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Secondary pulmonary alveolar proteinosis treated by lung transplant: A case report

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ABSTRACT

Background.

Pulmonary alveolar proteinosis (PAP) is a pulmonary disease characterized by disruption of surfactant homeostasis resulting in its accumulation in the alveoli. PAP is classically classified into three categories (Table 1): 1/primary (or autoimmune) with antibodies targeting the GM-CSF pathway, 2/secondary to another disease, typically a hematologic malignancy, and 3/genetic.

Case-report.

A 30 year-old woman received an allogenic hematopoietic stem cell transplantation (HSCT) after treatment for acute myeloid leukemia (AML). Within the first 6 months post HSCT, she developed an ocular, oral, digestive and hepatic graft-versus-host disease associated with a mixed ventilatory defect with a very severe obstructive syndrome and a severe CO diffusion impairment. High resolution computed tomography showed a classical "crazy paving" pattern. Aspect and differential cell count of BAL were normal. All microbiological samples remained culture negative. Histo-pathological analysis of transbronchial biopsies was unremarkable. Because of the severity of the respiratory insufficiency, open-lung biopsy (OBL) could not be performed. Despite multiple immunosuppressive therapies, lung function deteriorated rapidly; the patient also developed an excavated fungal lesion unresponsive to treatment. She underwent a bilateral lung transplant 48 months after HSCT. Histo-pathological analysis of explanted lungs showed obliterative bronchiolitis (OB), diffuse PAP and invasive cavitary pulmonary aspergillosis.

Conclusions.

This case illustrates the simultaneous occurrence of OB, PAP and a fungal infection in a 30-year old female patient who underwent HSCT for acute myeloid leukemia (AML). To our knowledge this is the only documented case of PAP associated with OB treated by lung transplantation.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a pulmonary disease characterized by disruption of surfactant homeostasis resulting in its accumulation in the alveoli, due to abnormalities of either production or clearance by alveolar macrophages [1].

PAP is classified into three categories: primary (or autoimmune), secondary to another disease and genetic. Primary PAP is characterized by the existence of auto-antibodies targeting the GM-CSF pathway (granulocyte-macrophage colony-stimulating factor) of alveolar

Abbreviations: PAP, Pulmonary Alveolar Proteinosis; HSCT, Hematopoietic Stem Cell Transplantation; BAL, Bronchoalveolar lavage; OLB, Open-lung biopsy; OB, Obliterative Bronchiolitis; AML, Acute myeloid leukemia; GVHd, Graft-versus-host disease; PFT, Pulmonary Function Tests; HRCT, High Resolution Computed Tomography; TBB, Transbronchial Biopsy; BLT, Bilateral Lung Transplant.

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macrophages. This affects their surfactant clearance capacity since GM-CSF is a growth factor which regulates production and activation of macrophages and all granulocytes. Primary PAP is the most common form of the disease accounting for more than 90% of PAP cases [2]. Secondary PAP is due to surfactant accumulation resulting from alveolar macrophage destruction by an external aggression such as a hematologic disorder, infection or toxic inhalation [3]. Secondary PAP accounts for 8–10% [2,4] of all PAP cases and, among secondary PAP, hematological disorders are the most frequent cause. Genetic PAP is linked to abnormal surfactant production caused by genetic mutations (i.e. SFTPB, SFTPC, ABCA3 and TTF1 gene mutations) and is the less common form, typically occurring in neonates and children [5].

Throughout this report we will focus on the form that our patient presented: secondary PAP. This is a purely descriptive report of a case for which anonymity has been fully preserved and as such, our case-report was exempt from approval from an ethics' board.

1.1. CASE-REPORT

A 30 year-old female patient was diagnosed with acute myeloid leukemia (AML) in November 2013. Multiple cures of chemotherapy (idarubicine, cytarabine, fludarabine and amsacrine) led to a remission. In March 2014 (T0) (Fig. 1), because of a high risk of relapse, she received an allogenic hematopoietic stem cell transplantation (HSCT). At T0 + 6 months, she developed ocular, oral, digestive and hepatic graft-versus-host disease (GVHd). Immunosuppressive therapy by tacrolimus, ruxolitinib and oral corticosteroids induced a transient stabilization of GVHd.

