A clinical case of late diagnosis of PAP with good response to whole lung lavage

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Abstract

Pulmonary Alveolar Proteinosis (PAP) is a rare syndrome characterized by the accumulation of surfactant in alveoli and terminal airways resulting in respiratory failure. PAP comprises part of a spectrum of disorders of surfactant homeostasis (clearance and production). We describe the case of a 54 years-old woman hospitalized in March 2017 with diagnosis of acute hypoxemic respiratory failure secondary to pulmonary interstitial disease. In our case, the patient arrived at our observation after developing a severe respiratory insufficiency although a long term history of respiratory symptoms. This diagnostic delay suggests that alveolar proteinosis should always be considered as a possible diagnosis in patients with dyspnea, cough and crazy paving at HRTC. In spite of this the disease resolved with a cycle of total lung lavage and the symptomatology has improved with the resolution of the radiological picture without any other therapeutic approach.

Introduction

Pulmonary Alveolar Proteinosis (PAP) is a rare lung disorder characterized by an abnormal accumulation of lipoprotein compounds within the alveoli of the lung. The accumulated substances interfere with the normal gas exchange and expansion of the lungs, ultimately leading to difficult breathing and a predisposition to developing lung infections. In adults, the most common cause of PAP is the autoimmune nature, due to the presence of autoantibodies to GM-CSF (macrophage granulocytic colony stimulating factor) which influence macrophage maturation and alter surfactant clearance with recurrent infections. Rarer forms of PAP are the congenital genetic alteration of the GM-CSF receptor as well as the those secondary to infections, hematologic tumors (myeloproliferative syndrome and myeloid leukemia), immunodeficiencies, inhalation of inorganic dustinvolving macrophage dysfunction.[1,2]

The signs and symptoms of PAP include shortness of breath and dry cough, common with other respiratory diseases. For this reason, patients with PAP are at high risk for diagnostic delay.[3]

The symptoms and the clinical course of PAP is unpredictable. Spontaneous remission is recognized, and some patients have stable symptoms. Death may occur due to the progression of PAP or of any underlying associated disease. Individuals with PAP are more vulnerable to lung infections such as bacterial pneumonia, mycobacterium avium intracellular infection, or fungal infections.

The standard treatment for PAP is Whole-Lung Lavage (WLL) in which the lung is filled with sterile fluid with subsequent removal of the fluid along with the abnormal surfactant material. This is generally effective at improving PAP symptoms, often for a prolonged period of time. The use of GM-CSF injections has also been attempted, with variable success. Lung transplantation may be performed in refractory cases.[4]

Once diagnosed it is necessary that patients are followed in specialized centers.[3]

Case Report

We describe the case of a 54 years-old woman, housewife, smoker of 20 cigarettes a day, affected by moderate obesity and gastroesophageal reflux in drug treatment.

The patient was hospitalized in March 2017 to the Respiratory Subintensive Care Unit of Monaldi Hospital, arriving from another hospital. Initial diagnosis was acute hypoxemic respiratory failure secondary to pulmonary interstitial disease resistant to broad-spectrum antibiotic and steroid therapy. The patient referred that almost five months before she had noted the onset of wheezing and a dry cough. There were bilateral crackles to the auscultation of the chest. Hemogasanalysis showed severe hypoxemic respiratory failure (PAO2/FIO2 <200) treated with High-flow Nasal Oxygen Therapy. Due to severe clinical conditions, pulmonary function tests could not be performed.

Echocardiography, doppler ultrasound arteriovenous of the lower limbs and abdominal ultrasonography were normal. Blood tests showed polycythemia, an increase LDH levels and neoplastic markers. The chest X-ray showed bilateral opacities to the middle and lower lung fields with butterly pattern and normal lung hilum (Figure 1).

The High-Resolution chest CT showed a "crazy paving" pattern, suspecting of alveolar proteinosis: in all pulmonary lobes there were multiple ground-glass areas associated with thickening of intra and interlobular septa (Figure 2). The total body PET / CT documented a modest metabolic activity in both lungs (SUV max 4).

A diagnostic bronchoscopy was performed with bronchioloaveolar lavage

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Consent for publication: The patient gave his written consent to use his personal data for the pub-lication of this case report and any accompanying images.

