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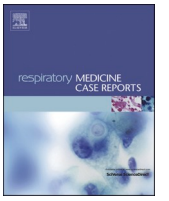

Case report

Sirolimus-induced secondary pulmonary alveolar proteinosis

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A B S T R A C T

Pulmonary alveolar proteinosis (PAP) is a rare pulmonary syndrome that is characterized by the accumulation of excess surfactant in the alveolar space, leading to impaired gas exchange. Sirolimus-induced PAP is an extremely rare entity that has only been described in the literature in a small number of case reports. We present a case of a 39-year-old female with acute lymphocytic leukemia who underwent stem cell transplant, complicated by graft-versus-host-disease (GVHD) involving the skin for which she was treated with steroids, photopheresis, sirolimus, and ruxolitinib. She was admitted to the intensive care unit (ICU) for acute on chronic hypoxic respiratory failure requiring intermittent mechanical ventilation. Computed tomography (CT) of the chest showed thickened inter- and intralobular septa with ground glass opacities and consolidation with a limited geographic pattern. Bronchoalveolar lavage fluid was stained with Periodic acid-Schiff (PAS), which was positive for extracellular proteinaceous material. Autoimmune studies including antibody levels for primary autoimmune pulmonary alveolar proteinosis (PAP) were negative. The patient was diagnosed with sirolimus-induced secondary PAP, and sirolimus was discontinued. A year later, she no longer required supplemental oxygen, and repeat CT imaging showed only faint residual disease. This is the only documented case of sirolimus-induced PAP in a stem cell transplant recipient and the first case reported in which the patient developed severe hypoxic respiratory failure requiring mechanical ventilation. In the right clinical context, PAP can be diagnosed with characteristic high resolution computed tomography (HRCT) findings, serum GM-CSF antibody levels, and bronchoscopy with bronchoalveolar lavage.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare pulmonary syndrome that is characterized by the accumulation of excess surfactant in the alveolar space, leading to impaired gas exchange [1]. A number of heterogenous disease mechanisms can lead to this clinical syndrome. The most common form is primary or autoimmune PAP, where autoantibodies to granulocyte-monocyte colony-stimulating factor (GM-CSF) disrupt its downstream signaling, leading to a defect in the clearance of surfactant by alveolar macrophages [2,3]. Secondary PAP, on the other hand, is an acquired impairment in alveolar macrophage function with the most common etiologies being hematologic disorders, malignancies, immune deficiencies, drug toxicities, inhalation injuries, and infections [4]. Sirolimus-induced PAP is an extremely rare entity that has only been described in the literature in a small number of case reports.

2. Case presentation

We present a case of a 39-year-old female with acute lymphocytic leukemia who underwent stem cell transplant in early 2010. The stem cell transplant was complicated by graft-versus-host-disease (GVHD) involving the skin in 2011, for which she was initially

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treated with steroids, followed by photopheresis and sirolimus in September 2014 and ruxolitinib in September 2016. Both sirolimus and ruxolitinib were continued. She was hospitalized for respiratory syncytial virus pneumonia in 2017, after which she became oxygen-dependent. Her hypoxia slowly progressed, and a computed tomography (CT) scan of the lungs showed interstitial changes. She was seen by a pulmonologist, who started her on pirfenidone for presumed idiopathic pulmonary fibrosis; however, the diagnosis was never clearly established. Another pulmonologist recommended a diagnostic bronchoscopy with bronchoalveolar lavage (BAL) and possible transbronchial biopsy, but the patient was hesitant and ultimately lost to follow-up.

In 2018, she was admitted to the ICU for acute on chronic hypoxic respiratory failure that was unresponsive to 3 days of high-dose steroids and was thus transferred to our institution for higher level of care on high-flow oxygen. The differential diagnosis at the time included graft-versus-host disease involving the lung; however, given the acute decompensation, other more common causes of acute hypoxia were also considered, including pulmonary embolism and infectious etiologies.

On arrival, chest radiograph showed worsening airspace opacities in both lungs, right greater than left, concerning for pneumonia as well as underlying pulmonary fibrosis. CT angiography of the chest showed thickened inter- and intralobular septa with ground glass opacities and consolidation with a limited geographic pattern and a nonocclusive small right lower lobe posterior basal segment pulmonary embolism (Fig. 1). Given the imaging findings, idiopathic pulmonary fibrosis was thought to be less likely as the etiology, and pirfenidone was discontinued. She was treated with anticoagulation, although the pulmonary embolism was not thought to be a significant contributor to her respiratory failure.