Between T0 + 6 and T0 + 12 months, she developed a progressive dyspnea, a dry cough and severe asthenia. Pulmonary function tests (PFT) showed a mixed ventilatory pattern with a very severe obstructive syndrome and severe CO diffusion impairment. Extensive blood analyses and non-invasive microbiological samples did not reveal any sign of infection. High-resolution computed tomography (HRCT) showed a bilateral perihilar mosaicism with zones of ground glass attenuation in a "crazy paving" pattern (Fig. 2, panel A). HRCT was completed by Single Photon Emission Computed Tomography with a ventilation/perfusion phase, which showed that the zones of ground glass attenuation where hypoperfused and hypoventilated when compared to adjacent hypodense lung areas. A bronchoscopy with broncho-alveolar lavage (BAL) and transbronchial biopsies (TBB) was performed. Differential cell count of BAL was normal. All microbiological samples remained culture negative. Histo-pathological analysis of lung parenchyma samples was unremarkable. Because of the severity of the respiratory insufficiency, a surgical lung biopsy was not performed.

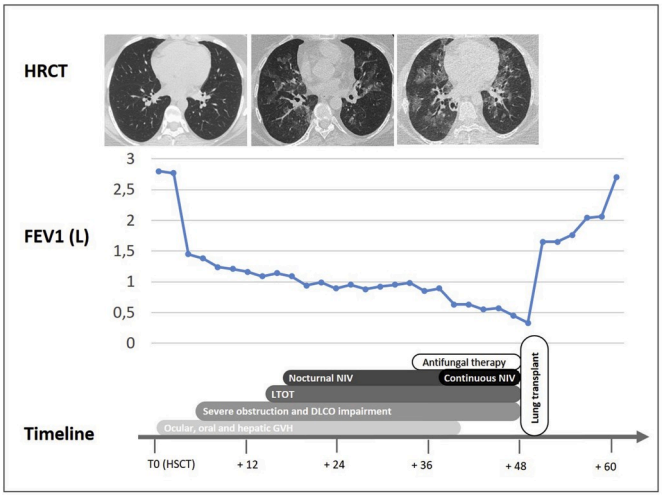

Fig. 1. Timeline with CT scan and FEV1 evolution over time.

Table 1
Overview of PAP.

	Primary	Secondary	Genetic
Etiology	Auto-immune (anti-GM-CSF Antibody)	Systemic disease (>75% 2nd to hematologic malignancy)	Genetic mutations (i.e. SFTPB, SFTPC, ABCA3 and TTF1 genes)
Prevalence	>90%	8–10%	<1%
Symptoms/ signs	Dry cough, dyspnea, asthenia, variable severity of respiratory failure		
CT-Scan	Ground-glass opacities and « crazy-paving »	More diffuse ground-glass opacities and less « crazy-paving » pattern	Ground-glass opacities and « crazy-paving »
Treatment	- Immunosuppressive treatment (i.e. Rituximab) - Plasmapheresis - GM-CSF subcutaneous injections or inhalation (in trial)	- Treatment of the underlying condition - Whole-lung lavage	- Gene and stem-cell therapy
Prognosis	75% survival at 5 years	45% survival at 2 years	Variable prognosis

At this stage, our patient presented simultaneously a severe obstructive airway disease, potentially attributable to obliterative bronchiolitis (OB), and a parenchymal disorder, with a "crazy paving" mosaic pattern of ground glass attenuation, for which an infection had been reasonably excluded.

To control the probable OB, immunosuppressive treatment was intensified with high-dose oral corticosteroids, and inhaled corticosteroids. Macrolides (as immunomodulators) were added and extracorporeal photopheresis was implemented. This failed to impact on the progression of the airway obstruction and the patient developed a progressive respiratory failure requiring continuous oxygen therapy and subsequently nocturnal non-invasive ventilation. Furthermore, because of her immunosuppression, she underwent recurrent hospitalizations for IV treatment of lower respiratory tract infections.

At T0 + 34 months, indication for a bilateral lung transplant (BLT) was confirmed by the local transplant center. At T0 + 45 months, because of worsening of PFT, appearance of a cavitary subpleural lesion on HRCT (Fig. 2, panel A (red circle)), and high levels of serum galactomannan, posaconazole was introduced for suspicion of a locally invasive pulmonary aspergillosis.

In spite of several adaptations of anti-fungal therapy, the size of the cavitary lesion increased (20 × 24mm with a 4 mm wall). At HSCT +47 months, her respiratory condition required continuous high pressure non-invasive ventilatory support, and high flow of oxygen. After three weeks in the Intensive Care Unit, BLT was performed.

Macroscopically, the explanted lungs were firm and showed a yellow cut surface and a cavity with necrosis (Fig. 2, panel B).

