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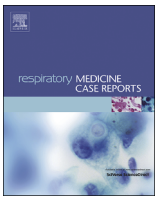

Case Report

Pulmonary alveolar proteinosis following severe COVID - 19 infection: A case report

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ABSTRACT

A 67-year-old male, with a history of severe COVID-19 infection and exposure to talc was seen for worsening shortness of breath for months, requiring supplemental oxygen. He was treated for COVID-19 infection and suspected pneumonia with no improvement. His pulmonary function test (PFT) worsened and computed tomography (CT) showing bilateral airspace opacities with ground-glass opacities (GGO), also worsened over time. He underwent bronchoscopy, bronchoalveolar lavage and pathology revealed pulmonary alveolar proteinosis (PAP). He subsequently underwent whole lung lavage (WLL) which significantly improved his crazy paving pattern on CT and was successfully weaned off supplemental oxygen.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterized by abnormal accumulation of periodic acid-schiff (PAS)-positive lipoproteins in alveolar and terminal bronchioles. It can be due to mutations in the GM-CSF receptor genes, inhalation of toxins, or infections. There are less than 5 reports of COVID-19 associated with PAP. Diagnosis is based on medical history, imaging and bronchoalveolar lavage findings. Severe forms are treated with whole lung lavage. Lung transplantation is reserved for patients who do not respond to treatments. We present a case of a 63-year-old male found to have Pulmonary Alveolar Proteinosis (PAP) following a severe COVID-19 infection.

2. Case presentation

A 67-year-old male, lifetime nonsmoker who worked at a chemical plant with some exposure to talc was referred to us due to worsening shortness of breath and cough for a few months duration. His past medical history included allergic asthma, severe obstructive sleep apnea and obesity. His most recent PFT done a year prior to presentation was essentially normal without any restriction or obstructive disease (Fig. 1a).

Weeks prior to his visit he was hospitalized for 10 days secondary to COVID-19 infection. During his hospital stay, computed tomography with angiography (CTA) of the chest showed extensive bilateral airspace opacities along with ground-glass opacities (GGO) with linear components (Image 1). Home COVID-19 testing was positive a week prior, but COVID-19 PCR was negative during hospitalization. He was treated with Decadron, Remdesivir, Lasix, Baricitinib, Solu-Medrol, breathing treatments, and supplemental Oxygen. He was discharged with a prednisone taper.

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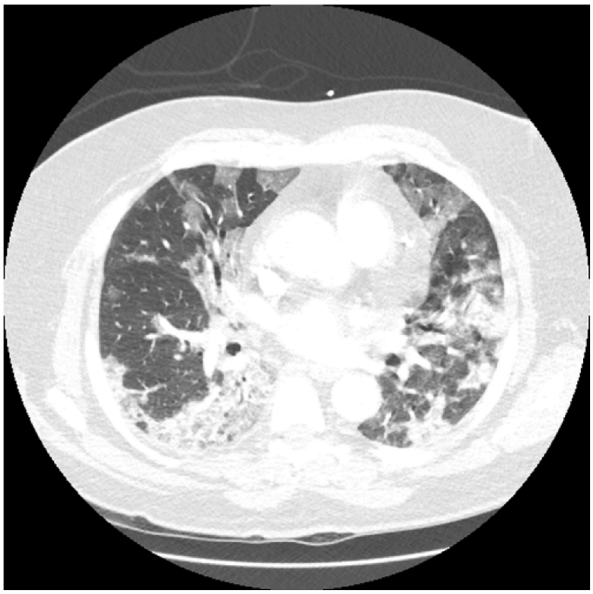

Image 1. Computer tomography angiography (CTA) pulmonary Embolism (PE).

A week post discharge, he was readmitted for worsening hypoxic respiratory failure and repeat CTA of the chest showed extensive bilateral pulmonary airspace opacity, areas of airspace disease which correspond to opacities seen on the prior CT, that appeared less extensive. However, new GGO with linear components in some of the areas that were previously not involved by airspace disease became apparent (Image 2). At that time, he was treated with Solu-Medrol and antibiotics (ceftriaxone and azithromycin) for presumed bacterial pneumonia. He was discharged on 1-month Eliquis for VTE prophylaxis, Omnicef, Zithromax along with a steroid taper and supplemental oxygen (3L nasal cannula), which he was not on prior to COVID- 19 infection.

