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# Pulmonary alveolar proteinosis: another autoimmune disease associated with sarcoidosis?

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**Abstract.** Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterized by the accumulation of surfactant phospholipids and lipoproteins within the alveoli. Here we report on a female patient who was diagnosed with autoimmune PAP and successfully treated with whole lung lavage (WLL). 15 months after PAP diagnosis the patient developed marked fatigue. Additional tests revealed the diagnosis of sarcoidosis. We can only speculate that PAP and sarcoidosis in our patient are linked to each other based on the fact that other autoimmune disorders have also been associated with sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 90-94)*

**Key words:** pulmonary alveolar proteinosis (PAP), sarcoidosis, whole lung lavage

## Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disorder characterized by the accumulation of surfactant lipids and proteins within the pulmonary alveoli. Autoimmune PAP (aPAP) is the most frequent form, accounting for 90% of cases of PAP, and is defined by the presence of neutralizing serum autoantibodies to granulocyte-macrophage colony stimulating factor (GM-CSF) (1). By neutralizing GM-CSF, the pathogenic antibodies prevent maturation of pulmonary monocyte/macrophage populations with consequent perturbation of surfactant lipoprotein degradation. (2). This leads to increasing alveolar protein accumulation and progressive respiratory failure due to impaired gas exchange, intrapulmonary shunting and decreased lung volume (3). It has been hypothesized that environmental exposure could play a role in triggering autoimmunity (4, 5).

Sarcoidosis is a multisystem granulomatous disorder, with thoracic involvement occurring in more than 90% of patients. Although some putative agents and causes have been described for the etiology of sarcoidosis, the real underlying cause remains unknown. For the first time, we report a case of aPAP associated with sarcoidosis. Sarcoidosis became clinically evident and was diagnosed while aPAP was in remission.

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## Case Study

A 55 year old female patient was admitted for gradually increasing dyspnea on exertion and cough to the Red Cross Hospital in Stuttgart. The patient

reported occupational exposure to dusts at work in a printing office over 20 years and a positive smoking history (10 pack years). She had no pets or a hobby linked with dust or fume exposure, and she never used hair spray.

In the initial lung function test forced vital capacity (FVC) was normal and the diffusion capacity (DLco) was 60% predicted. $PaO_2$ was 58 mm Hg at rest and 50 mm Hg at exercise (40 Watts over 5 min). Alveolar-arterial gradient ($AaDO_2$) was 44 mm Hg at rest and 59 mm Hg at exercise.

Chest x-ray showed a typical butterfly appearance of shadows in the hilar region without enlargement of mediastinal lymph nodes (figure 1a). High-resolution computed tomography (HRCT) showed ground glass opacities with crazy paving pattern and geographical distribution compatible with PAP (figure 1b).

Bronchoalveolar lavage showed periodic-acid-Schiff stain-positive foamy macrophages, acellular globules, and debris typical for PAP. Transbronchial lung biopsy showed alveolar spaces filled with eosinophilic acellular, finely granular material, detached type II pneumocytes, foamy macrophages, and ghost cells (figure 2). Particulate material (birefrigent particles within the intraalveolar exudates)

