

Pulmonary Alveolar Proteinosis: A Case of Acute Respiratory Failure and Crazy Paving

Antonella Spacone*

Respiratory Medicine Unit, Hospital "Santo Spirito", Pescara, Italy

***Corresponding Author:** Antonella Spacone, Respiratory Medicine Unit, Hospital "Santo Spirito", Pescara, Italy.

Received: March 29 2020; **Published:** April 17, 2020

Abstract

Introduction: Pulmonary alveolar proteinosis (PAP) is a rare diffuse parenchymal lung disease in which lipoproteinaceous material accumulates in distal air spaces. It is more common in male than in female and in smokers. PAP is diagnosed by computed tomography (CT) as reticulations that are frequently superimposed on ground-glass opacities, forming a "crazy paving" pattern in the bilateral middle and lower lung zones and confirmed by the staining of bronchoalveolar lavage fluid (BALF) and a lung biopsy. PAP is treated by whole lung lavage (WLL), but the clinical benefit from lavage is often temporary. Thus novel therapies that target alveolar macrophages (recombinant granulocyte macrophage colony-stimulating factor - GM-CSF - therapy) and anti-GM-CSF antibodies are being examined.

It is described a case report of a patient with PAP who experienced acute respiratory failure with a diffuse crazy paving pattern on imaging.

Case Report: S.O, a 43-years-old female obese, non-smoker without any underlying hematological or autoimmune disorders. Her initial presentation was with dyspnoea and cough.

She was admitted with hypoxemic respiratory failure and had an unremarkable physical examination. Carbon monoxide diffusion capacity was moderately impaired and a restrictive pattern was observed by spirometry. Chest x-rays showed bilateral and consolidating infiltrates and a computed tomography (CT) scan revealed the presence of multiple ground-glass opacities with a diffuse "crazy-paving" pattern. BALF and transbronchial biopsy confirmed the diagnosis of PAP. The patient met the criteria for WLL and responded favorably to this therapy.

Conclusion: Although PAP is a rare disease, a crazy paving pattern on CT in young people, should alert the clinician to this potential disease. This report underscores the importance of considering PAP when crazy paving is observed, to facilitate the correct diagnosis early and provide the best treatment. This report describes the improvement due to treatment with WLL.

Keywords: *Pulmonary Alveolar Proteinosis; Crazy Paving; Acute Respiratory Failure*

Introduction

Pulmonary alveolar proteinosis (PAP) was first described by Rosen in 1958 [1].

It is a rare condition with an estimated prevalence of 3.7 - 6.2 cases per million people, usually affecting those who are middle-aged, with a 2:1 predilection for males [2,3].

PAP is characterized by the alveolar accumulation of surfactant composed of proteins and lipids, typically due to macrophage dysfunction as a result of a defect in the anti-granulocyte macrophage colony-stimulating factor (GM-CSF) pathway [5], impeding macrophage maturation and their ability to clear surfactant, and, secondarily lung infections [4,5].

Three forms of PAP have been defined based on the etiology: autoimmune (previously termed primary or idiopathic), secondary and genetic, the latter of which is seen especially in children. Adult forms are primarily autoimmune with GM-CSF antibodies or secondary to toxic inhalation or haematological disorders, without anti-GM-CSF antibodies [3].

Imaging is crucial in the diagnosis of PAP. Chest radiography is nonspecific but classically demonstrates bilateral alveolar opacities that are most visible in the perihilar region, resembling pulmonary edema or an opportunistic infection [6,7]. Chest computered tomography (CT) is a more specific diagnostic method for PAP; the pattern observed is highly suggestive of the disease, although it is not pathognomonic. Reticulations are frequently superimposed on ground-glass opacities, thus forming a “crazy paving” pattern [6] as has been described for other pulmonary conditions by CT scan (Table 1) [8].

Acute diseases	Subacute/chronic diseases
<ul style="list-style-type: none"> • Pulmonary edema 	<ul style="list-style-type: none"> • Usual interstitial pneumonia
<ul style="list-style-type: none"> • Infection (viral, bacterial, Mycoplasma, Pneumocystis). 	<ul style="list-style-type: none"> • Non specific interstitial pneumonia
<ul style="list-style-type: none"> • Pulmonary hemorrhage 	<ul style="list-style-type: none"> • Pulmonary alveolar proteinosis
<ul style="list-style-type: none"> • Acute interstitial pneumonia 	<ul style="list-style-type: none"> • Organizing pneumonia
<ul style="list-style-type: none"> • Acute respiratory distress syndrome 	<ul style="list-style-type: none"> • Vasculitis
<ul style="list-style-type: none"> • Radiation pneumonitis 	<ul style="list-style-type: none"> • Eosinophilic pneumonia <ul style="list-style-type: none"> • Sarcoidosis • Lipoid pneumonia • Alveolar microlithiasis • Barium aspiration • Lymphangitic spread of malignancy • Bronchioloalveolar carcinoma

Table 1: Differential diagnosis of crazy paving on CT scan.