The patient eventually underwent a bronchoscopy with BAL. Periodic acid-Schiff (PAS) stain was positive for extracellular proteinaceous material (Fig. 2). Infectious studies were notable for a positive cytomegalovirus (CMV) qualitative PCR in the BAL fluid but a negative serum CMV quantitative PCR; the remainder of the work-up was negative. She was not treated for CMV given that it was not thought to be pathogenic. Autoimmune studies including antibody levels against granulocyte-monocyte colony-stimulating factor (GM-CSF) for primary pulmonary alveolar proteinosis (PAP) were sent and found to be negative. The patient was thus diagnosed with sirolimus-induced secondary pulmonary alveolar proteinosis, and the sirolimus was discontinued.

Given her critically ill state in the ICU requiring intermittent ventilator support, she required 3 right-sided whole lung lavages (WLLs) and 2 left-sided WLLs for her respiratory failure. Despite the diagnosis of secondary PAP, she was also trialed on inhaled GM-CSF in an attempt to stimulate the maturation of new alveolar macrophages that were unimpaired by sirolimus toxicity. Her hypoxia slowly improved, and she was discharged to an acute rehabilitation unit with nasal cannula oxygen after a 3-month hospitalization. Inhaled GM-CSF was discontinued after 6 months, and a repeat CT scan performed 7 months after diagnosis showed interval improvement of diffuse ground glass attenuation with both intra- and interlobular septal thickening (Fig. 3). The patient was able to discontinue oxygen therapy completely a year after she was diagnosed with secondary PAP. Of note, the patient has remained on ruxolitinib for her GVHD during the entire time, suggesting that sirolimus was the likely culprit.

Two years after discontinuation of the sirolimus, the patient continues to improve clinically and is now only mildly symptomatic. Her most recent CT scan shows marked improvement of the ground-glass opacities with only evidence of some faint residual disease (Fig. 4). Her pulmonary function tests have similarly improved as has her oxygenation and functional capacity. Her original six-minute walk test (6MWT) showed a desaturation to 85% with ambulation while her most recent 6MWT showed an SpO2 of 97%–92% with ambulation of 333 m. Overall, the patient has clinically and radiographically improved significantly since the discontinuation of sirolimus and has returned to work and an independent life with no further need for oxygen therapy.

3. Discussion

Prior to this patient, there have been 7 documented cases of mammalian target of rapamycin (mTOR) inhibitor-induced PAP with the vast majority implicating sirolimus and only one report involving everolimus (Table 1). All of the reported cases were in solid organ

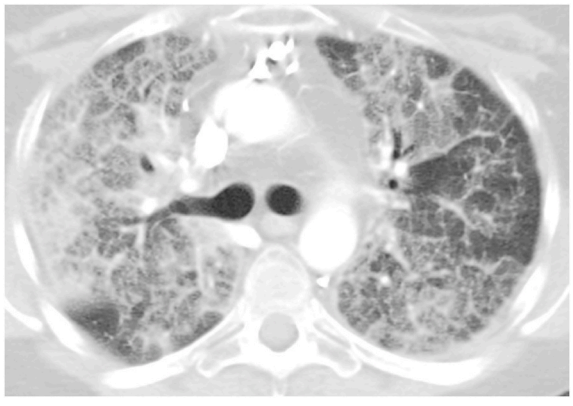

Fig. 1. Computed tomography (CT) scan of chest at the time of diagnosis. Imaging was performed on a GE medical systems scanner, and axial images were reformatted at 6mm slice thickness during administration of intravenous contrast (dFOV = 36 cm). CT scan shows dense bilateral thickened inter and intralobular septa, ground-glass opacification, and consolidation involving the right greater than the left lung. Other findings include a nonocclusive small right lower lobe posterior basal segment pulmonary embolism.