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(BAL), which excluded the presence of pathogenic micro-organisms in the lung and lung cancer cells, confirmed the diagnosis of alveolar proteinosis. BAL has a "milky" composition, with abundant extracellular proteinaceous material of a granular appearance which is positive for Periodic Acid-Schiff staining (PAS). Foamy alveolar macrophages with intracellular accumulations of proteinaceous material which stains strongly positive on Pas stain (Figure 3) and with Oil Red O-positive granules for intracytoplasmic lipid inclusion (Figure 4 and 5).

A subsequent blood sample confirmed the diagnosis of autoimmune PAP due to positive anti-GM-CSF (granulocyte-macrophage colony-stimulating factor) antibodies.

In the differential diagnosis of the "crazy paving" chest CT pattern should be considered (Table 1): i) bronchioloalveolar carcinoma; ii) lung infections; iii) eosinophilic pneumonia; iv) cardiogenic pulmonary edema; v) diffuse alveolar hemorrhage; vi) non-specific interstitial pneumonia.

These diseases were excluded because BAL in our patient was negative for neoplastic cells, microorganisms, eosinophils, blood and macrophages containing hemosiderin. Echocardiography was normal, blood tests did not show anemia, increased pro-BNP, autoantibodies for connective tissue disorders.[5]

The patient was initially treated with High-flow Nasal Oxygen Therapy (HFNC), empirical antibiotic therapy (meropenem and levoxacin) and corticosteroids, until confirmation of diagnosis. For the severe respiratory failure, in agreement with the bronchological and anesthetic team, it was performed a total lung lavage (WLL) to remove the lipoproteinaceous material. Under general anesthesia, the patient underwent four bronchoscopic sessions with multiple bilateral segmental washes after one week from another associated with thoracic percussion physiotherapy.

The patient also developed a cytomegalovirus pneumonia (CMV-DNA in serum: 1208 gEq/mL) so, due to the worsening of respiratory failure, she was tracheotomized percutaneously and connected to the mechanical ventilator.

Pneumonia resolved with the somministration of ganciclovir 800 mg per day endovenous for 10 days.

The patient practiced respiratory and motor physiotherapy with weaning from mechanical ventilation in May 2017 (Figure 6), subsequent transfer to a respiratory rehabilitation and then discharged home, tracheotomized in ambient air (Figure 7).

Table 1. Differential diagnosis with PAP.

Acute Diseases	Subacute/Chronic Diseases
Pulmonary oedema	Usual Interstitial Pneumonia (UIP)
Pulmonary infection (bacterial, viral, pneumocystis jiroveci, mycoplasma)	Non-Specific Interstitial Pneumonia (NSIP)
Pulmonary haemorrhage	Alveolar proteinosis
Acute Interstitial Pneumonia (AIP)	Organising pneumonia
Adult (acute) Respiratory Distress Syndrome (ARDS)	Vasculitis (Churg-Strauss syndrome)
Radiations pneumonitis	Eosinophilic pneumonia (chronic)
Eosinophilic Pneumonia	Tumour Lymphangitic spread of tumour Sarcoidosis Lipid pneumonia Alveola microlithiasis Barium aspiration

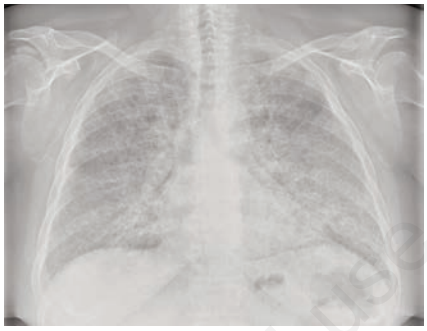

Figure 1. Chest X-ray of March 2017 with evidence of bilateral opacities to the middle and lower lung fields with butterly pattern and normal lung hilum.

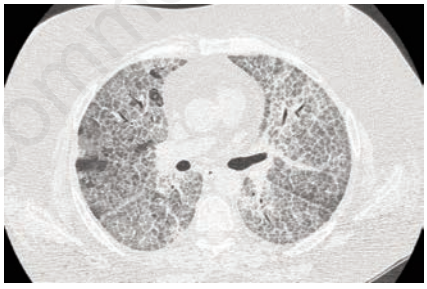

Figure 2. HRTC March 2017 with evidence of "crazy paving" pattern, suspecting of alveolar pro-teinosis: in all pulmonary lobes there were multiple ground-glass areas associated with thickening of the intra and interlobular septa.

