

Sirolimus-Induced Interstitial Pneumonitis in a Renal Transplant Patient

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We report interstitial pneumonitis caused by sirolimus (Rapamune, an immunosuppressive agent) in a renal transplant patient. This rare manifestation was recently recognized as a troublesome adverse effect of sirolimus in many solid-organ transplant recipients, the majority of whom are kidney transplant recipients. While on sirolimus our patient developed cough, fever, and patchy infiltrates, which failed to respond to multiple courses of antibiotic therapy. Biopsy showed findings characteristic of drug-induced hypersensitivity pneumonitis, and excluded other entities, such as opportunistic infection. Improvement occurred only upon discontinuation of the sirolimus. *Key words: interstitial pneumonitis, sirolimus, kidney, transplant.* [Respir Care 2005;50(12):1659–1661.]
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Introduction

Sirolimus (Rapamune) is a potent immunosuppressive drug widely used in organ transplantation. The 2 most common adverse effects are thrombocytopenia and hyperlipidemia.¹ Sirolimus is often used in addition to or as an alternative to calcineurin inhibitor (eg, tacrolimus, cyclosporine) therapy, as it has a different mechanism of action and it does not carry the risk of nephrotoxicity that has been reported in association with tacrolimus or cyclosporine.²

We encountered a patient with suspected sirolimus toxicity, who presented with persistent cough (white sputum) and dyspnea, along with the radiologic finding of patchy bilateral interstitial infiltrates. The patient's presentation was consistent with a community-acquired pneumonia, except that the patient failed antibiotic therapy. Biopsy supported a drug-induced hypersensitivity reaction. This entity must be considered in post-transplant patients who have persistent pneumonia-like illness while undergoing immunosuppression with sirolimus.

Case Report

A 30-year-old black female with a history of cadaveric renal transplant secondary to immunoglobulin A (IgA) nephropathy presented with productive cough, chest pain, intermittent fever, and dyspnea of approximately 5 weeks duration. She had a history of type-II diabetes mellitus, hypertension, hyperlipidemia, mitral valve prolapse, tricuspid valve prolapse, and gastritis. The patient was treated with a course of moxifloxacin for presumed pneumonia, with no improvement. The patient was then seen in the renal transplant clinic for a routine visit, where a chest radiograph showed a lingular consolidation consistent with a persistent pneumonia. The patient was then started on a 10-day course of levofloxacin. Some symptoms improved after treatment, but cough actually worsened. A few days later the patient developed a right-sided frontal headache, as well as nausea and nonbloody, nonbilious vomiting. Fever continued and cough was productive of brownish sputum. The patient was admitted to the hospital for further evaluation. Medications at the time of admission included atenolol, amlodipine, prednisone 10 mg once daily, sirolimus 1 mg once daily, atorvastatin, ranitidine, estrogen, calcitriol, and furosemide. The patient had been receiving sirolimus for 6 months.

On admission, the patient was afebrile, with a blood pressure of 107/65 mm Hg, pulse of 78 beats/min, respiratory rate of 18 breaths/min, and had a blood oxygen saturation of 99% on room air. She was observed to have a cough productive of greenish sputum, but was not in

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Fig. 1. Anterior-posterior chest radiograph showing density in the left lower lung zone, which obscures the lateral left heart border, consistent with air-space consolidation in the lingula.

overt respiratory distress. The chest examination found a few rales diffusely, and rhonchi over the lingular area when auscultated at the left anterior axillary line. The patient also had edema (1+) in her lower extremities, bilaterally. The renal allograft was palpable in the left lower quadrant and was nontender.

Admission laboratory results revealed a normal white blood cell count of 5.7 cells/ μ L, a hemoglobin of 12.4 g/dL, and a platelet count of 279,000/mL. She had an abnormal laboratory value for creatinine, 2.0 mg/dL, but this was baseline for this patient. An initial chest radiograph showed a persistent lingular infiltrate that was not substantially changed from her last radiograph, approximately one month prior, without any new infiltrates or effusions (Figure 1).

Our initial assessment was that she had persistent pneumonia. We empirically started intravenous ceftriaxone 1 g and intravenous azithromycin 250 mg daily. We obtained cultures of urine, blood, and sputum. We ordered measurement of sirolimus level, cytomegalovirus antigen, herpes virus antigen, and influenza titer, to evaluate possible antibiotic-resistant etiologies of the pulmonary disease process. The sirolimus level was 13.1 μ g/L (normal 4–12 μ g/L).

Despite the intravenous antibiotics, the patient's symptoms persisted. Two days into the hospital stay, she had an episode of hemoptysis, and chest auscultation revealed bilateral basilar crackles. At this time we obtained a non-contrast computed tomogram, which showed patchy parenchymal opacities (Figure 2), with areas of confluence in the lingula and left lower lobe, and less confluent areas



Fig. 2. Computed tomogram taken concurrently, showing patchy air-space disease in the lingula and the left lower lobe, as well as focal nodular consolidation at the extreme right costophrenic angle.

seen in the right upper and right middle lobe. A soft-tissue density was noted at the right lung base. These findings were interpreted as being consistent with a multilobar pneumonia.

We then performed a bronchoscopy with biopsy and bronchoalveolar lavage for unresolving pneumonia. The differential diagnosis at that point expanded to include a drug-induced pneumonitis, bronchiolitis obliterans organizing pneumonia, capillaritis, and Henoch-Schönlein purpura.