Microscopic analysis of the explanted lungs (Fig. 2, panel C) revealed the presence of 1/obliterative bronchiolitis predominating in the upper lobes; 2/diffuse alveolar lipoproteinosis with xanthomatous pneumonia and 3/a subpleural cavity with aspergillus fragments (confirmed by PCR) without signs of vascular or extrapleural invasion, confirming the co-existence of three disorders: OB, PAP and invasive cavitary pulmonary aspergillosis.

More than two years after BLT, the patient is in good clinical condition, and has normalized her PFT and her lung parenchyma appears normal on HRCT.

2. Discussion

This case illustrates the simultaneous occurrence of OB, PAP and a fungal infection in a 30-year old female patient who underwent HSCT

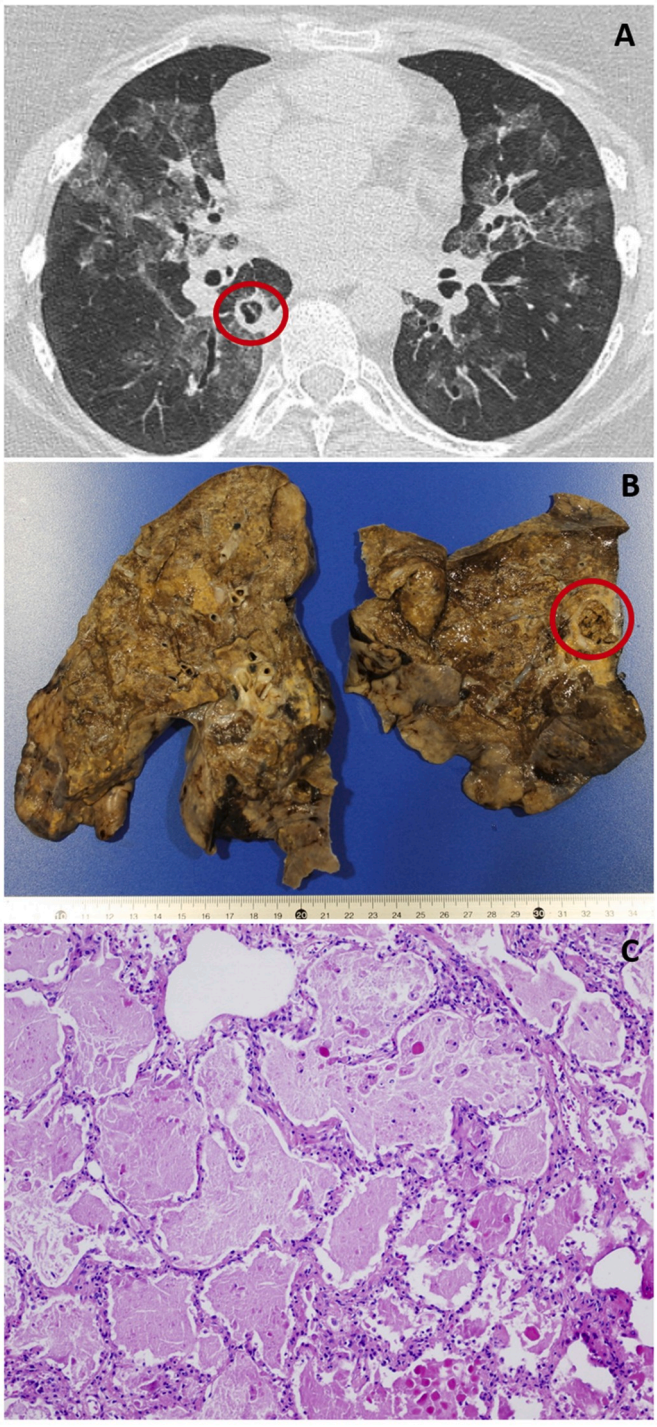

Fig. 2. A) Lung CT-scan: "Crazy Paving" pattern with excavated subpleural lesion (circled) B) Explanted lung showing diffuse diffuse yellow cut surface and the fungal cavity (circled) C) Photomicrograph of pulmonary parenchyma: alveoli are filled by eosinophilic amorphous or finely granular material that is periodic acid–Schiff-positive. Haematoxylin and eosin stain (x100). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

after treatment for AML. To our knowledge this is the only documented case of PAP associated with OB treated by lung transplantation.