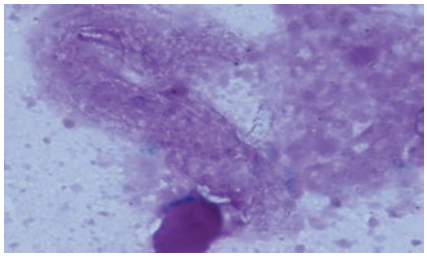

Figure 3. PAS staining of bronchoalveolar lavage fluid.

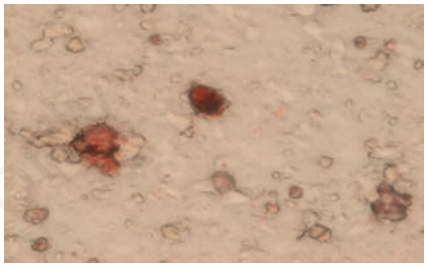

Figure 4. Oil red O staining of bronchoalveolar lavage fluid.

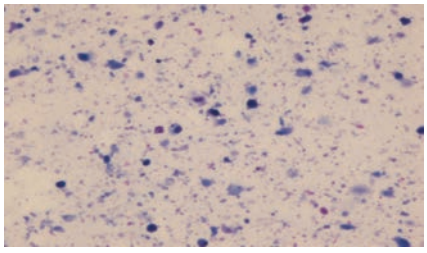

Figure 5. Giemsa staining of the bronchoalveolar lavage fluid.

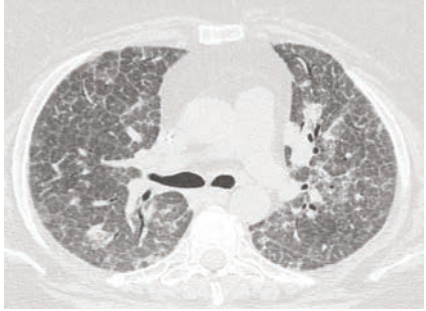

Figure 6. HRTC May 2017: improvement of ground-glass areas associated with thickening of the intra and interlobular septa.

After four months the tracheotomy was complicated with a tracheal stenosis in the inferior cervical tract that required two laser therapy interventions with mechanical dilation, and a subglottic stenosis.

In the revaluation in November 2019 there are no clinical and radiological signs of recovery from the disease. The HRCT shows residues and widespread perilobular thickening, but the patient cannot decannulate for the subglottic stenosis (Figure 8)

Discussion

PAP has a prevalence of 0.37/100,000 people, it generally occurs in males between 30 and 50 years of age.[2] In 90% of the cases is the autoimmune nature, due to the presence of autoantibodies to GM-CSF (macrophage granulocytic colony stimulating factor) which alter macrophage maturation with altered surfactant clearance and recurrent infections.[6,7] Rarely, PAP has a congenital nature, with genetic alteration of the GM-CSF receptor[8] or secondary to systemic inflammatory diseases, haematological neoplasms (myeloproliferative syndrome and myeloid leukemia), immunodeficiencies, inhalation of inorganic dust (silicon, aluminum, titanium oxide) involving macrophage dysfunction.[9]

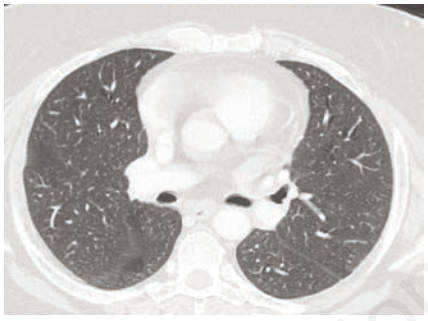

Figure 7. HRTC March 2018: reduction of ground glass area.

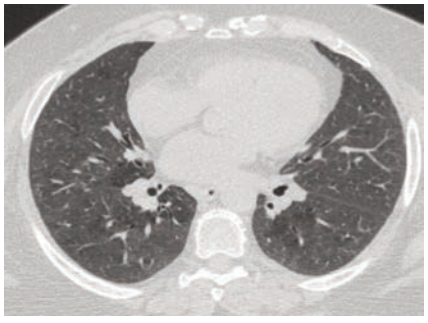

Figure 8. HRTC November 2019: widespread perilobular residues and thickening.