Pulmonary function tests typically demonstrate a restrictive defect. Traditionally bronchoalveolar lavage (BAL) has been required for diagnosing PAP. BAL fluid is milky wherein the cytological examination shows macrophages that contain eosinophilic granules, with extracellular globular hyaline material, that is homogeneously positive by periodic acid-Schiff (PAS) stain and negative on Alcian blue staining [3].

Biopsies are seldom necessary for the diagnosis, but they might be performed to exclude other conditions: histological samples show lipoproteinaceous material in the terminal bronchioles with little or no inflammation [9]. Whole lung lavage (WLL) is performed as the first line of treatment for this disease because it removes the proteinaceous material from the alveoli to increase effective oxygenation and ventilation by physically ‘washing’ the alveoli with saline, particularly in with moderate to severe disease [3,10]. There is no standardization of and international consensus on the procedure, although they are very much needed [11].

WLL is performed under general anesthesia with lung separation through a double-lumen endobronchial tube. While mechanical ventilation is maintained in one lung, the contralateral lung is washed with saline and then drained by gravity. Typically, the lavage is continued until the lavage fluid becomes clear, by visual inspection.

Supplemental GM-CSF is also useful, but the exact indications, choice of agent, and doses remain unknown. Other therapies, including rituximab, plasmapheresis, and lung transplantation have been described but should be reserved for refractory cases [12].

Once PAP is diagnosed, it is recommended that the patients be managed and followed in specialized expert centers. This report highlights that a crazy paving pattern in combination with clinical features and bronchoscopic examination constitutes a diagnosis of the rare syndrome PAP.

Case Report

SO, a 43-years-old female, obese, non-smoker, was referred to our Respiratory Unit due to her having at least 1 year of declining general health, with recurrent episodes of acute respiratory worsening, interpreted as pneumonias. She experienced dyspnea, cough, fatigue, and weight loss and subsequently respiratory failure.

Her history revealed no exposure to radiation, chemotherapy, dusts, solvents, smoke, livestock, or other causes of interstitial lung disease. There was no exposure to sick contacts or tuberculosis and no features of connective tissue disease. The patient had no allergies.

On examination, she was afebrile, with a heart rate of 92 beats per minute, a respiratory rate of 18 breaths per minute, and oxygen saturation of 86%. An arterial blood gas analysis at rest showed: pH 7.45, PaO₂ 50 mmHg, PaCO₂ 43 mmHg, pH 7.43, SatO₂ 88% and HCO₃ 25 mmol/L. Her physical examination was negative and her BMI (body mass index) was 23 kg/m².

The laboratory findings revealed a normal complete blood count and differential blood counts. The biochemical analysis showed normal serum electrolytes and liver and renal function tests, with an elevation in lactate dehydrogenase (450 U/l; reference 105 - 205 U/l).

The chest radiograph demonstrated bilateral alveolar opacities, without an air bronchogram. A CT scan of the thorax revealed diffuse bilateral ground-glass opacities with intralobular septal thickening and mild mediastinal, pretracheal, and para-aortic lymphadenopathy (Figure 1). The findings were reported as a crazy paving pattern.