At his follow up visit he reported improvements in his respiratory symptoms but had not returned to his baseline exercise tolerance. Repeat PFT showed new findings of restrictive lung disease with restrictive pattern and forced vital capacity (FVC) decreased from 4.25 L to 3.38 L (Fig. 1b). CT chest improved but persistent bilateral diffuse GGO (Image 3). Subsequently, he was lost to follow-up.

He returned for a follow up visit over a year later and reported worsening shortness of breath with exertion since his COVID-19 infection two years prior. He was also having issues with working around his house and property, requiring multiple breaks while mowing his lawn and doing other housework like vacuuming and dusting. He reported feeling significantly winded after walking one block or up one flight of stairs. At that time, he was requiring 4–6L of oxygen with activity but could maintain saturation over 90% on room air at rest. He retired early after being unable to keep up with the work demands. Repeat PFT should further decrease in FVC to 3.27 L

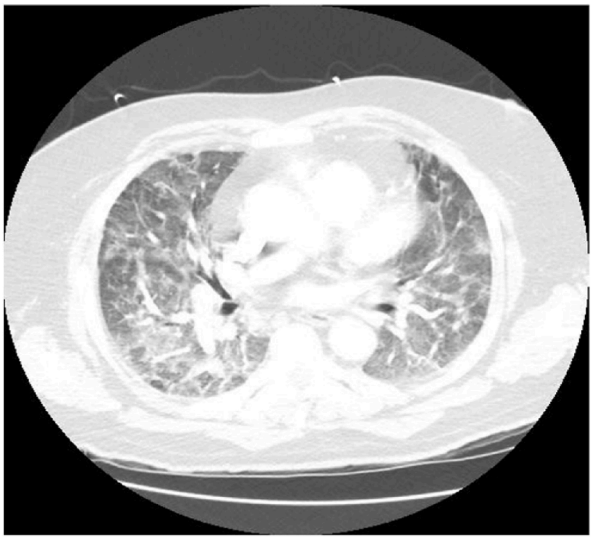

Image 2. CTA PE: Extensive bilateral pulmonary airspace opacity.

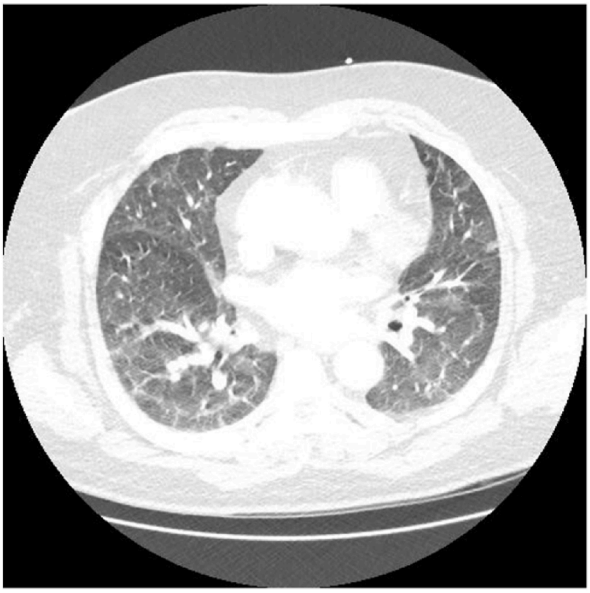

Image 3. CTA PE: Bilateral reticular and hazy lung opacities.

(Fig. 1c). He underwent a repeat CT chest that showed a diffuse bilateral crazy paving pattern of infiltrates most predominant in the upper lobes (Image 4). He then underwent bronchoscopy and transbronchial biopsy and cryobiopsy. Bronchoalveolar lavage (Image 5) and pathology (Image 6) revealed pulmonary alveolar proteinosis. He subsequently underwent WLL that significantly improved his crazy paving pattern on the CT (Image 7) and was successfully weaned off supplemental oxygen.