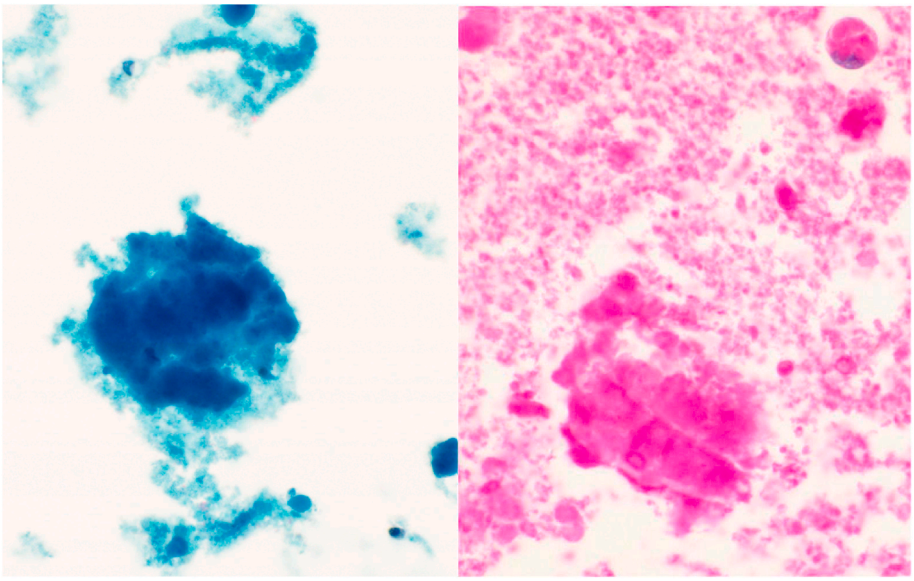

Fig. 2. Bronchoalveolar lavage showed a paucicellular specimen with abundant extracellular granular material (left panel, Papanicolaou stain, 400x magnification) that was Periodic acid-Schiff (PAS) positive; PAS-positive material is also present in pulmonary macrophages (upper right) (right panel, PAS stain, 400× magnification).

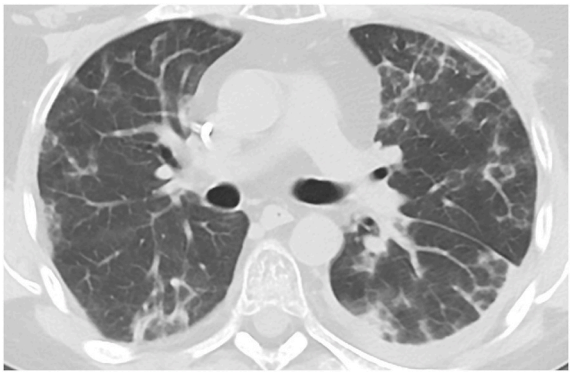

Fig. 3. High-resolution computed tomography (HRCT) scan obtained 7 months after discontinuation of sirolimus. Imaging was performed on a Siemens Multidetector scanner, in helical mode supine at suspended maximal inspiration with 1mm slice thickness. CT scan shows further decrease in diffuse ground glass attenuation with both intra- and interlobular septal thickening and essentially unchanged mild underlying pulmonary fibrosis.

transplant recipients, and all of the patients demonstrated resolution of their PAP within a year of discontinuation of the drug. In contrast, there have been two documented cases of ruxolitinib-induced PAP (Table 1).

PAP is often difficult to diagnose because its clinical presentation tends to be non-specific with dyspnea being the most common presentation [5]. Because PAP is difficult to diagnose clinically, four out of the five cases of mTOR-inhibitor induced PAP reported in the literature were ultimately diagnosed via lung biopsy; in the other case, biopsy was performed but the results were inconclusive [6–10]. While the gold standard for diagnosis of PAP used to be a lung biopsy, this is no longer routinely recommended because of the invasive nature of the procedure. Instead, PAP can be readily diagnosed with characteristic high-resolution computed tomography (HRCT) findings, blood testing, and bronchoscopy with BAL [11]. In the setting of secondary PAP, high clinical suspicion along with characteristic BAL fluid and imaging findings may be sufficient to make the diagnosis, again circumventing the need for a biopsy.