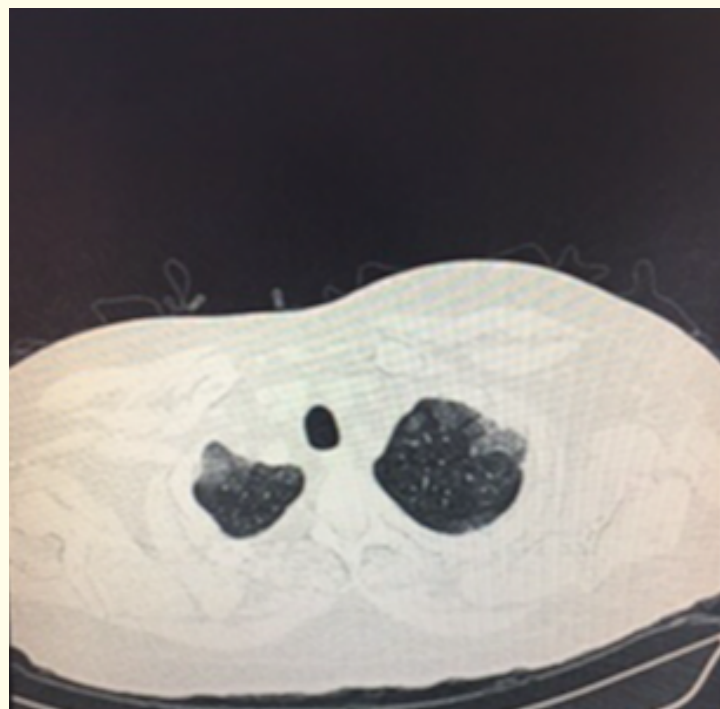


Figure 1A

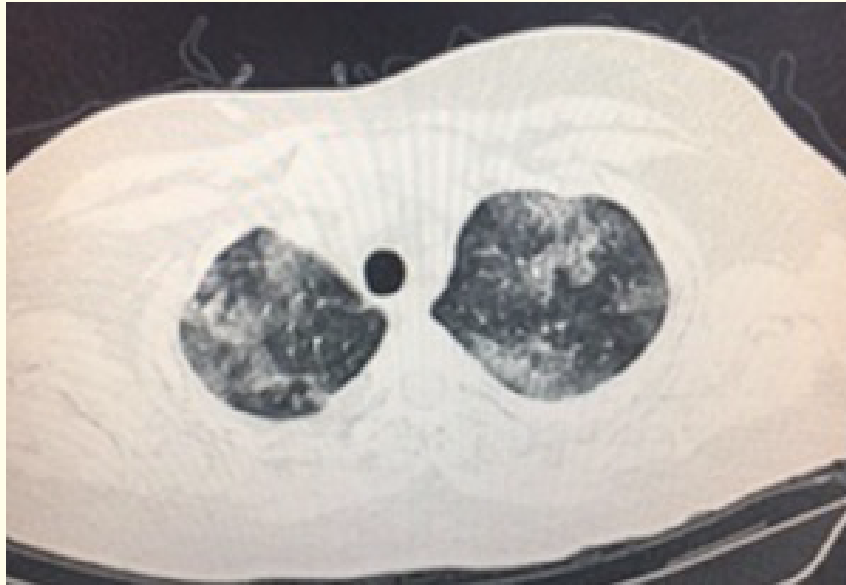


Figure 1B

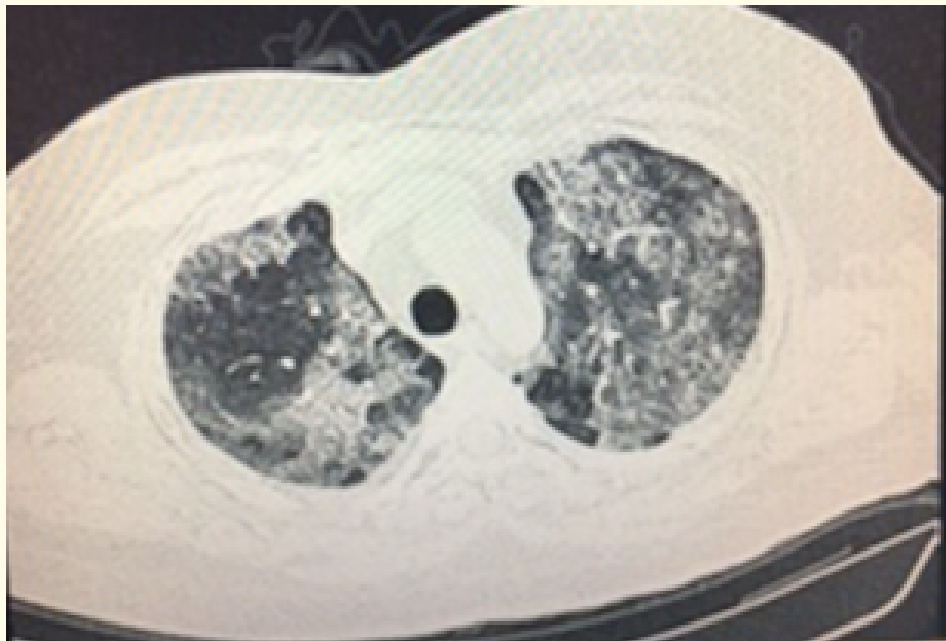


Figure 1C