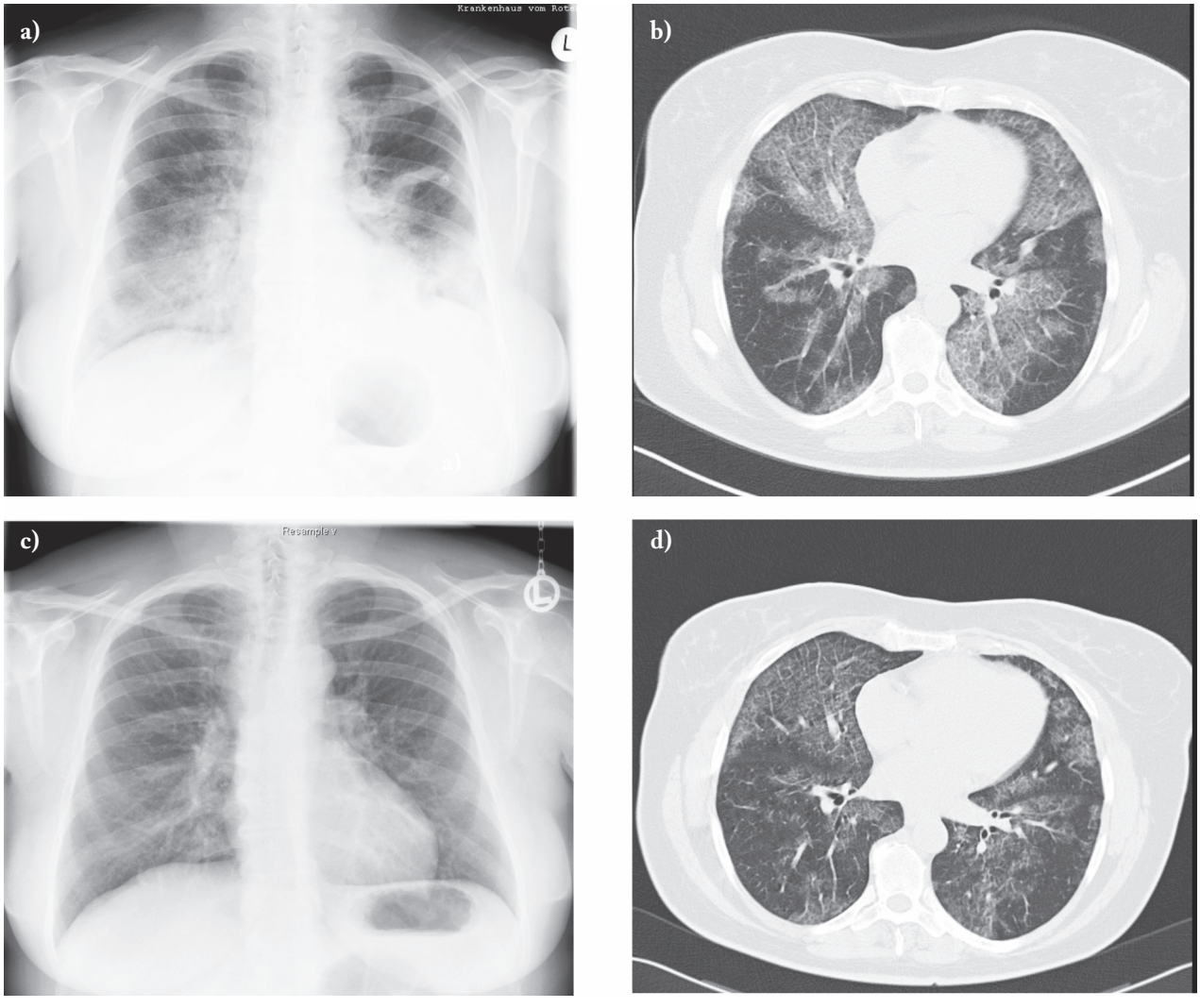



**Fig. 1.** Radiologic findings at diagnosis: (a) Chest x ray shows increased bilateral opacities with basal accentuation; (b) HRCT shows bilateral ground glass opacities with crazy paving pattern. (c) chest x-ray 7 months after the diagnosis shows reduction of bilateral opacities and (d) HRCT shows regression of ground glass opacities

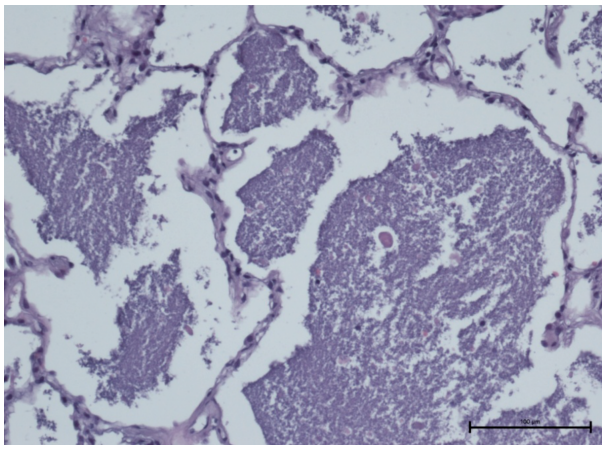


**Fig. 2.** Histology findings of PAP: alveolar spaces filled with acellular, finely eosinophilic granular material, detached type II pneumocytes, foamy macrophages, and ghost cells (Haematoxylin-eosin stain, magnification 200x)

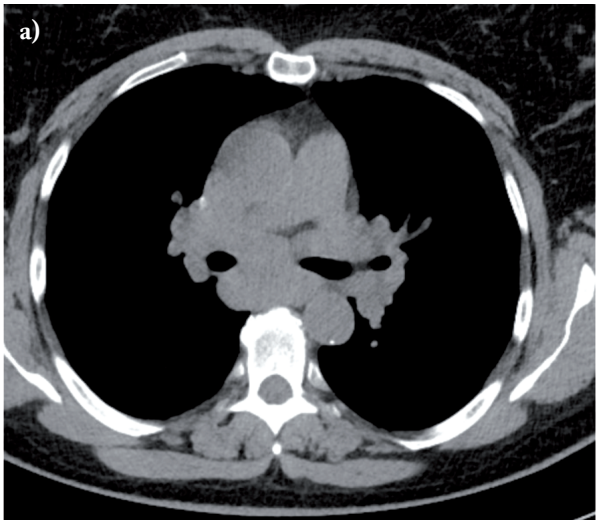
was not identified with polarization microscopy. Therefore electron microscopy and energy dispersive x-ray analyses were not performed. Serum GM-CSF autoantibodies (Abs) were positive (Abs titer not available), and the diagnosis of autoimmune PAP was made.

The patient underwent whole lung lavage (WLL) because of desaturation and increased alveolar-arterial gradient ($AaDO_2$) at exercise test. One week after the WLL the patient was discharged from the hospital in a better condition and improved oxygenation; $paO_2$ had increased to 65 mm Hg at rest. Three months after the performance of WLL HRCT showed a partial regression of the previously seen ground glass opacities (figure 1d).