3. Discussion

PAP is a rare lung disease characterized by abnormal accumulation of PAS-positive lipoprotein in alveolar spaces and terminal bronchioles. The incidence and prevalence remain quite low at 0.24–0.49 cases per million inhabitants, and 2.04–6.2 cases per million inhabitants, respectively. Epidemiologically it's seen twice as common in males than females with a median age of 50 [1]. Clinical symptoms include progressive dyspnea and cough with associated fever, pain, and/or hemoptysis. Although, close to 35% of patients could remain symptomatic. PAP may be idiopathic, secondary, or congenital. Idiopathic PAP is most common; it accounts for 90% of cases and often has an autoimmune basis. Congenital/hereditary PAP accounts for less than 1% and is due to mutations in the GM-CSF

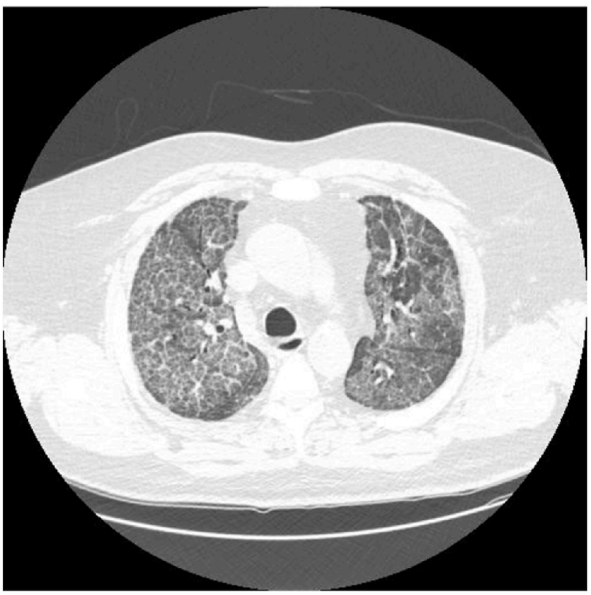

Image 4. Computer Tomography (CT) Chest high-resolution without contrast: Upper lobe predominant hazy paving pattern.

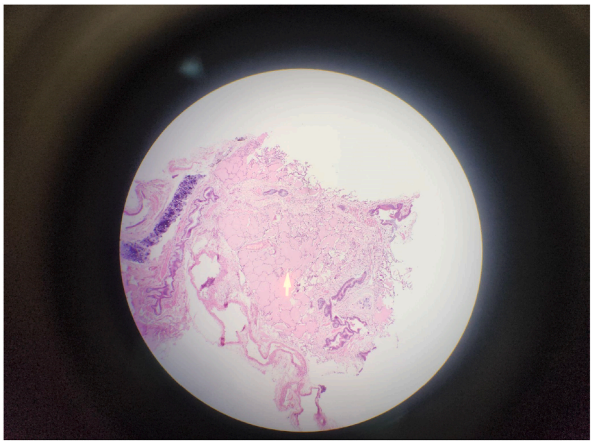

Image 5. BAL cell block
CP-23-03288 1A, 2A
Negative for malignant cells. Paucicellular granular exudate consistent with alveolar proteinosis.

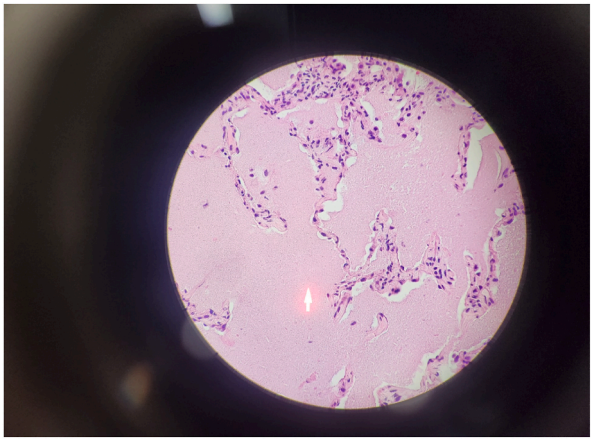

Image 6. Pathology
Well preserved alveolated parenchyma in which there is a paucicellular airspace exudate comprising granular eosinophilic debris with cholesterol-like clefts and cell ghosts. Alveolar septa in areas of abnormality show no significant histologic abnormalities.

receptor genes (CSF2RA and CSF2RB). Anti-GM-CSF antibodies cause macrophage dysfunction that results in impaired clearance of surfactant, leading to accumulation in primary as well as congenital/hereditary PAP. Secondary PAP accounts for 5–10% of cases and is associated with hematological cancers (lymphoma, leukemia, and myelodysplastic syndrome), immunodeficiency, inhalation of toxic substances, and infection [2].