The time interval between the appearance of cough and dyspnea and the diagnosis of PAP is long, since these symptoms are also present in other respiratory and non-respiratory pathologies. Suspicion of PAP is posed by the clinical picture and the presence of crazy pavement at HRTC. The diagnosis of certainty comes from the BAL, which has a milky appearance and abundant granular extracellular protein material positive to Schiff Acid Periodic Staining (PAS), foamy alveolar macrophages with intracellular accumulations of protein material (PAS +) and grains positive to oil red O for intracytoplasmic lipids.

In 80% of cases serum LDH is increased and in the autoimmune forms the serum anti-GSM-CSF antibodies are positive. Functional respiratory tests show a restrictive ventilatory deficit with reduction of diffusion capacity to carbon monoxide (DLCO).

The PAP treatment is the WLL, which removes the lipoproteinaceous material, with a respiratory and radiographic improvement in most patients (30-70%). In case of relapses the WLL is repeated. WLL is not necessary for asymptomatic patients or those with only mild symptoms. In patients with severe dyspnea, as in our case, whole lung washing is performed under general anesthesia using intravenous propofol and remifentanyl and using a double lumen endotracheal tube. Each lung is washed up to 15 times with 1-2 liters of physiological solution for a total of 15 liters, while the other lung is ventilated. To improve the distribution of the solution, the manual percussion of the hemithorax and the inclination of the bed are associated. The process is then reversed.[10]

If the WLL is not effective and the patient is affected by autoimmune PAP, inhalation or subcutaneous therapy with rGM-CSF is performed with a functional respiratory and radiographic improvement in 50-70% of cases.[11]

Conclusions

In our case, the patient arrived at our observation after developing a severe respiratory insufficiency although a long term history of respiratory symptoms. This diagnostic delay suggests that alveolar proteinosis should always be considered as a possible diagnosis in patients with dyspnea, cough and crazy paving at HRTC.

In spite of this the disease resolved with a cycle of WLL and the symptomatology has improved with very important improvement of the radiological picture (The HRCT shows only residues and widespread perilobular thickening) without any other therapeutic approach. BAL is the gold standard for diagnosis and WLL is the gold standard of therapy that can lead to complete resolution of the disease.[4]

References

1. Suzuki T, Trapnell BC. Pulmonary Alveolar Proteinosis Syndrome. Clin Chest Med 2016;37:431-40.
2. Trapnell BC, Whitsett JA, Nataka K. Pumonary alveolar proteinosis. N Engl J Med 2003:349:2527-39.
3. Nobili I, Parrachini E. Proteinosi alveolare polmonare: caratteristiche cliniche della casisti-ca raccolta da un centro nazionale di riferimento. Bollettino Società Medico Chirurgica di Pavia 2013:126;439-44.
4. Khan A, Agarwal R. Pulmonary Aleolar Proyeinosis. Respir Care 2011;56:7
5. Skov IR, Bendstrup E. Pulmonary alveolar proteinosis- acrazy presentation of dyspnea. Eur Clin Respir J 2018;6: 1552065.
6. Shah PL, Hansell D, Lawson PR, Reid KB, Morgan C. Pulmonary alveolar proteinosis: Clini-cal aspects and current concepts on pathogenesis. Thorax 2000;55:67−77.
7. Inoue Y, Trapnell BC, Tazawa R, et al. Characteristics of a large cohort of patients with au-toimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med 2008;177:752-62.
8. Suzuki T, Sakagami T, Young LR et al.Hereditary pulmonary alveolar proteinosis. Patho-genesis, presentation, diagnosis, and therapy Am J Respir Crit Care Med 2010;182:1292-1304.
9. Cordonnier C, Fleury-Feith J, Escudier E et al. Secondary alveolar proteinosis is a reversible cause of respiratory failure in leukemic patients. Am J Respir Crit Care Med 1994;149:788-94.
10. Simpson RI, Ramsay MAE. Management of pulomonary alveolar proteinosis by repeated bronchoalveolar lavage. BUMC Proceedings 2000;13:119-20.
11. Mariani F, Poracchini E. GM-CSF inalatoria nella proteinosi alveolare autoimmune refratta-ria al trattamento standard. MR La Rivista delle Malattie Rare 2018;2.