Case Report

# Autoimmune pulmonary alveolar proteinosis and sarcoidosis in the same patient: Case report and systematic review

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## ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disorder characterized by surfactant accumulation in the alveolar spaces while sarcoidosis is a multisystem granulomatous disease of unknown etiology. The occurrence of PAP and sarcoidosis in the same patient is rare. A 37-year-old woman presented with cough and breathlessness and was diagnosed to have autoimmune PAP. She responded well to subcutaneous injections of recombinant granulocyte macrophage colony stimulating factor. Three years later, she developed fever, chest pain, cough, and facial palsy. The evaluation revealed a diagnosis of sarcoidosis that responded to immunosuppressive treatment. We discuss the link between PAP and sarcoidosis and review the literature on this association.

**KEY WORDS:** Diffuse parenchymal lung disease, granuloma, interstitial lung disease, pulmonary alveolar proteinosis, sarcoidosis

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## INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a diffuse lung disorder characterized by surfactant accumulation in the alveolar spaces, resulting in hypoxemia that can progress to respiratory failure.[1] It is a rare disease with estimated incidence and prevalence of 0.5 and 6.2 per million population.[2] Autoimmune PAP (aPAP) is the most common form of PAP accounting for 90% of cases, characterized by antibodies against granulocyte macrophage colony stimulating factor (anti-GM-CSF antibodies).[1] The anti-GM-CSF antibodies cause macrophage dysfunction resulting in surfactant accumulation.[3]

Sarcoidosis is a multisystem granulomatous disease of unknown etiology, characterized by noncaseating granulomatous inflammation in the affected organs, the lungs and lymph nodes being involved in most cases.[4,5] The coexistence of sarcoidosis and aPAP is rare.[6–11] Herein, we report a case of aPAP where the patient developed sarcoidosis during follow-up. We have also performed a systematic review of reports describing the rare association of PAP and sarcoidosis.

## CASE REPORT

A 37-year-old woman presented with dry cough and progressive breathlessness of three months' duration. There was no wheeze, hemoptysis, fever, or weight loss.

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She had no exposure to pets, molds, fumes, or occupational dusts. On examination, the pulse rate was 80 beats/minute, respiratory rate 18 breaths/minute, blood pressure 112/74 mmHg, and pulse oximetric oxygen saturation was 93% while breathing ambient air. The oxygen saturation declined to 83% on minimal exertion. Chest auscultation revealed crackles at the lung bases; the rest of the physical examination was unremarkable.

Complete blood counts, and kidney and liver function tests were normal. Spirometry yielded a forced vital capacity of 2.81 L (98% of the predicted) and a forced expiratory volume in one second of 2.38 L (106% of the predicted). The arterial blood gas analysis showed an arterial partial pressure of oxygen ($PaO_2$) of 65.9 mmHg, with an alveolar-arterial gradient of 38 mmHg. The serum antinuclear antibody and rheumatoid factor were negative. Chest radiography showed reticulonodular opacities in the middle and lower zones of both the lungs. A thin-section computed tomography (CT) of the thorax revealed ground-glass opacities and mild interstitial thickening [Figure 1], involving the middle lobe and both the lower lung lobes without any enlarged intrathoracic lymph nodes. She underwent flexible bronchoscopy. Cellular analysis of the bronchoalveolar lavage (BAL) fluid showed few alveolar macrophages and mucin. The Xpert MTB/RIF test in the BAL fluid was negative and cultures did not grow any mycobacteria or fungi. Transbronchial lung biopsy showed dilated alveolar spaces filled with an acellular, periodic acid-Schiff stain positive, diastase-resistant, granular, eosinophilic material along with foamy macrophages [Figure 2]. She had an elevated anti-GM-CSF antibody titer in the serum (126.7 μg/mL; normal value <1.0 μg/mL). A diagnosis of aPAP was made.

We initiated treatment with subcutaneous injection of sargramostim (recombinant GM-CSF) 500 μg on alternate days. Her breathlessness and cough decreased, and resting oxygen saturation improved to 98% within two months.