A large database of 1.2 million symptomatic COVID-19 individuals across 22 countries, including mild cases not requiring hospitalization, an estimated 3.7% of total patients reported having ongoing respiratory problems [3]. In our case, the patient was initially diagnosed with a severe COVID-19 infection requiring hospitalization and non-invasive positive pressure ventilation. He was treated with antibiotics, steroids, Remdesevir and Baricitinib and subsequently diagnosed with long COVID-19 syndrome and treated with oral corticosteroid for 2 months without significant improvement. We suspected another cause, indicated fiberoptic bronchoscopy, and confirmed the diagnosis of PAP.

PAP involves abnormalities in macrophages and alveolar neutrophils, decreasing the efficiency of surfactant clearance, leading to accumulation of PAS-positive lipoprotein in alveolar spaces. Well known infectious microorganisms associated with the onset of PAP include Nocardia, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Pneumocystis jirovecii, Epstein-Barr virus, HIV and cytomegalovirus [4]. There are few reports of influenza associated with PAP and even fewer (less than 5) reported cases of COVID-19 association to date. Although some did have a history of PAP that was exacerbated with COVID-19 infection, most new reported cases of PAP had recent COVID-19infection [5,6]. The speculated pathogenic mechanisms could be due to the generation of inhibitory autoantibody to GM-CSF [7] or the impairment of alveolar macrophage that accentuates the proinflammatory state after COVID-19 infection [8]. On the other hand, this patient could have had pre-existing PAP which could have been exacerbated by COVID-19 infection and corticosteroid treatment.

Corticosteroids have been shown to be associated with the onset and progression of PAP. Initial evidence demonstrated improvement in radiographic patterns and lung function with prolonged steroid taper in a subset of patients who were suspected to have orga-

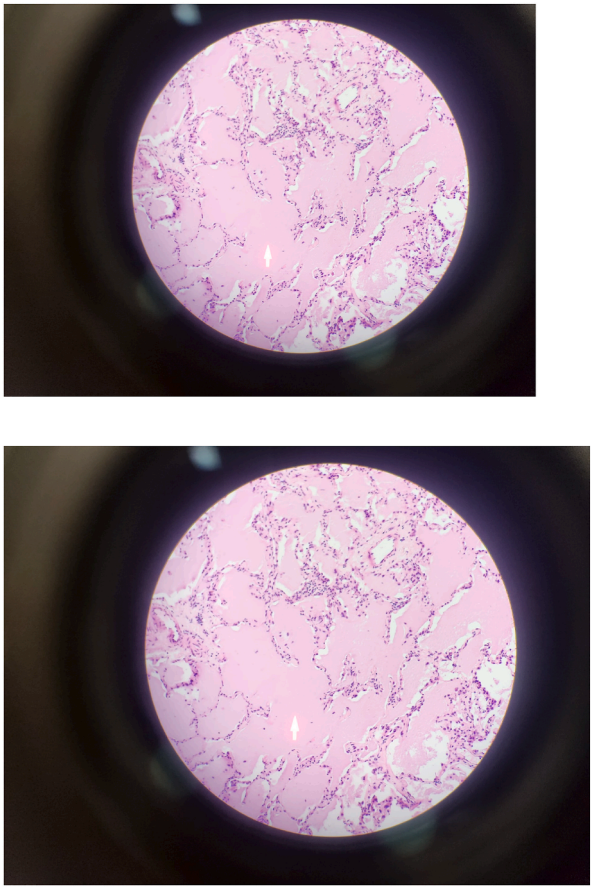

Image 7. Showing improved crazy paving pattern on infiltrates post whole lung lavage.

nizing pneumonia as a long term sequelae of COVID-19 infection, more recently, prolonged and higher dose steroid tapers showed no difference in overall outcomes among all COVID-19 infected patients. Organizing pneumonia as a subset in these studies was not evaluated [9]. However, immunosuppression can lead to clinical deterioration in PAP. One small study of 31 patients with autoimmune PAP who were prescribed glucocorticoid, 75% of them had clinical worsening of PAP. Proposed mechanism is that steroids inhibit production of GM-CSF [10]. Steroids can increase the susceptibility of infections and worsen the disease severity by accelerating surfactant production in type II pneumocytes, specifically in autoimmune PAP [11].

This further emphasizes the importance of considering PAP in post-COVID-19 patients.

