

# Atypical alveolar proteinosis

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## Abstract

Alveolar proteinosis is a rare pulmonary disease characterized by intra-alveolar accumulation of surfactant composed of lipoproteinaceous material, related to a lack of surfactant resorption by alveolar macrophages. Crazy paving pattern is characteristic, but not specific. The multinodular forms of this affection remain exceptional.

**Key words:** Alveolar proteinosis; crazy paving; multinodular

## Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease, characterized by the accumulation of intra-alveolar surfactant, composed of proteins and lipids, related to a lack of surfactant resorption by alveolar macrophages.<sup>[1,2]</sup> Diffuse alveolar-interstitial syndrome without air bronchogram is characteristic but not pathognomonic in imaging. We describe multinodular pattern of alveolar proteinosis that was never reported.

## Case History

A 73-year-old farmer was seen at the medical imaging department for dyspnea checkup in 2010. He had no personal or family medical history, particularly of neoplastic or any suspicious occupational exposure. His general condition was preserved, except that he had nonproductive dry cough. Clinical examination showed no abnormality other than rapid respiratory rate of 22/min. He was afebrile; blood tests for inflammation were

normal. Chest X-ray showed symmetrical bilateral basal alveolar opacities and nodular opacities of both lung fields [Figure 1A]. Thoracic computed tomography (CT) scan confirmed the presence of ground-glass opacities and multiple bilateral parenchymal nodules [Figure 1B]. The nodules were irregular contour, about a centimeter and low density with an average attenuation value of 10–40 HU [Figure 1C]. There was no pleural effusion or mediastinal lymphadenopathy. Due to the appearance of the lesions, two nodules were biopsied with a coaxial system under CT scan guidance [Figure 1D]. Histopathological examination revealed extracellular acidophilic material with fatty acid crystals but without pathogenic agent or tumor infiltration, evoking the diagnosis of alveolar proteinosis [Figure 1E and F]. As the patient's condition was well-preserved, follow-up was recommended. Twelve months later, the alveolar opacities of the two pulmonary bases disappeared on the radiograph while the nodular opacities were stable [Figure 2]. On the chest CT scan performed 24 months later, bilateral pulmonary nodules

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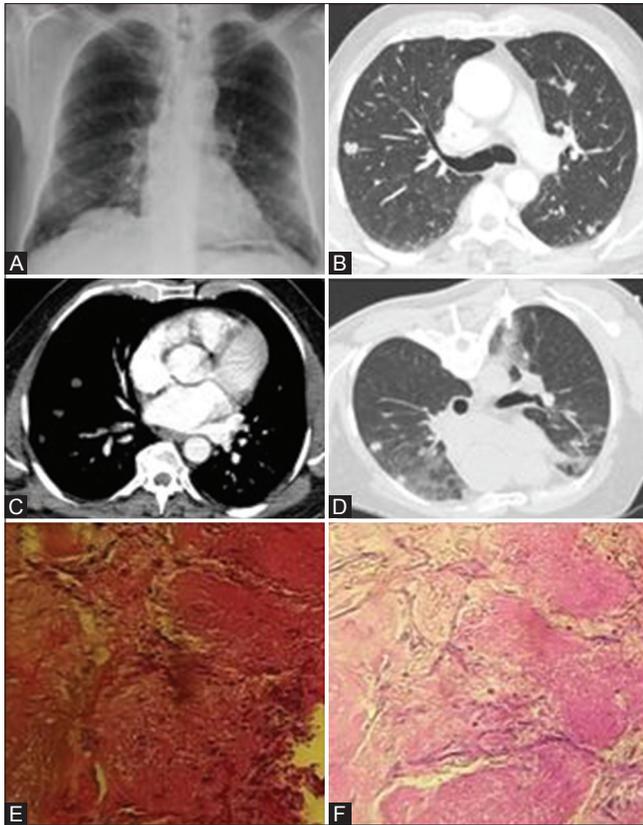
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**Figure 1 (A-F):** Bilateral multiple pulmonary nodules on frontal chest X-ray (A), axial CT image confirming the nodules and showing ground glass opacities in the right lower lobe (B), contrast-enhanced axial CT image showing nonenhancing nodules in the right lower lobe (C), biopsy of a nodule guided by CT scan (D), microphotographs of the biopsy specimen showing dense and amorphous eosinophilic materials, PAS +, filling the alveoli; without inflammatory reaction nor tumor proliferation (E: H-E stain, x100 and F: periodic acid-Schiff stain, x100)

persisted, most nodules were stable in size, others decreased in size, and there was no appearance of alveolar-interstitial opacities typical of “crazy paving” during the 8 years of follow-up. Because of the persistence of the nodules and to eliminate other underlying lesions including tumor, two other pulmonary nodules were biopsied at the fifth year but the pathological result was identical than before. There was no significant increase in nodule size during follow-up, whereas nodule’s calcifications appeared from the sixth year [Figure 3] and some nodules disappeared. The clinical condition of the patient remained stable.

