Case Report

Reversible sirolimus-induced pulmonary alveolar proteinosis in a renal transplant patient

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is characterized by accumulation of surfactant-like lipoprotein material within distal bronchioles and alveoli due to impaired clearance. Clinically, PAP presents with dyspnea and cough. A 58-year-old Hispanic man presented with 6 months of productive cough, weight loss, and progressively worsening dyspnea. He reported a long history of poorly controlled type 2 diabetes that led to diabetic nephropathy. The patient had a strong passive smoking history for over 30 years and exposure to woodsmoke. He had pulmonary tuberculosis in 2007 and 2012. In 2011, he was diagnosed with renal failure, was dialyzed for a year, and received a renal transplant in 2012. His posttransplant medication regimens included tacrolimus, mycophenolic acid, and prednisone. Six months after the transplant, he suffered graft rejection, managed with steroids and switching from tacrolimus to sirolimus. His physical examination demonstrated scattered inspiratory crackles, and a chest X-ray showed bilateral perihilar ground-glass opacities. PAP was diagnosed through lung biopsy, which showed eosinophilic granular infiltrate withing the alveoli. Sirolimus was switched back to tacrolimus 2 mg in September 2018. PAP diagnosis included hematoxylin and eosin and PAS. Clinical follow-up included oxygen saturation with pulse oximeter and chest X-rays. A 2-month follow-up showed only partial improvement in both symptoms and radiological findings. In January 2019, a follow-up showed complete radiological and symptomatologic resolution. After 5 months, the patient remains asymptomatic with adequate exertion tolerance. PAP remains a diagnosis of exclusion in patients undergoing immunomodulatory therapy with sirolimus and pulmonary symptoms. Reversal can be achieved by switching agents.

KEY WORDS: Pulmonary alveolar proteinosis, sirolimus, transplant

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INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a progressive lung disease characterized by accumulation of surfactant-like lipoproteinaceous material within the distal bronchi and alveoli due to impaired clearance by alveolar macrophages.[1] Three clinical variants of PAP have been described: primary (90%), congenital (~2%), and secondary (5%).[2] Primary PAP is caused by the presence of autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF), which results in impaired surfactant clearance by alveolar macrophages.[3]

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Congenital form occurs due to an innate mutation in the GM-CSF gene; in mice, GM-CSF knockout results in decreased expression of the transcription factor PU.1 in alveolar macrophages, which is required for their functional maturation, resulting in PAP-like pathologies.[4] Finally, secondary PAP is the result of a reduction or a functional impairment of alveolar macrophages due to other conditions such as tuberculosis, hematologic malignancies, exposure to inorganic dusts and fumes, and pharmacologic immunosuppression.[1] Clinically, PAP presents as worsening exertional dyspnea, cough, chest pain and/or hemoptysis, and in some cases, fever and/or elevated serum lactate dehydrogenase. Common radiologic findings are ground-glass opacities and interlobular septal thickening in characteristic crazy-paving pattern. Open lung biopsy has historically been the gold standard; however, up to 75% of cases can be diagnosed through a bronchoalveolar lavage.[1]

CASE REPORT

A 58-year-old Hispanic man with a significant 21-year medical history of poorly controlled type 2 diabetes (T2D) and hypertension presented with 6 months of productive cough, weight loss, and progressively worsening dyspnea. He denied hemoptysis, chest pain, lower extremity swelling, fever, night sweats, or arthralgias. During the interview, he reported multiple T2D-derived complications, including diabetic neuropathy, proliferative retinopathy, and renal failure. His medications included insulin, metformin, and vildagliptin for T2D; gabapentin for diabetic neuropathy; finasteride and alfuzosin for benign prostrate hypertrophy; and ocular injections of ranibizumab for proliferative diabetic retinopathy. The patient also had a strong passive smoking history, constantly exposed to two packs a day of indoor smoke for 32 years, as well as a 10-year exposure to woodsmoke for the first 10 years of his life due to cooking habits. An episode of pulmonary tuberculosis was recorded in 2007, which was successfully treated with 2 months of rifampicin, isoniazid, pyrazinamide, and ethambutol + 4 months of isoniazid and rifampicin. In 2011, he was diagnosed with renal failure due to TD2, undergoing a year of hemodialysis before receiving a renal transplant in 2012. His posttransplant medications included were PO tacrolimus 4 mg, mycophenolic acid 500 mg QID, and prednisone 5 mg daily. Six months after the transplant, he suffered graft rejection diagnosed through laboratories and biopsy. The graft was spared with steroid therapy and by switching tacrolimus for sirolimus 2 mg. In the same year, he presented a new episode of pulmonary tuberculosis, which again was successfully treated with standard therapy. In 2015, he was diagnosed with benign prostatic hyperplasia.