Secondary PAP represents 8–10% of all cases of PAP, with an incidence and prevalence of approximately 0.05 and 0.5 per million [2], respectively. Hematologic disorders account for the majority of these cases (75%, mostly myelodysplastic syndromes and AML) [7]. Secondary PAP has been reported after bacterial or parasitic infections, inhalation of toxic substances such as indium tin oxide [8] (used in the fabrication of flat screens), immune deficiency syndromes, non-hematological cancers and connective tissue diseases (dermatomyositis and rheumatoid arthritis) but these descriptions are rare and could simply correspond to fortuitous associations [8]. The pathophysiology of these secondary PAPs is not well understood. It seems that alveolar macrophages are numerically and/or functionally unable to ensure clearance of surfactant resulting in bronchial obstruction and impaired alveolar gas exchange [3]. By definition, no GM-CSF antibodies are present in secondary PAP as opposed to primary PAP.

One third of patients with PAP are asymptomatic [8]. PAP symptoms are unspecific: progressive dyspnea, dry cough and asthenia. Less frequently, fever, hemoptysis and chest pain may occur. Fever seems to be more frequent in secondary PAP vs primary PAP (30% versus 1%) [9]. Physical examination often shows diffuse fine crackles, signs of hypoxemia (cyanosis) and digital clubbing [9].

Chest radiography can show symmetric, bilateral, perihilar alveolar opacities with the "bat wing" appearance of pulmonary edema but without other radiographic signs of left-sided heart failure [10]. HRCT typically shows ground-glass opacities, septal reticulations and parenchymal consolidation with a ''crazy paving'' pattern, characteristic of PAP [11] although not specific, as this pattern is also associated with several other lung diseases [12]. The extent and severity of radiological abnormalities usually correlate with the degree of PFT impairment and hypoxemia [10]. In a Japanese retrospective cohort study, Ishii et al. showed that secondary PAP had a more diffuse radiological presentation and that crazy paving attenuation was less common in secondary PAP [11].

PFTs typically show a restrictive ventilatory defect with severe reduction of carbon monoxide diffusing capacity [13]. A low DLCO (<44% predicted) in secondary PAP has been associated with poor prognosis (survival < 2 years) [4].

In about 75% of cases suggestive of PAP, bronchoalveolar-lavage can establish the diagnosis [8]. The lavage fluid has a characteristic opaque and milky appearance. OLB remains the gold standard for PAP diagnosis. However, it is not always required, and can be confusing due to false negative results due to sampling error. Microscopic examination of biopsies typically shows alveoli filled with granular, eosinophilic material that stains with periodic acid–Schiff (PAS), reagent that highlights the polysaccharides related to high levels of surfactant proteins [1]. Ishii and al. also showed that the overall use of OLB was more common in secondary PAP vs. primary PAP (41% versus 7%), probably due to a less typical radiological presentation [11].

There is no specific treatment for secondary PAP. Therapy for secondary PAP generally involves treatment of the underlying condition: chemotherapy or bone marrow transplantation for hematologic disorders, antimicrobial treatment for infections and avoidance of exposure for toxic inhalation. PAP has been described following HSCT [14]; however many other reports described a resolution of PAP secondary to hematologic malignancy after HSCT [15]. Since the early 1960s, treatment by whole-lung lavage remains the standard of care, without any formal validation or comparison to other treatments.

The prognosis of secondary PAP is much more severe than that of autoimmune PAP, with a 2-year survival of 46%, and a median survival of 15 months [6] *vs* a 75% 5 year-survival for primary PAP. Mortality results from progression of respiratory failure induced by PAP, secondary infections and mortality related to the underlying hematologic disorder [6].

3. Summary

Our patient presented a severe form of PAP associated with an OB, 14 months after HSCT, with characteristic radiological PAP features. BAL was not contributive to the diagnosis and surgical lung biopsy was not an option due to respiratory limitation. Over a 2-year period, progression of

PAP and OB led to severe respiratory failure and BLT. Examination of the explanted lung confirmed the presence of 3 distinct lung diseases: OB, PAP and an opportunistic fungal infection. The diagnosis of PAP was not considered prior to BLT and GM-CSF antibody testing was not performed. However, the clinical presentation is strongly suggestive of secondary PAP. More than a year after BLT, the patient has normal PFT without any signs of relapse on HRCT.

This case illustrates the difficulty of diagnosing and managing secondary PAP, and its progression towards terminal respiratory failure.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

David Lawi: Writing - original draft. **Estelle Dubruc:** Data curation. **Michel Gonzalez:** Writing - original draft, Formal analysis, Data curation. **John-David Aubert:** Writing - original draft, Formal analysis, Data curation. **Paola M. Soccal:** Writing - original draft, Formal analysis, Data curation. **Jean-Paul Janssens:** Writing - original draft, Data curation.

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