

# A case of uncomplicated pulmonary alveolar proteinosis evolving to pulmonary fibrosis

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**ABSTRACT:** *A case of uncomplicated pulmonary alveolar proteinosis evolving to pulmonary fibrosis. A. Chroneou, N. Zias, B.S. Tronic, A.V. Gonzalez, J.F. Beamis Jr.*

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterised by intra-alveolar accumulation of surfactant components and cellular debris, with minimal interstitial inflammation or fibrosis. Since surfactant accumulates abnormally, a disturbance in the normal pathway of surfactant production, metabolism, recycling or degra-

tion has been postulated. This disease has a variable clinical course: from spontaneous resolution to respiratory failure and death due to disease progression or superimposed infections. PAP leading to pulmonary fibrosis is rarely seen, and few case reports describe this association. Here, we describe the case of a patient with a diagnosis of PAP confirmed by open lung biopsy, who developed interstitial pulmonary fibrosis years after disease onset. *Monaldi Arch Chest Dis 2007; 67: 4, 234-237.*

**Keywords:** *Bronchoalveolar lavage, fibrosis, high resolution CT, interlobular septum, pulmonary alveolar proteinosis.*

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## Case report

A 60 year-old, female, non-smoker, with a known diagnosis of PAP presented for re-evaluation of progressive dyspnea on exertion and increasing cough over the past several months. Her occupational, past medical and family history were unremarkable. The original diagnosis of PAP was established at the age of 55 by open lung biopsy. At that time, she had presented with cough, shortness of breath, and diffuse pulmonary infiltrates on chest radiograph. Chest CT revealed diffuse, bilateral ground-glass opacities (figure 1A). An open lung biopsy was performed, and revealed architecturally normal lung parenchyma with alveolar spaces filled with an amorphous PAS-positive proteinaceous material suggestive of active PAP (figure 1C). Anti-GM-CSF antibody titers were strongly positive. The patient was treated with bilateral whole lung lavage on two separate occasions, and received GM-CSF therapy for one year. She experienced marked symptomatic improvement, with significant radiologic clearing. She remained asymptomatic on no therapy for almost 2 years. Her cough and dyspnea on exertion then gradually recurred. Physical examination was normal except for crackles heard at both lung bases. Routine laboratory data were normal. Oxygen saturation was preserved at rest, and dropped to 90% during a 6-minute walk test. Pulmonary function testing revealed a mild restrictive defect with a dif-

fusion capacity of 50% of predicted. A high resolution CT of the chest demonstrated prominent interstitial septal thickening and scattered ground glass opacities (figure 2A). There was also evidence of traction bronchiectasis. Mediastinal lymphadenopathy in the right paratracheal region was also present but had been stable for several years (figure 1B, 2B). The patient was found to have a slightly elevated carcinoembryonic antigen (CEA) in serum with no suggestion of a primary neoplasm or other non-malignant lung conditions associated with elevated CEA levels (normal smokers [1], IPF [2]).

## Discussion

Pulmonary alveolar proteinosis is a rare disorder in which lipoproteinaceous material accumulates within alveoli [3]. An important feature of the disease is susceptibility to pulmonary infections, sometimes with opportunistic organisms. PAP occurs in three clinically distinct forms: congenital, secondary (associated with hematologic cancers, inhalation of organic dusts such as silica or certain infections), and acquired.

While the term pulmonary alveolar proteinosis implies an alveolar disease this term is misleading because the CT appearance is not purely alveolar. Many patients with pulmonary alveolar proteinosis have a "crazy paving" pattern of ground-glass opacities or air-space opacities on