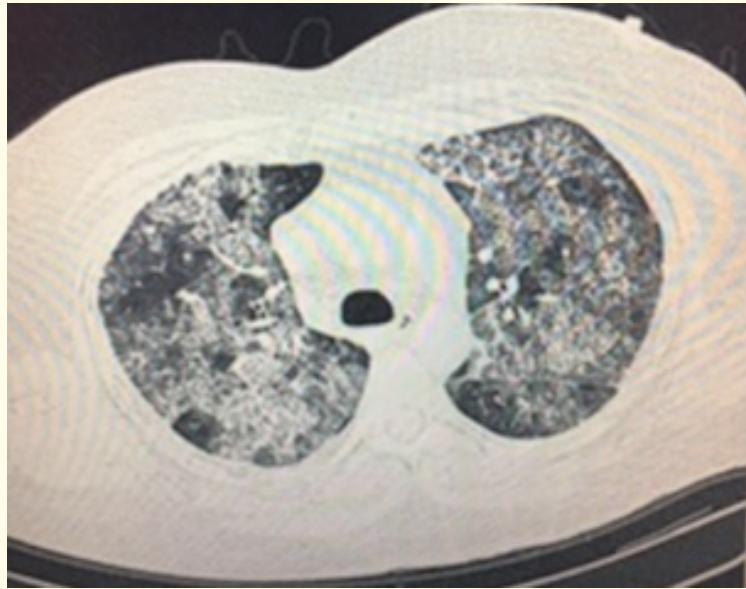


Figure 1D



Figure 1E

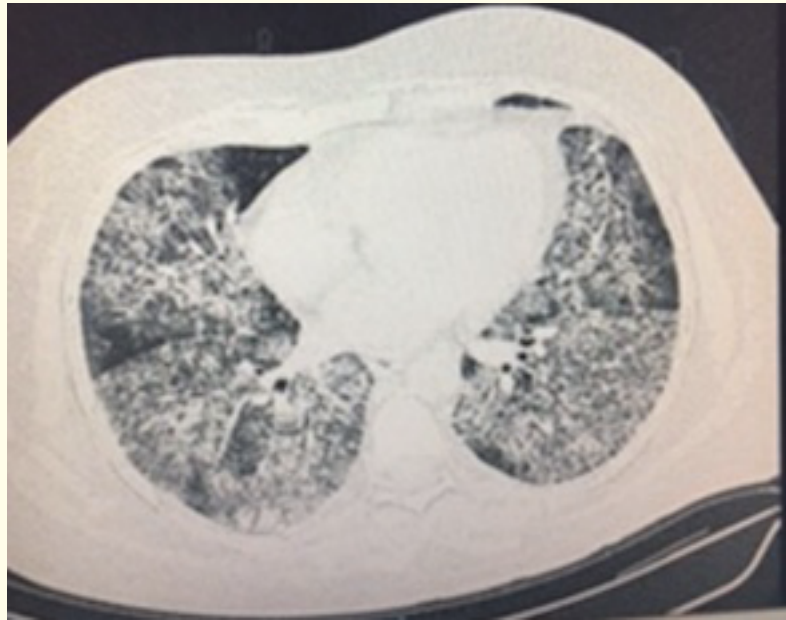


Figure 1F

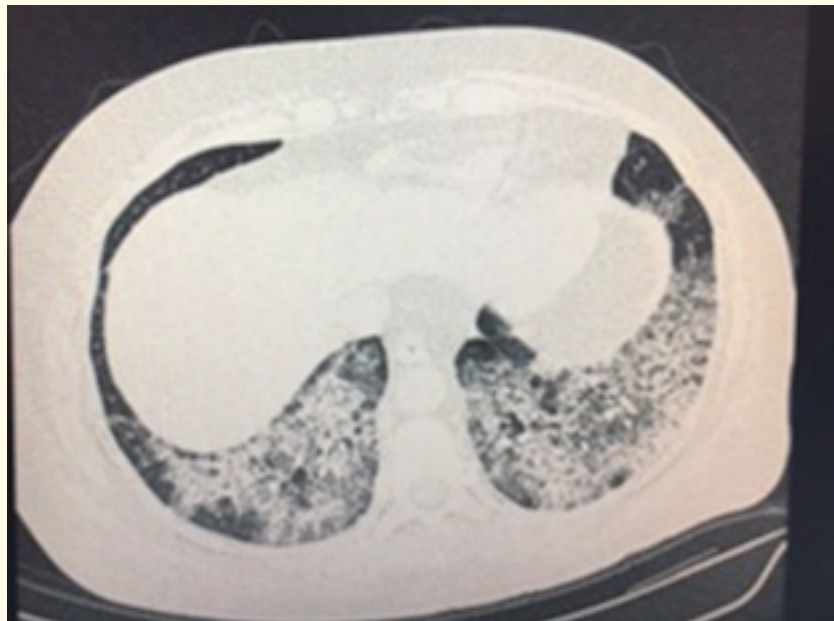


Figure 1G

Figure 1: CT images.