Physical examination was otherwise unremarkable except for his lung assessment, which exhibited scattered inspiratory crackles without any rales, rhonchi, or wheezes. The patient's comprehensive metabolic panel and complete blood count with differential revealed a serum glucose of 152 mg/dL, serum creatinine of 1.32 mg/dL, hemoglobin of 10.8 g/dL, and hematocrit of 33.70%. Venous blood gas analysis on room air revealed a pH of 7.451, PCO_2 33.0 mmHg, PO2 45.4 mmHg, and HCO3 22.4 mEq/L, and all other parameters were within normal values. A chest X-ray showed bilateral perihilar and infrahilar ground-glass opacities. A biopsy by bronchoscopy yielded inconclusive results. Another biopsy was obtained through/by thoracotomy, which reported the presence of eosinophilic granular material within the alveolar spaces, and overall lung architecture was preserved, through which the diagnostic of PAP was made [Figure 1]. Sirolimus toxicity was chosen as the most probable etiology; thus, the patient was switched from sirolimus back to tacrolimus (2 mg) in September 2018. A 2-month follow-up showed only partial improvement in both symptoms and radiological findings, with a diffusion lung capacity of carbon monoxide (DLCO) of 38% [Table 1]. A follow-up in January 2019 showed complete radiological resolution, and improvement of his DLCO to 63% [Table 1], as well as complete symptomatologic resolution [Figure 2]. After 5 months, the patient remained asymptomatic, with adequate exertion tolerance.

DISCUSSION

Mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, are a key component of renal posttransplant immunosuppressive therapy, due to their decreased nephrotoxicity when compared to calcineurin inhibitors.[5,6] Nevertheless, immunosuppressive therapy does not come without added risks such as increased incidence of neoplasia, development of metabolic syndrome, and antiandrogenic effects.[7-9] The incidence of pulmonary toxicity in patients on mTOR inhibitors has been reported to be up to 11%.[10,11] The mechanism through which mTOR inhibitors cause PAP is yet to be clearly elucidated; however, a clear association between mTOR

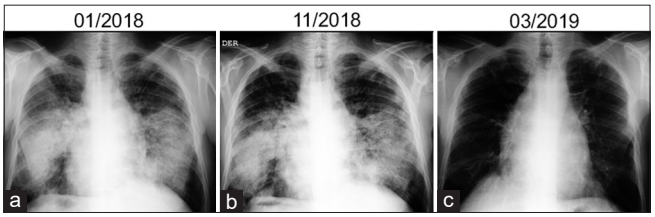

Figure 1: Chest X-rays were used to evaluate the patient's evolution. (a) Chest X-ray on January 2018 shows a bilateral perihilar and infrahilar ground-glass opacity. (b) Two months after adjusting the medication, a similar pattern was observed (November 2018). (c) Six months later, the lungs appeared cleared which correlated with the clinical evolution (March 2019)

Table 1: DLCO before and after switching to tacrolimus

Predicted diffusing capacity for CO adjusted for hemoglobin	
November 2018	38% severe impairment
March 2019	63% mild impairment

Diffusing capacity of the lung for CO improved after sirolimus treatment was stopped, which correlated with the chest X-rays and the patients' symptomatology. CO: Carbon monoxide

Table 2: PAP cases in renal transplants with mTOR inhibitors

Author	Gender	Age	Other present conditions	Organ transplanted	Immunomodulation therapy	Onset of symptoms after starting mTOR inhibitor	Treatment	Resolution time since mTOR discontinuation	Outcome
Lopez *et al.*[12]	Male	47	End-stage renal disease due to HTN and nephrosclerosis	Kidney	Everolimus 5.2 ng/mL trough Basiliximab induction Cyclosporine Steroids	11 months after starting treatment	-	-	Death after 4 months because of pneumonia and sepsis
Kirby *et al.*[20]	Male	71	IgA nephropathy	Kidney	Sirolimus Cyclosporine Prednisone	114 months after starting treatment	-	-	-
Pedroso *et al.*[21]	Female	34	End-stage renal disease	Kidney	Sirolimus MMF Steroids Furosemide Losartan Atenolol Simvastatin	2 years after starting sirolimus	Withdrawal of sirolimus and change for tacrolimus Levofloxacin	3 months for PAP to resolve	Normalization of pulmonary function tests and imaging of the thorax
Dhawan *et al.*[22]	Male	54	End-stage renal disease secondary to polycystic kidney disease and 45 packs a year history	Kidney	Sirolimus Mycophenolate Prednisone Bactrim	-	Withdrawal of sirolimus	-	Discharged home with supplemental oxygen. Follow-up 2 months later, CXR showed improvement and the patient stated only the need for supplemental oxygen
Garcia *et al.*[19]	Male	40	-	Kidney	Sirolimus MMF Prednisone	5 years with the same immunosuppressive regimen	Substitution of sirolimus for tacrolimus, whole-lung lavage in a hyperbaric chamber	The patient discharged after 4 days with normal oxygen saturation	4 months later, the patient was still asymptomatic
Kadikoy *et al.*[23]	Female	49	End-stage renal disease secondary to hemolytic–uremic syndrome	Kidney	Sirolimus 6 mg/day Mycophenolate sodium Steroids	3 years 2 months with sirolimus (as initial posttransplant immunosuppression)	Replacement of sirolimus with tacrolimus	Following sirolimus discontinuation, symptoms began to improve. Within 1 month, CXR showed near-total resolution	-