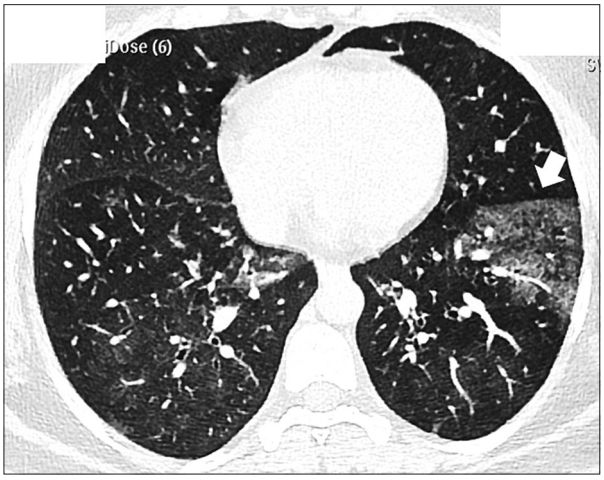


**Figure 1:** High-resolution computed tomography of the chest showing ground-glass opacities (arrow) in both lower lobes of the lungs with mild interstitial thickening

A chest CT performed three months after GM-CSF therapy showed significant resolution of abnormalities. We stopped the treatment after nine months due to financial constraints. Chest CT performed three months after the completion of treatment showed normal lung parenchyma. The patient remained asymptomatic during follow-up.

After 42 months of her initial presentation, the patient developed hyperpigmented, papular lesions on the forehead and the cheeks. Skin biopsy showed epidermal hyperkeratosis, basal cell degeneration, and pigmentary incontinence in the dermis. A diagnosis of lichen planus pigmentosus (LPP) was made. Around the same time, she also developed fever, cough, and chest pain. Chest radiograph showed the presence of bilateral hilar enlargement. CT chest showed few areas of crazy paving in the lower lobes, along with multiple enlarged mediastinal and hilar lymph nodes [Figure 3]. The tuberculin skin test (TST) showed a 13-mm induration. We performed endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from the intrathoracic lymph nodes that revealed non-necrotic granulomatous inflammation; the smear for acid-fast bacilli, GeneXpert MTB/RIF, and culture for *Mycobacterium tuberculosis* were negative. The clinical presentation, the existence of aPAP (with the consequent susceptibility to lung infections), positive TST, and high endemicity of tuberculosis in our region prompted us to diagnose tuberculosis. We started the patient on rifampicin, isoniazid, pyrazinamide, and ethambutol. Fever and dry cough persisted despite five weeks of therapy. She developed dry eyes with enlarged lacrimal glands and a lower motor neuron type of left facial nerve palsy. Magnetic resonance imaging of the brain was normal, but orbit imaging showed enlarged lacrimal glands bilaterally. The serum angiotensin-converting enzyme level was elevated 113 U/L (normal range, 8-65 U/L). We revised the diagnosis to sarcoidosis and initiated the patient on prednisolone at 0.75 mg/kg/day. Fever and cough subsided. The patient was started on mycophenolate mofetil for the diagnosis of LPP that allowed us to taper prednisolone. Mediastinal lymphadenopathy resolved on the subsequent chest CT. The patient continues to remain well two years later.

## SYSTEMATIC REVIEW OF LITERATURE

We searched the PubMed and Embase databases (from inception till 15 November 2021) using the

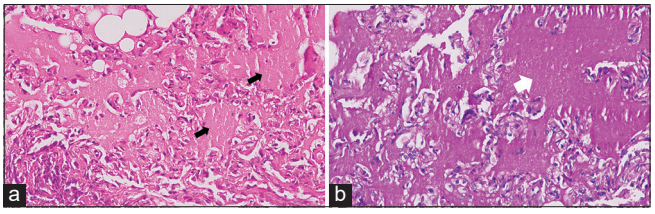


**Figure 2:** (a) Photomicrograph of transbronchial lung biopsy showing dilated alveolar spaces filled with an acellular, eosinophilic granular material (black arrows). (b) Photograph showing bright staining of the same alveolar material with the Periodic acid–Schiff stain (white arrow)

following search string: sarcoid* AND pulmonary alveolar proteinosis. Of the total 240 citations, seven cases from six articles were identified that reported the co-occurrence of sarcoidosis and PAP in the same patient [Table 1].[6–11] Four cases were from Japan and one each from Germany, Poland, and the United Kingdom.