Spirometry showed a forced vital capacity (FVC) of 2.79l (69% of predicted) and a forced expiratory volume in 1 second (FEV1) of 4.04l (81% of predicted). The diffusion capacity - diffusion capacity of the lung for carbon monoxide, (DLCO) and coefficient (KCO) were 56% and 68% respectively.

The ecocardiography was normal. The analysis of the BALF reported a turbid milky appearance. Due to suspected PAP, the patient was sent to an interventional pulmonology center where the diagnosis of PAP was confirmed: the BAL contained few white blood cells (30/mm³, predominantly macrophages), cultures of the lavage fluid were negative for the growth of any microbe and the cytology reported no evidence of malignant cells. The presence of periodic acid-Schiff (PAS) positive granular material and alveolar macrophages with intracytoplasmic debris was consistent with PAP. Supplemental transbronchial biopsies (TBB) that were performed during the bronchoscopy revealed intra-alveolar accumulation of a proteinaceous material, which was consistent with the diagnosis of PAP. Two additional sessions of WLL were held, without complications but improving the symptoms and lung physiological parameters.

A follow-up CT scan 4 months later showed evident regression.

Discussion

PAP is a rare interstitial lung disease with an estimated annual incidence, and prevalence of 0.24 - 0.49 and 2.04 - 6.20 cases per million respectively [13]. Whereas one-third of patients are asymptomatic, they often present with progressive exertional dyspnea and cough. Less commonly, patients present with chest discomfort, weight loss, fatigue, fever and small-volume hemoptysis [14]. PAP is a rare cause of respiratory failure that requires mechanical ventilation [14-18] and resembles a wide range of differential respiratory diagnoses [13]. The median age at presentation is 39 years with a male predominance (male:female ratio 2.7:1.0) [3]. Although it is not specific, CT images show a characteristic "crazy paving" pattern, comprising bilateral ground-glass opacities with widespread distribution that are superimposed by thickened intra- and interlobular septa predominantly in the middle to lower lung zones [7,19,20].

This pattern was first described in association with pulmonary alveolar proteinosis nearly 20 years ago [1] and was thought to be specific for alveolar proteinosis, but has subsequently been reported in a variety of interstitial and airspace pulmonary disorders, including infectious, neoplastic, inhalational, toxic, sanguineous and idiopathic disorders. Specific infectious disorders that are linked to a crazy-paving pattern include *Pneumocystis jirovecii* (carinii) pneumonia, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, and Coronavirus-associated severe acute respiratory syndrome were reported to be associated with a crazy-paving features [21-24]. The differential diagnosis for a crazy paving pattern is broad [8].

The diagnosis of PAP is based on a combination of symptoms, CT scan findings and bronchoscopy with BAL, which sometimes includes a transbronchial lung biopsy and finally auto-antibodies against GM-CSF in BAL/serum.

Once PAP is diagnosed, it is recommended that patients be managed and followed in specialized expert centers.

The treatment for PAP depends on the severity of disease. Patients who have asymptomatic and mild disease can receive symptomatic treatment and undergo close observation. Spontaneous improvement has been reported. For those with more advanced disease or even respiratory distress, WLL, a safety invasive procedure is the standard therapy [3].

GM-CSF therapy is considered an alternative to whole lung lavage and anti-GM-CSF antibodies (rituximab and plasmapheresis) are being investigated. Immunosuppressive therapy, particularly corticosteroids not appear to be effective in PAP [25] and could increase the risk of pulmonary infection. Lung transplantations have been performed in refractory patients.

Conclusion

This report highlights the importance of considering PAP in the differential diagnosis of patients with lung conditions that manifest as ground-glass opacities. A crazy paving pattern is suggestive of, but not specific, to PAP. Presentation of a crazy paving pattern in young persons and adults should alert the clinician to the potential of this rare disease requiring further examination in order to make the correct diagnosis and provide the best treatment.

Although it is a rare disease, our knowledge of the pathophysiology of PAP has improved tremendously in recent years. This case supports the efficacy of WLL in its treatment.

Conflict of Interests

All authors declare that they have no competing interests.

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Volume 9 Issue 5 May 2020

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