Summary of PAP cases related to immunosuppression with mTOR inhibitors. Dosages of mediations that are not shown were not published. CKD: Chronic kidney disease, ILD: Interstitial lung disease, COPD: Chronic obstructive pulmonary disease, PAP: Pulmonary alveolar proteinosis, HTN: Essential hypertension, MMF: Mycophenolate mofetil, CXR: Chest X-ray, mTOR: Mammalian target of rapamycin

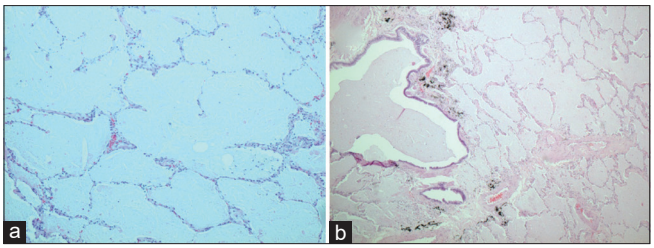

Figure 2: (a and b) Eosinophilic granular material within the alveolar spaces with overall lung architecture preservation

inhibitors and PAP has been established due to the number of reports of PAP in solid organ-transplanted patients, which have been resolved by replacing mTOR inhibitors with alternate drugs.[12] PAP may also be associated with other diseases such as tuberculosis and pneumocystosis; however, it tends to resolve when the underlying pathology is treated. The role of therapeutic GM-CSF remains unclear due to the lack of circulating antibodies against GM-CSF in secondary PAP.[13,14] Hwang *et al*. suggested that cigarette increases the risk of developing PAP, whether smoking and immunosuppressive therapies have an additive relation on risk is unknown.[15]

Usual radiologic findings include ground-glass opacities with interlobular septal thickening in a characteristic crazy-paving pattern. Open lung biopsy has historically been the gold standard for diagnosis; however, up to 75% of cases can be diagnosed through a bronchoalveolar lavage.[1] Diagnosis is usually delayed due to the rarity of the disease, and it is mostly achieved by exclusion. The substitution of the offending agent remains the mainstay treatment, which typically leads to the resolution of symptoms in 2–4 months.[16] Whole-lung lavage (WLL) remains a symptomatic therapeutic option for patients with severe diseases; however, this treatment modality may be limited in severely hypoxemic patients who can be offered WLL within a hyperbaric chamber or with extracorporeal membrane oxygenation.[17-19] The limited number of reported cases makes establishing the prognosis difficult; however, most of the cases tend to improve when therapy is adequately replaced.

A review of the current literature shows 12 reported cases of PAP secondary to immunosuppression with mTOR inhibitors in renal transplant cases [Table 2]. A PubMed search for "sirolimus AND proteinosis" yields 45 results, "rapamycin AND proteinosis" 72 results, and "mTOR AND proteinosis" 44 results as of late September 2019, all of which only seven cases were related to renal transplant. Darley *et al*.[24] report was found to relate PAP in everolimus use, whereas Arunachalam *et al*.[20] reported noninfectious pneumonitis caused also by everolimus.[19,25] Regarding PAP secondary to sirolimus, this is the eight reported case in renal transplant recipients. There is, however, a single reported case of not PAP but sirolimus-induced granulomatous interstitial pneumonitis.[26] Replacement of Sirolimus with other immunosuppresors achieved resolution of pulmonary clinical symptoms and radiological findings in most published cases. PAP is an uncommon adverse reaction of mTOR inhibitors. Secondary PAP has been described as early as 4 weeks after the beginning of an mTOR inhibitor and as late as 10 years of an mTOR-based immunosuppression regimen; the average onset of secondary PAP of the case reports found is of 29 months after starting immunosuppression with rapamycin. The incidence of PAP in the usage of sirolimus for transplant patient remains unknown. Nevertheless, clinicians that utilize sirolimus/rapamycin on their practice must acknowledge the potential risk it encompasses.

CONCLUSION

PAP remains an elusive diagnosis due to its rarity, which is usually achieved through biopsy when other options have been exhausted. The impact on life quality is severe, and the wide use of mTOR inhibitors should encourage clinicians to suspect use-related pulmonary complications. As in previously reported cases, therapeutic regimen change has proven to be the adequate treatment option.

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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