Radiographic findings for PAP on plain films are non-specific with the most classic pattern being bilateral perihilar opacities with sparing of the costophrenic angles, also known as a "bat-wing" distribution [1]. HRCT scan usually shows a "crazy-paving" appearance, which is characterized by scattered or diffuse ground-glass attenuation with superimposed interlobular septal thickening and intralobular lines. It is a linear pattern superimposed on a background of ground-glass opacities that resembles irregularly shaped paving stones. While it was initially described in cases of PAP, "crazy-paving" is nonspecific and can be seen in many other pulmonary conditions including *Pneumocystis carinii* pneumonia, mucinous bronchioloalveolar carcinoma, sarcoidosis, nonspecific interstitial pneumonia, organizing pneumonia, exogenous lipoid pneumonia, acute respiratory distress syndrome, pulmonary hemorrhage syndromes, and congestive heart failure (Table 2). Differences in the location of the radiographic abnormality, the presence of additional

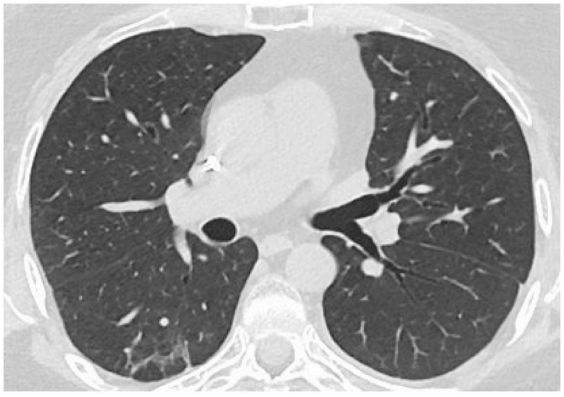

Fig. 4. High-resolution computed tomography (HRCT) scan obtained 24 months after discontinuation of sirolimus. Imaging was performed on a Siemens 64-detector scanner, in helical mode supine at suspended maximal inspiration with 1mm slice thickness (dFOV = 30 cm). CT scan shows subtle residual areas of nodular groundglass predominating in the upper lobes.

Table 1
Cases of mTOR-inhibitor and ruxolitinib induced PAP.

	Authors	Age/ Gender	Drug	Organ transplanted	Time to symptom development after drug initiation	CT chest findings	Biopsy	Severity of respiratory failure	Time to resolution
1	Pedroso et al. [7]	34F	Sirolimus	Kidney	2 years	Ground-glass opacities, "crazy-paving"	Open lung biopsy attempted, with inconclusive results	F_iO_2 0.35	3 months
2	Seethamraju et al. [17]	N/A	Sirolimus	Lung	N/A	N/A	N/A	N/A	N/A
3	Seethamraju et al. [17]	N/A	Sirolimus	Lung	N/A	N/A	N/A	N/A	N/A
4	Kadikoy et al. [6]	49F	Sirolimus	Kidney	3 years	Interstitial infiltrates, ground-glass opacities	Transbronchial biopsy	Room air	1 month
5	Hinojosa-Gonzalez et al. [8]	58M	Sirolimus	Kidney	6 years	N/A	Open lung biopsy	Room air	5 months
6	Darley et al. [9]	56F	Everolimus	Lung	3 years	Centrilobular nodules and ground-glass opacities	Video-assisted thoracoscopic biopsy	Room air	N/A
7	Narotzsky et al. [10]	25F	Sirolimus	Heart, lung	6 months	Ground-glass infiltrates with alveolar septal thickening	Transbronchial biopsy	F_iO_2 0.28	12 months
8	Sugiura et al. [22]	70M	Ruxolitinib	N/A	12 months	Diffuse ground glass opacity with crazy-paving pattern		N/A	Patient expired
9	Salvator et al. [23]	66F	Ruxolitinib	Hematopoetic stem cell transplant	7 months	Bilateral ground-glass opacities and thickened interlobular septa		N/A	12 months

radiographic features, as well as the patient's history and clinical presentation are useful in distinguishing these diseases [12]. Lung architecture is typically preserved, with fibrosis less commonly seen [13]. Of note, pleural effusions, mediastinal lymphadenopathy, and pulmonary nodules are not typically seen and presence of these findings warrants an evaluation for an alternative diagnosis [12].

In contrast to primary PAP, secondary PAP does not typically have the "crazy-paving" appearance; the most common presentation is ground-glass opacities (~60% of patients). The "crazy-paving" appearance is seen in ~70% of patients with primary PAP, while it is only seen in ~15% of patients with secondary PAP. In addition, patients with secondary PAP are more likely to have findings in the craniocaudal distribution, while patients with primary PAP have findings predominantly in the lower lung fields [14].

Table 2
Differential diagnosis for the "crazy-paving" pattern on CT scan of the lungs.