## Discussion

PAP is a rare disease, characterized by intra-alveolar accumulation of surfactant composed of proteins and lipids due to defective surfactant clearance by alveolar macrophages.<sup>[3]</sup> This affection was first described in 1958 by Rosen and revealed clinically by progressive dyspnea.<sup>[4]</sup> This condition is more prevalent in men than in women and has a prevalence of between 4 and 40 per million population

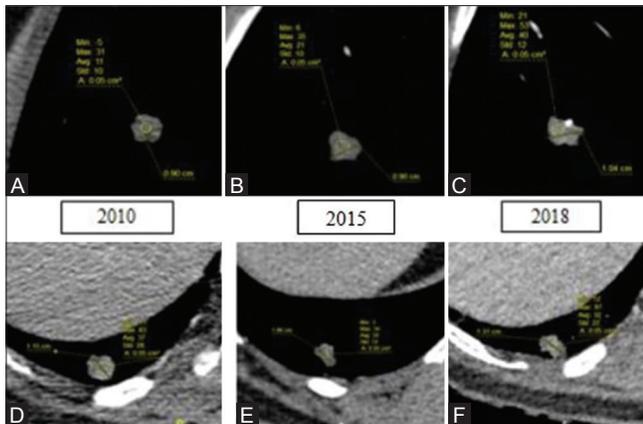


**Figure 2:** Frontal chest X-ray and thoracic CT scan in coronal reconstruction showing the persistence of multiple pulmonary nodules

and an incidence of 0.2 per million population per year.<sup>[1]</sup> Symptoms are not specific; dyspnea is present in 39% and cough in 21%.<sup>[1]</sup>

The radiological presentation is characteristic but not pathognomonic. Chest X-ray shows bilateral, diffuse, and symmetrical alveolar opacities. The lesion generally predominates at the basal and in perihilar regions simulating pulmonary edema and is rarely asymmetrical.<sup>[4]</sup> The absence of cardiomegaly and pleurisy would make the difference with heart failure.

High-resolution CT scan is essential to the diagnosis. It allows to define the alveolar filling lesions with ground-glass opacity associated with intra- and perilobular reticulations giving the characteristic irregular polygonal pavement or “crazy paving.”<sup>[1,5,6]</sup> These lesions are symmetrical, diffuse, or predominantly basal. They have a typically geographic distribution, with adjacent regions of healthy and sick zones. Asymmetrical or predominantly apical forms are rare. Although Holbert reported in 2001 that there is no nodular form for PAP,<sup>[5]</sup> a Japanese author reported a case of solitary nodule (1.0 cm) of PAP in a 74-year-old woman in 2011;<sup>[7]</sup> while two cases of focal involvement, one of the solitary nodule type (1.2 cm) in a young 21-year-old patient and the other of unilateral “crazy paving” type in a 31-year-old patient, were published by a Korean team in 2014.<sup>[8]</sup> Mediastinal lymphadenopathy is possible in cases of complications (infections) or other associated lesion.<sup>[5]</sup> Multinodular form of PAP was never reported. In our patient, there were multiple bilateral pulmonary nodules, with no predominance in one side or one lobe or segment; they were near centimeter size, with irregular contours and spiculated. These nodules of low density remained stable for the most part, although some disappeared or decreased in size, on 8-year follow-up. The foci of alveolar-interstitial opacities disappeared spontaneously at the 12<sup>th</sup> month image. Calcifications began appearing from the sixth year of follow-up for some nodules. Besides the known differential diagnosis of PAP (infectious, tumoral, idiopathic, inhalation, and hemorrhagic),<sup>[9]</sup> metastases and infections should be differentiated from this multinodular form.



**Figure 3 (A-F):** Thoracic CT images in axial section, focussed zoom on a lesion in the right upper lobe (A-C) and in the right lower lobe (D-F) showing the stability of the lesions on the exams realized in 2010, 2015 and 2018 respectively. Note the appearance of calcification of the lesion of the right upper lobe (C)

Diagnosis is based on clinical arguments (progressive dyspnea), radiological, bronchoalveolar lavage (acidophilic material in the broncho-alveolar liquid), and histopathological (intra-alveolar lipoproteinaceous material, normal architecture of the alveoli devoid of tumoral, or inflammatory infiltration). The recent demonstration of anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibodies in the serum or in the alveolar fluid, rarely available in practice, makes possible to evoke an autoimmune cause of this affection.<sup>[2]</sup> The initial treatment of this condition is mechanical, by total alveolar lavage. Other types of treatment such as inhalation or subcutaneous injection of GM-CSF, injection of rituximab into autoimmune PAP to decrease the production of anti-GM-CSF antibodies, plasmapheresis, or lung transplantation can be performed according to the clinical severity and the evolution of patient presentations. Thus, the clinical and radiological monitoring can be recommended, as in our patient, if the clinical condition is good and stable.<sup>[2,10]</sup> In a series of 24 cases, 10 patients did not require special treatment for 10 years of follow-up in the study by Lawrence *et al.*<sup>[10]</sup>

## Conclusion

PAP is a rare disease characterized by intra-alveolar lipoproteinaceous material. Although the typical radiological presentation is of intra- and peribubular reticulations associated with ground-glass opacities giving the characteristic image of irregular polygonal

pavement or “crazy paving,” multinodular appearance that may be spiculated is possible. Nodules are low density and nonenhanced by contrast media. Histopathological examination after biopsy is required to confirm the diagnosis. CT scan monitoring shows the stability and calcification of these nodules.

## 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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