The median (range) age of the eight patients (including the index case) was 51 (20–64) years; six of them were women. Sarcoidosis was diagnosed first in three patients, while the initial diagnosis was PAP in three other patients. In the remaining two, the disorders were diagnosed simultaneously. The diagnosis of PAP was confirmed by lung biopsy or BAL cellular analysis in all the cases. The anti-GM-CSF antibody levels were found elevated in the sera of all the six patients in whom they were tested. Sarcoidosis was diagnosed by demonstrating non-caseating granulomas in tissue biopsy except in one patient where only histiocyte collections were seen on histology. PAP was managed with lung lavage in three cases. One patient each received inhaled GM-CSF and inhaled N-acetylcysteine (and saline), respectively. Two patients did not receive any treatment for aPAP, while our patient received subcutaneous recombinant GM-CSF. For sarcoidosis, five patients received immunosuppressive treatment, while three were observed without any drug therapy. All the patients improved with the respective treatments.

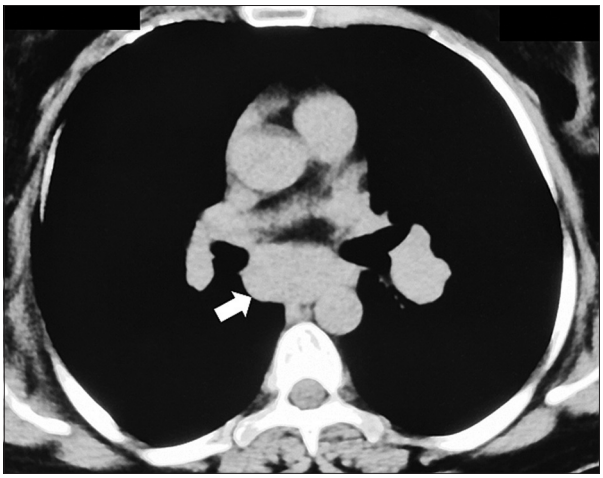

**Figure 3:** Computed tomography of the chest showing enlarged left interlobar and subcarinal lymph nodes (arrow)

## DISCUSSION

The coexistence of PAP and sarcoidosis remains rare; only eight cases (including the index case) have been reported to date. While the association of the two diseases might be by chance, alternatively, the diseases may share a common pathophysiologic basis. Sarcoidosis is characterized by aberrant granulomatous inflammation in response to an unknown environmental antigen. Despite several pointers to its autoimmune nature, sarcoidosis is not considered a classic disorder of autoimmunity.[12] However, sarcoidosis has an association with several autoimmune disorders and aPAP might be another such association. There are several unconfirmed hypotheses proposed for the co-existence of aPAP and sarcoidosis. Boerner, *et al*. have speculated that a common environmental, microbiologic, or predisposing factor might trigger the immune system causing both autoantibody production and granuloma formation in the same patient.[8] Certain microbes such as non-tuberculous mycobacteria, which may accumulate in the lungs of aPAP patients due to the underlying macrophage dysfunction, might trigger sarcoidosis.[11,13] Some serum markers such as chitinase-3-like protein 1 (YKL-40) and Krebs von den Lungen-6/mucin 1, although non-specific, may be raised in patients with