7 months after the diagnosis the patient was referred to the Ruhrlandklinik in Essen for a second opinion regarding treatment options, especially GM-CSF administration. At presentation in our center, chest x-ray showed significant regression of bilateral opacities (figure 1c). Forced vital capacity was normal and DLco significantly improved to normal (84% predicted). At rest saturation was 98%, and there was no more impairment of gas exchange during exercise. Serum LDH was 309 U/l (N<248 U/l), KL-6 was 1322 U/ml (N<458 U/ml) and GM-CSF autoAbs was 57 mcg/mI (N<0.5 mcg/ml). PAP was in stable remission and no further treatment was recommended.

12 months after the WLL the patient was admitted again to the first hospital in Stuttgart because of marked fatigue without respiratory symptoms. Surprisingly, chest x-ray and computed tomography showed marked enlargement of mediastinal and hilar lymph nodes, and the ground glass opacities had completely resolved (figure 3a, 3b).

In order to clarify the nature of enlarged lymph nodes endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) was performed.



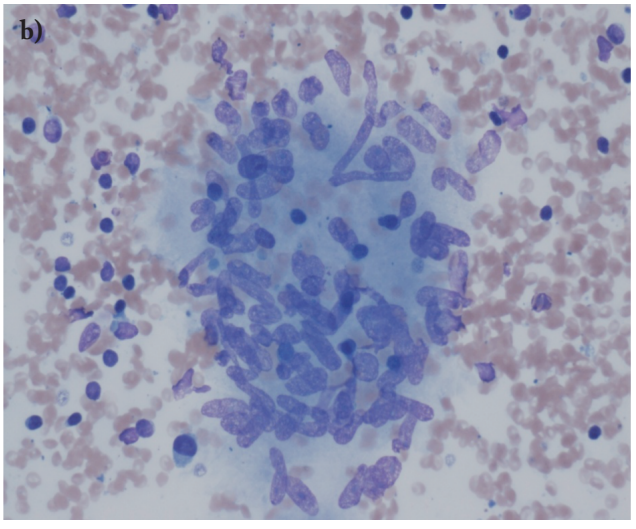




**Fig. 3.** (a) HRCT 15 months after diagnosis showing complete resolution of ground glass opacities and enlarged hilar and mediastinal lymph nodes, (b) Non-caseating granuloma in the lymph nodes samples obtained through EBUS-TBNA

The cytological examination revealed non-caseating granuloma consistent with sarcoidosis (figure 3c). The gamma interferon test (T-SPOT®) was negative. The culture of endobronchial samples was negative for M. tuberculosis and other bacteria or fungi. Serum biomarkers for sarcoidosis were also measured: ACE was 71 U/l (N: 20-70 U/l) and IL- 2 receptor was 1601 kU/ml (N: 158-623 kU/l). Pulmonary function tests were normal (FVC 112% predicted, DLco 86% of predicted). A diagnosis of sarcoidosis stage I was made. There was no evidence of cardiac or ocular involvement, and a non-interventional strategy with careful observation was undertaken.

## Discussion

To the best of our knowledge this is the first description of the occurrence of aPAP and sarcoidosis in the same patient. Autoimmune PAP is the most common form of PAP and is characterized by the presence of GM-CSF autoantibodies (6, 7). The association of sarcoidosis with autoimmune diseases such as rheumatoid arthritis (8, 9), multiple sclerosis (10), IgA nephropathy (11-15), celiac disease (16, 17), autoimmune hemolytic anemia (18-21), and ANCA-associated vasculitis (22-28) has been previously described.

Interestingly, in our patient sarcoidosis became clinically evident and was diagnosed in mediastinal lymph nodes as PAP was going into remission after one bilateral WLL with resolving ground glass opacities and improvement of DLco.

We can only speculate that PAP and sarcoidosis in our patient are linked to each other. Recent studies have shown that the aberrant relationship of T regulatory cells (Treg) and Th17 cells is a pivotal pattern involved in immune mediated diseases, including autoimmune arthritis, psoriasis, inflammatory bowel disease, systemic lupus erythematosus, and several others (29, 30). A significant increase in the Th17/Treg cell ratio was also observed in sarcoidosis patients and has been hypothesized as a link between sarcoidosis and autoimmunity (30, 31). On the other hand, the autoimmune nature of PAP is explained only by the presence of GM-CSF autoantibodies and by the fact that B cell depletion through anti-CD-20 monoclonal antibody (rituximab) administration seems to be an effective treatment approach for PAP (32).

In conclusion, whether a common environmental, microbiologic or predisposing factor can trigger the immune system causing both autoantibody production and granuloma formation in the same patient remains an intriguing question.

## Authors' contributions

Boerner EB has drafted the manuscript

Boerner EB, Wessendorf TE, Bonella F and Hetzel M visited and followed the patient

Theegarten D reevaluated the histologic specimens

Drent M, Costabel U and Bonella F revised, corrected and finalized the article

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