Evidence suggested that COVID-19 infection related autoantibodies were detected up to a year and may even increase with time irrespective of severity of illness [12]. Various hypotheses have been presented to explain this new-onset autoimmunity including molecular mimicry, bystander activation triggered by a hyperinflammatory state ("cytokine storm" or "cytokine release syndrome"), persistence of viral antigens and formation of neutrophil extracellular traps [13,14]. Vasculitis and arthritis were the most common autoimmune diseases, followed by idiopathic inflammatory myositis (IIM), systemic lupus erythematosus (SLE), and other autoimmune diseases in a study with post covid patients. The study did not include cases of autoimmune PAP. Severe covid-19 infection was associated with more severe manifestations of IIM, SLE and vasculitis [15].

Although the characteristic findings of PAP on CT are diffuse bilateral ground-glass areas superimposed on the thickening of the interlobular and intralobular septal lines, resulting in a crazy-paving pattern. Radiologically, the pattern for COVID-19 pneumonia is similar making it difficult to delineate between the two based on CT imaging. Abnormal radiological findings of COVID-19 pneumonia can persist for over a year irrespective of severity of illness [16]. In our case, the patient had two CT scans during the time of his acute COVID-19 infection. The first showing diffuse bilateral GGO (Image 2) followed by significant improvement in the following CT scan done months later (Image 3). However, a CT chest done a year after hospitalization for progressive worsening of symptoms with increased oxygen requirements of up to 6L with activity showed significant worsening bilateral diffuse crazy paving pattern GGO infiltrates (Image 4).

Our case is unique as it seems to be the first reported case of PAP following a severe COVID-19 infection in the United States, to the best of our literature review. There was a prolonged interval between contracting COVID-19 infection and the appearance of characteristic clinical/radiological findings of PAP, indicative of important aspects of long COVID. We have not found other causes to justify hereditary PAP (negative genetic study) or secondary PAP (no exposure to inhaled substances or known hematological diseases). Of

note, he did report exposure to talc at his work place which could also be a plausible contributing etiology. However, he had been working in that industry with similar exposures for over two decades before becoming symptomatic with radiological worsening after COVID-19 infection. He also had normal PFTs prior to his COVID-19 infection.

The diagnosis of PAP is usually based on a conglomeration of appropriate medical history accompanied by typical CT imaging findings and milky bronchoalveolar lavage fluid which stains positive for PAS reaction. Lung biopsy should be considered in patients who's radiological or bronchoalveolar lavage findings are not characteristic. Pathological features include intra alveolar acellular, amorphous, eosinophilic material (seen clearly with PAS staining), and foamy alveolar macrophages [1].

Mild and moderate forms of PAP require monitoring, since spontaneous resolution has been described. Severe PAP is generally treated with whole lung lavage (WLL) as treatment of choice. It is when each lung is selectively intubated at a time and a large volume lavage is performed one lung at a time until the saline lavage return becomes clear [1,2]. More recently, simultaneous use of extracorporeal membrane oxygenation (ECMO) enabling sequential lavage of both lungs has been described [17]. Segmental lung lavage has been described for a patient who was thought to be a poor candidate for WLL due to severe hypoxia [18].

The therapeutic benefit of inhaled or subcutaneous GM-CSF analogs with about 50% favorable response have been reported but are not well studied [4]. Reports of using Rituximab as second line treatment exists but larger data from a clinical trial show that Rituximab did not improve reduced anti-GM-CSF antibody levels [19]. Lung transplantation is reserved for patients who have not responded to any of the aforementioned treatments. PAP has been shown to relapse after initial resolution.With 5-year survival more than 80% in PAP. Extremes of spontaneous resolution and death from pneumonia have been reported [1,2,20]. In conclusion, it is important to consider PAP as part of long-term sequelae of COVID-19 infection that can become apparent even years down the line.

4. Conclusion

The aim of this novel case of post-COVID -19, new-onset autoimmune PAP is to sensitize the treating provider(s) about this new entity and enable them to make an early diagnosis based on history, clinical reasoning and imaging findings. This would lead to prompt initiation of therapy, in turn resulting in successful recovery and prevention of end-organ damage and fatality.

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CRediT authorship contribution statement

Samina Martin: Writing – review & editing, Writing – original draft, Resources, Conceptualization. **Shivu Kaushik:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Bharat Bajantri:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2024.102017.

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