**Table 1: Summary of cases reporting the co-occurrence of autoimmune PAP and sarcoidosis**

| Authors (Year) | Country | Age (years)/ Sex | First diagnosis | Interval between sarcoidosis and PAP diagnosis | Diagnostic basis of sarcoidosis | Diagnostic basis of PAP | Treatment for sarcoidosis | Treatment for PAP |
|---|---|---|---|---|---|---|---|---|
| Kurgan *et al*. (1974)[6] | Poland | 20/male | Sarcoidosis | 7 months | Right supraclavicular lymph node biopsy | Surgical lung biopsy | Prednisone | N-acetylcysteine and normal saline nebulization |
| Mirchandani *et al*. (2010)[7] | United Kingdom | Young female | PAP and sarcoidosis | Simultaneously diagnosed | Mediastinal node biopsy | BAL | None | Whole lung lavage |
| Boerner *et al*. (2016)[8] | Germany | 55/female | PAP | 12 months | EBUS-TBNA of intrathoracic lymph nodes | BAL, TBLB, anti- GM-CSF antibody | None | Whole lung lavage |
| Yamasue *et al*. (2017)[9] | Japan | 64/female | Sarcoidosis and Scleroderma | 13 months | Mediastinal node, liver, and muscle biopsy | BAL, anti-GM-CSF antibody | Prednisolone, cyclophosphamide, tacrolimus | Sequential segmental lung lavage |
| Tanaka *et al*. (2019)[10] | Japan | 58/female | Sarcoidosis | 96 months | TBLB | Surgical lung biopsy, anti-GM-CSF antibody | None | None |
| Arai *et al*. (2020)[11] | Japan | 29/female | PAP | 120 months | Lung, skin biopsy | BAL, anti-GM-CSF antibody | Prednisolone | Inhaled GM-CSF |
| Arai *et al*. (2020)[11] | Japan | 51/male | PAP and sarcoidosis | Simultaneously diagnosed | Surgical lung biopsy, skin biopsy | Surgical lung biopsy, anti-GM-CSF antibody | Prednisolone | None |
| Index case | India | 42/female | PAP | 42 months | EBUS-TBNA | TBLB, anti-GM-CSF antibody | Prednisolone and mycophenolate mofetil | Subcutaneous GM- CSF |

BAL, bronchoalveolar lavage; EBUS-TBNA, endobronchial ultrasound guided transbronchial needle aspiration; GM-CSF, granulocyte monocyte colony stimulating factor; PAP, pulmonary alveolar proteinosis; TBLB, transbronchial lung biopsy

sarcoidosis and PAP.[14–16] Peroxisome proliferator-activated receptor γ expression is reduced in alveolar macrophages from patients with both pulmonary sarcoidosis and alveolar proteinosis, suggesting a common pathogenetic pathway.[17]

The immunosuppressive treatment for sarcoidosis may trigger the development of aPAP in some patients.[9] In fact, elevated GM-CSF autoantibodies have been detected in the serum of a few patients with sarcoidosis.[18] Immunosuppressants cause a disproportionate reduction in GM-CSF level than anti-GM-CSF antibodies,[9] possibly leading to a relative excess of the antibody causing macrophage dysfunction and surfactant accumulation.[9] Had this phenomenon been common, considering the large number of patients being treated with immunomodulatory therapy for inflammatory and autoimmune diseases, one would expect PAP to be much more frequent than what is currently observed. Alternately, exogenous recombinant GM-CSF for PAP might also result in a sarcoidosis-like granulomatous disorder.[19] However, in our patient, the GM-CSF therapy had been stopped more than a couple of years before symptoms of sarcoidosis appeared. Thus, the mechanism underlying the co-existence of PAP and sarcoidosis remains unclear.

The coexistence of sarcoidosis and PAP may also pose diagnostic and management challenges. Subjects with PAP are known to develop infections including tuberculosis. Therefore, in the index case, we initially considered a diagnosis of tuberculosis based on granulomatous mediastinal lymphadenopathy and a positive tuberculin skin test. We diagnosed sarcoidosis only when the patient failed to improve with anti-tuberculosis treatment and incidentally developed facial palsy. Also, glucocorticoid treatment for sarcoidosis might further increase the susceptibility of PAP patients to infections, thus making management decisions difficult.

## CONCLUSION

The coexistence of PAP and sarcoidosis is rare in clinical practice. A high index of suspicion is thus required to recognize this association.

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### Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest
There are no conflicts of interest.

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