Category	Disease	Typical radiographic manifestations	Additional radiographic features
Infection	*Pneumocystis carinii* pneumonia	Bilateral, perihilar reticular and poorly defined ground-glass opacities which often progress to alveolar consolidation	
Neoplasm	Bronchioloalveolar carcinoma	Ill-defined consolidation or ground-glass opacities in focal or multilobar distribution	Lymphadenopathy, pleural effusion
Inhalational disorders	Exogenous lipoid pneumonia	Low attenuation consolidation	
Pulmonary hemorrhage syndromes	Idiopathic pulmonary hemosiderosis Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis Goodpasture syndrome Collagen-vascular disease Drug-induced coagulopathy Hemorrhage associated with malignancy	Symmetric acinar and ground-glass opacities or attenuation	
Other disorders	Pulmonary alveolar proteinosis	Bilateral, symmetric alveolar consolidation or ground-glass opacity, particularly in perihilar or hilar distribution	
	Sarcoidosis	Irregular thickening of bronchovascular bundles and small nodules along vessels	
	Nonspecific interstitial pneumonia	Ground-glass attenuation with tendency for subpleural and basal predominance	Honeycombing typically absent
	Organizing pneumonia	Scattered and asymmetric consolidation bilaterally, mostly subpleural and peribronchovascular	
	Acute respiratory distress syndrome	Bilateral consolidation and ground-glass attenuation	Reticular and linear attenuation
	Congestive heart failure	Interlobular septal thickening with associated ground-glass opacification	Pleural effusion

On gross pathologic examination, the lungs of patients with PAP are filled with milky, pus-like fluid [1]. Histologic examination reveals filling of the alveolar spaces and bronchioles with PAS-positive, extracellular, proteinaceous surfactant. Cytologic examination of BAL fluid shows a paucicellular or acellular specimen with granular, extracellular material. Occasionally alveolar macrophages are present with intracellular, cytoplasmic, PAS-positive granules. The PAS-stain will be positive, while an alcian blue stain will be negative [15]. Serum GM-CSF autoantibody testing is useful to distinguish autoimmune, or primary, PAP from secondary causes with a sensitivity and specificity approaching 100% [16].

Treatment of secondary PAP is focused on reversing the underlying cause. For drug-induced PAP, discontinuation of the offending agent usually leads to resolution of the disease. In most cases, patients achieve complete or near complete resolution of the disease with the time to resolution ranging from 3 to 12 months. Four out of the five reported cases of mTOR inhibitor-induced secondary PAP resolved without any other clinical intervention; the last one underwent whole lung lavage (WLL) and GM-CSF therapy [6–10,17]. WLL remains the main therapeutic option for PAP and can be a temporizing measure for secondary PAP while addressing the underlying cause [18].

mTOR inhibitors have been shown to cause a myriad of pulmonary toxicities, including organizing pneumonia, interstitial pneumonitis, pulmonary fibrosis, alveolar hemorrhage, and PAP [19]. The exact mechanism through which mTOR inhibitors lead to PAP remains unknown; however, the mTOR signaling pathway has been implicated in macrophage activation [20]. In addition to solid organ transplant recipients, mTOR inhibitors were recently approved for the treatment of solid malignancies, leading to more widespread use. A meta-analysis of mTOR inhibitors for malignancy showed that the incidence of pulmonary toxicity was 10.4% with 2.4% of cases being classified as high-grade. Compared to controls, the relative risk was 31- and 8.8-folds, respectively, for all- and high-grade pulmonary toxicity [21]. As the use of mTOR inhibitors become more widespread, it will become exceedingly important to maintain a high degree of clinical suspicion for pulmonary toxicity due to mTOR inhibitors, including secondary PAP.

4. Conclusion

In the right clinical context, PAP can be diagnosed with characteristic HRCT findings, blood testing for GM-CSF antibody levels, and bronchoscopy with bronchoalveolar lavage. Given more widespread use of mTOR inhibitors both in the setting of solid organ transplant recipients and solid organ malignancies, pulmonary toxicity associated with the use of these medications will be more commonly observed. Secondary PAP, although rare, is a clinically difficult diagnosis, making it important to maintain a high degree of suspicion so the offending agent can be promptly discontinued.

Authors' contributions

SW performed the writing of the manuscript. EL, RL, and TW contributed ideas and edited the manuscript.

Declaration of competing interest

None.

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