assess for familial autoimmune PAP.

He was lost to follow up until March 2020. In March, he presented to the emergency department (ED) with SOB, cough with green phlegm, myalgias, and fever. His chest x-ray showed patchy infiltrates consistent with pneumonia and CT chest showed diffuse ground glass opacities and consolidation with interlobular thickening. He was found to be COVID negative and discharged with a course of doxycycline.

He then presented to the ED in December 2020 with complaints of SOB, headache, and fever for one week. He was found to be hypoxic as low as 55% and admitted to MICU on 40mL/min high nasal flow cannula (HFNC) at 60% inspired oxygen fraction (FiO2). He was found to be COVID+ and started on Remdesivir and Dexamethasone with cefepime and azithromycin to cover for superimposed bacterial pneumonia. Due to his history of PAP, he was started on GM-CSF nebulizers twice a day.

Expectorated sputum was sent for culture, periodic acid Schiff (PAS) stain, and acid fast bacilli (AFB) and bronchoscopy was deferred due to COVID positivity and severe hypoxia. Sputum showed granular PAS+, fungal hyphae suggestive of candida, and rare alveolar macrophages. AFB cultures were negative x3.

Over the next 4 days his oxygen requirement decreased to 15mL/min HFNC on 100% FiO₂ and he was transferred to the intensive medical unit. Six days into his admission, the patient reported clinically feeling better but chest imaging was stable and oxygen requirements remained the same. Ten days into his admission, his oxygen requirements were unchanged and CT chest showed crazy paving consistent with PAP (Figure 1).

Due to his inability to wean from HFNC, ongoing sputum production, and completion of a full course of Remdesivir and Dexamethasone concern was that his underlying pathology was more likely due to a PAP flare than his known COVID infection. The patient remained persistently positive for COVID on PCR throughout his entire admission so a decision was made to use another course of Remdesivir to hopefully lower his viral load in anticipation of a bronchoscopy and possible WLL. Unfortunately, his oxygen saturations worsened and his O₂ requirements increased. He was transferred back to the MICU on HFNC to 40L on 100% FiO₂ with worsening chest x-ray findings.

After a discussion in consensus conference composed of physicians from infectious disease, pulmonology, critical care, surgery and pathology regarding this atypical course of COVID pneumonia, the cause of his ongoing symptoms and worsening oxygen requirements was thought to be much more likely from a PAP flare. Thus, the decision was made to undergo a bronchoscopy and perform a WLL with cardiothoracic surgery for extracorporeal membrane oxygenation backup. Sixteen days into his admission, we performed a WLL on the patient's left lung with 18L NS (Figure 2). The following day, WLL was performed on the right lung with 18L NS. The patient was successfully extubated the following day and was discharged 3 days later on 3L NC O₂ at rest and 4L with exertion. He was started on one nebulized GM-CSF for a total of 24 weeks, 1 week on and 1 week off.

The first and last specimens from the left WLL were tested (details can be provided upon request). The viral load in first BAL specimen with the highest concentration of proteinosis had a high viral load of 8.6 log₁₀ copies/mL of N1. The viral load reduced to 7.7 log₁₀ copies/mL of N1 in the last lavage specimen obtained, which was also reflected by a decrease in the level of proteinosis. This suggested that between the lavage samples the viral load in the alveolar space dropped by approximately 10-folds, however the magnitude of the viral load was substantial in both lavage samples.

As of 3/15/21, the patient reports he is clinically improving and fully compliant with his inhaled GM-CSF. He is off the oxygen and saturation remains >95% during exertion.

Summary and discussion

PAP is a rare disease characterized by interalveolar accumulation of surfactant impairing gas exchange and resulting in progressive respiratory insufficiency. [1] PAP has three distinct clinical forms: primary, secondary and congenital [1,2]. Primary or idiopathic PAP accounts for 90% of PAP cases. Secondary PAP occurs as a consequence of various underlying diseases [5]. Congenital PAP is a heterogeneous collection of disorders caused by homozygous mutation of the genes encoding surfactant protein (SP)-B, SP-C and the ABCA3 transporter or by the absence of granulocyte/macrophage colony-stimulating factor (GM-CSF) receptor [6].

The prevalence of PAP has recently been determined to be 6.87 ± 0.33 per million in the general population and it affects men and women similarly [7]. Autoimmune PAP represented 89.9% of cases and had a minimum incidence and prevalence of 0.49 and 6.2 per million, respectively [8].

Autoimmune PAP generally presents as progressive dyspnea of insidious onset unless secondary infection is also present, in which case fever, cough and rarely hemoptysis may also be seen. Chest CT typically shows bilateral patchy or diffuse air-space consolidation or hazy ground-glass opacity similar to pulmonary edema but without other features of left heart failure. WLL is current gold standard of care, however, GM-CSF augmentation strategies are also used in autoimmune PAP [9].

Management of PAP patients infected with COVID-19 is challenging. The present case demonstrates that WLL may benefit the patient as it not only removes the excessive surfactant, but also decreases the viral load.

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Figure 1. CT chest showed crazy paving consistent with PAP.

Figure 2. The 3-liter canisters (total of 18L) that used for WLL. The one on the far right is the product of the first wash, which gradually becomes clear as lavage continues. The one on the far left is the product of the last wash.

Table 1 . This table shows the trend of pulmonary function tests in the patient.

Date	06/2018	07/2018	10/2018
FVC (L)		314	4.45
FVC (%)		68	97
FEV1 (L)		2.44	3.85
FEV1 (%)		63	101
TLC (L)		4.52	5.75
TLC (%)		79	101
DLCO		9.17 (adj)	24.91 (unadj)
DLCO (%)		27	74
6MWD (meters)	240 meters; nadir 90% on 3L/min O ²	330 meters; nadir 90% on 3L/ min O ²	445 meters; required

FVC: forced vital capacity, FEV1: forced expiratory volume in one second, TLC: total lung capacity, DLCO: diffuse capacity of the lung for carbon monoxide, 6MWD: 6-minute walking distance