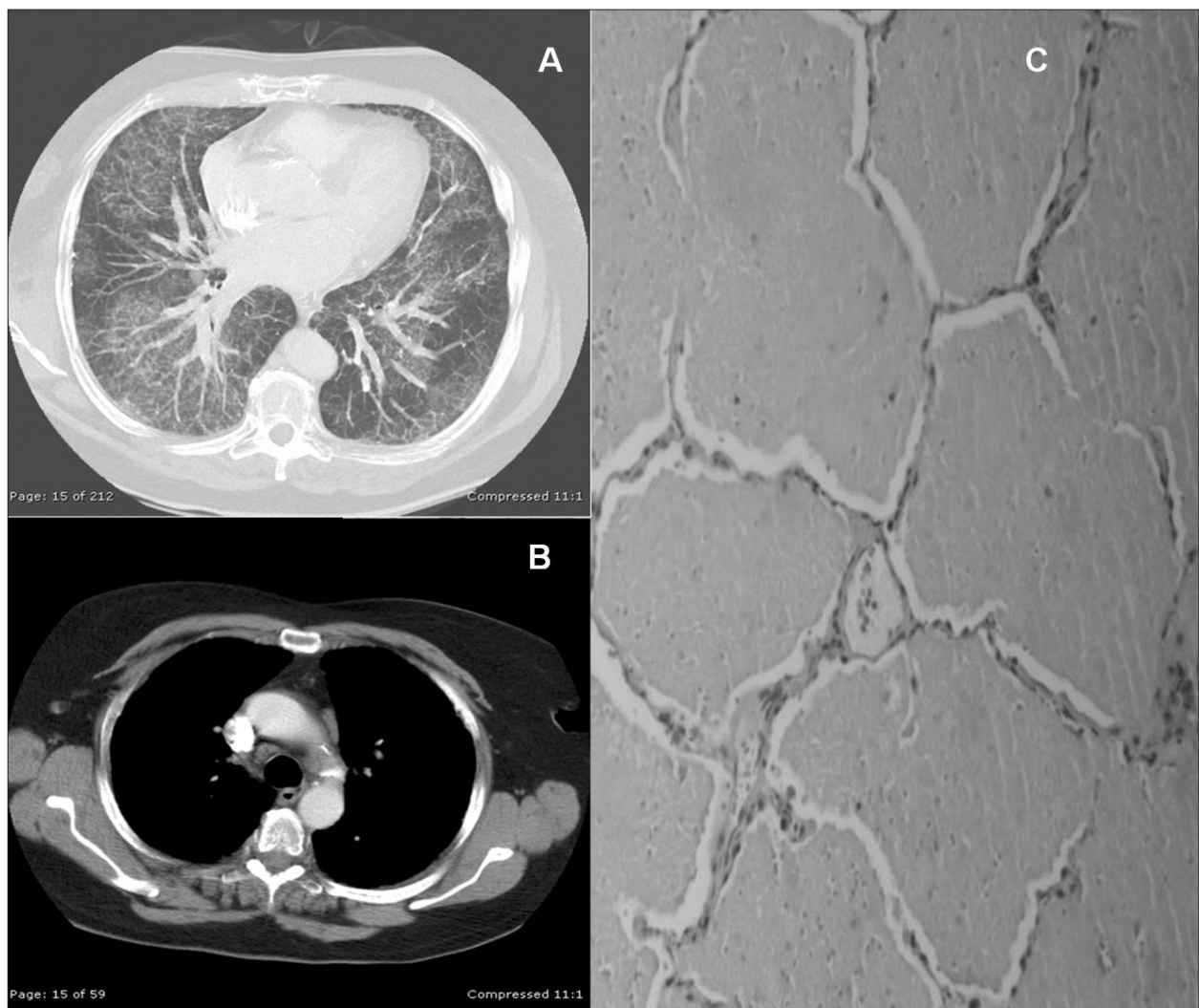


Fig. 1. - Chest CT images, at the time of the original PAP diagnosis. A) "crazy paving" pattern in a "geographic" distribution B) Evidence of mediastinal lymphadenopathy C) Lung biopsy specimen showing architecturally normal lung parenchyma, with alveolar spaces filled with eosinophilic amorphous material typical of alveolar proteinosis. Alveolar septa are thin throughout the section.

a background of smooth interlobular thickening in a geographic distribution. The "crazy paving" pattern has been described as a characteristic of PAP [4], though it can be seen in other air-space and interstitial diseases [5].

There are several reports of focal interstitial fibrosis of varying degree associated with PAP [6, 7, 8, 9, 10, 11, 12, 13, 14]. The impression that fibrosis and PAP are only coincidental is supported by observations that the lipoproteinaceous material may remain in the alveoli for years without eliciting a cellular reaction [15]. In rare cases, fibrosis can be seen and is usually mild. Extensive fibrosis is a very rare occurrence and only a few cases where significant fibrosis developed have been reported [7, 16, 17, 18, 19, 20]. Among these, only 2 cases clearly establish the onset of PAP prior to fibrosis using serial lung biopsies [18, 20]. In a retrospective review of the CT findings in 27 patients with PAP, substantial fibrosis (>70%) was described in only 2 patients [17].

In our case report significant fibrosis developed several years after the onset of PAP. There was neither an occupational exposure to account for the fibrosis, nor clinical or HRCT findings

suggestive of Idiopathic Pulmonary Fibrosis (IPF) or other diseases associated with pulmonary fibrosis (e.g. collagen vascular diseases). The presence of patchy mild interstitial fibrosis has in some cases been attributed to the presence of opportunistic infections by unusual organisms such as *Nocardia*, *Aspergillus*, *Cryptococcus*, *Mucormycosis* [19]. However, no lung infections were ever documented in our case; interstitial fibrosis appears to represent a late response to alveolar proteinosis. Hudson *et al.* have reported the case of a patient who died with severe pulmonary fibrosis 13 years after the initial diagnosis of alveolar proteinosis [18].

Recently, concerns about increased risk of pulmonary fibrosis due to GM-CSF therapy have been raised in an adenovirus-mediated GM-CSF transgenic animal model [21]. However the fibrosis in this transgenic model is likely due to the vector used, as other GM-CSF treated transgenic animals did not show such propensity. GM-CSF therapy was provided to our patient for one year only, with significant radiologic and clinical improvement. At the time of presentation with pulmonary fibrosis, she was receiving no specific therapy for her

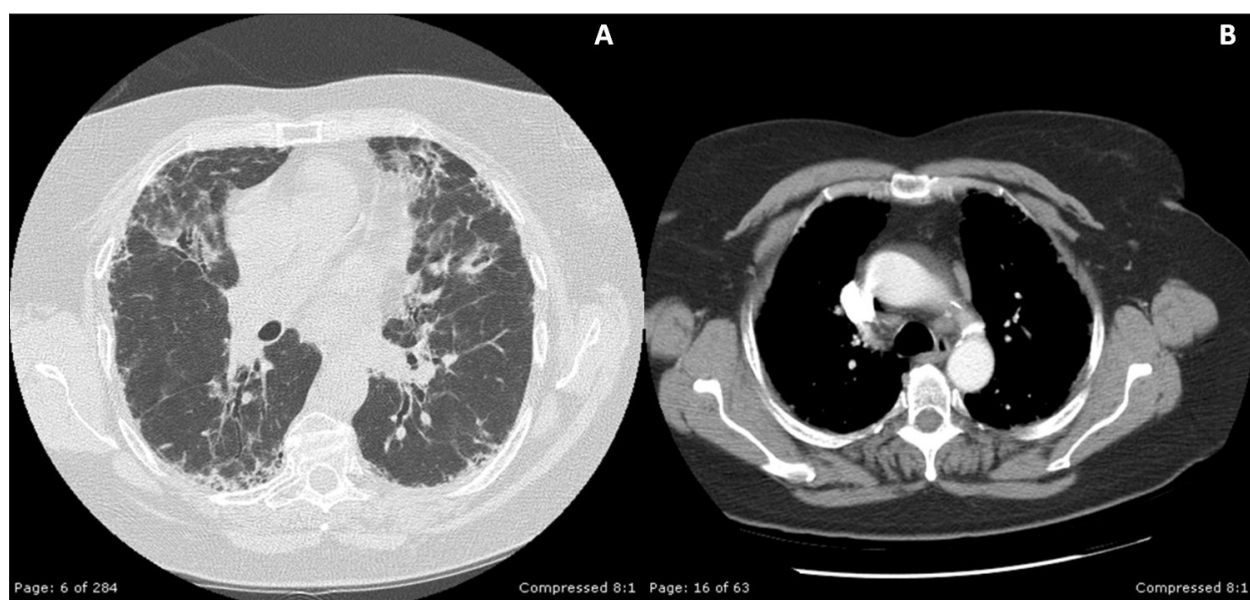


Fig. 2. - CT scan of the same patient 5 years after diagnosis. A) Septal thickening and traction bronchiectasis seen predominantly in the subpleural areas of both lungs. B) Mediastinal lymphadenopathy is still evident.

lung disease. Although there have been no reports of late toxicity from GM-CSF therapy, more follow-up data are needed.

This case of PAP is also unique in that the interstitial linear-reticular shadows were associated with mediastinal lymphadenopathy. Since Rosen *et al.* [3] first reported this disease in 1958, the interstitial architecture of the lung has been reported as essentially normal. The chest roentgenogram in patients with PAP is said to show bilateral alveolar or nodular infiltrates without cardiomegaly, pleural effusions or lymphadenopathy [22]. A similar report of PAP with interstitial involvement, mediastinal lymphadenopathy and elevated CEA has been described by Usui *et al.* [23]. This report suggests that the mechanism of inadequate alveolar clearance by lymphatics is due to the decreased migratory capacitance of alveolar macrophages. This mechanism could also explain our patient's atypical findings. First, mediastinal lymphadenopathy may be produced by pulmonary lymphatic stasis of overfed macrophages and their decreased clearance. CEA elevation may also fit with this theory, as it accumulates within alveoli with the surfactant-like lipoproteinaceous material, is phagocytosed by the alveolar macrophages and then migrates into blood vessels, through the lymphatics. Usui and associates demonstrated a decrease in CEA in both bronchoalveolar lavage (BAL) and serum after therapeutic lung lavage supporting the above mechanism of pulmonary accumulation and explaining a previously unclear phenomenon in non-malignant lung diseases. Also, elevation of CEA and other tumour markers has been proposed as a marker of disease activity in PAP.

The clinical course of alveolar proteinosis may follow several pathways. Death may result directly from respiratory failure. The disease may completely resolve without therapy or remain unchanged for as long as 20 years. Serious complicating infections may result in a fulminating course. Observing the

natural history of PAP may now be more difficult because of therapeutic BAL. It is not clear whether all patients with PAP should undergo lavage. However, bronchoalveolar lavage may prove beneficial not only by relieving the respiratory distress caused by alveolar filling, but also by improving the lungs defense mechanisms against infection and fibrosis, and by removing bronchial plugs, thus improving alveolar clearance. Long term observation of patients, whether or not they undergo lavage, is needed to determine whether pulmonary fibrosis results from PAP or is coincidental. In our case the patient responded well to bronchoalveolar lavages early in the course of the disease, with gradual worsening of symptoms suggesting a natural progression of the disease. More studies are needed to understand the pathogenesis of pulmonary fibrosis in PAP, and the individual differences in the reaction of the lung parenchyma in this disease.

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