The bronchoalveolar lavage revealed 9% macrophages, 0% neutrophils, 91% lymphocytes, and 0% eosinophils. Cytologic examination, with appropriate stains, of the fluid was negative for malignant cells, Legionella, *Pneumocystis carinii*, and fungi. The biopsy found multiple giant cells, both intra-alveolar and interstitial, without evidence of vasculitis or bronchiolitis. The biopsies were negative for acid-fast bacilli, as well as negative for IgG, IgA, IgM, C3, and C1q. The findings were consistent with prior descriptions of a rare entity among solid-organ transplant recipients, known as sirolimus-induced interstitial pneumonitis (Figure 3). Sirolimus was stopped and tacrolimus was substituted. Antibiotics were discontinued. We did not treat with increased doses of prednisone.

Following the discontinuation of sirolimus, the patient began to improve symptomatically, with decrease in cough and improvement in dyspnea. A chest radiograph prior to discharge, approximately 8 days later, revealed partial clearing of the lingular and left-lower-lobe consolidation. Improvement continued after discharge, with complete resolution of cough. A follow-up computed tomogram 6 weeks later confirmed improvement in all parenchymal infiltrates, and a final follow-up computed tomogram 12 weeks after hospitalization showed complete resolution. The patient

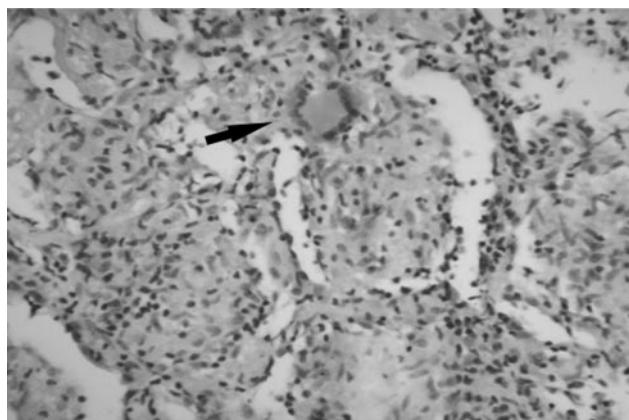


Fig. 3. Biopsy specimen obtained via transbronchial biopsy, showing giant cell formation (dark arrow) as well as intense lymphocytic inflammation, without bronchiolitis or vasculitis.

remained asymptomatic from a respiratory standpoint, with alternative immunosuppressive therapy.

Discussion

We describe a renal transplant recipient who developed cough, fever, and dyspnea with pulmonary infiltrates while on immunosuppressive therapy with sirolimus. As with other reported cases of this entity,²⁻⁴ certain conditions were met before we were able to come to the conclusion of sirolimus as the causative agent: occurrence of pulmonary symptoms and radiographic symptoms during sirolimus therapy, failure of standard therapy for community-acquired pneumonia, and resolution of symptoms and radiographic findings only after discontinuation of sirolimus. We noted a lymphocytic predominance of the cell-count differential in the bronchoalveolar lavage fluid, which supports a drug-induced hypersensitivity. The finding of giant cells on transbronchial biopsy was also supportive. We believe that the giant cells constituted evidence of poorly formed granulomas. A surgical lung biopsy was not pursued.

Controversy exists as to whether this disease process is due to dose-dependent toxicity or an immune-mediated

toxicity. One report proposed that both could be involved, in that sirolimus toxicity may expose cryptic antigens, which could thus trigger an autoimmune response, leading to the characteristic features of a lymphocytic alveolitis and interstitial pneumonitis.³ The patient experienced pulmonary toxicity even at a low sirolimus dose (1 mg daily), which appears to favor the argument that this disease is an immune-mediated or hypersensitivity reaction more than a dose-related toxicity. This is also supported in our patient by the striking lymphocytic-predominant alveolitis (91% lymphocytes in the bronchoalveolar lavage fluid). In another reported case, however, simply reducing the sirolimus dose (from 5.0 mg daily to 2.5 mg daily) led to improvement.⁵

While it is well-established that instituting sirolimus therapy as a replacement for either cyclosporine or tacrolimus will provide adequate immunosuppression as well as avoid the possibility of nephrotoxicity⁶ in organ transplant recipients, the development of pulmonary symptoms must be recognized by the clinician as an important potential complication of sirolimus therapy. This entity can be easily treated by discontinuing the drug; in this case higher-dose corticosteroid therapy was not required.

REFERENCES

- Morelon E, Stern M, Kreis H. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant patients. *N Engl J Med* 2000;343(3):225-226.
- McWilliams TJ, Levvey BJ, Russell PA, Milne DG, Snell GI. Interstitial pneumonitis associated with sirolimus: a dilemma for lung transplantation. *J Heart Lung Transplant* 2003;22(2):210-213.
- Morelon E, Stern M, Israel-Biet D, Correas JM, Danel C, Mamzer-Brunel MF, et al. Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation* 2001;72(5):787-790.
- Pham PT, Pham PC, Danovitch GM, Ross DJ, Gritsch HA, Kendrick EA, et al. Sirolimus associated pulmonary toxicity. *Transplantation* 2004;77(8):1215-1220.
- West M. Bronchiolitis obliterans and organizing pneumonia in renal transplant recipients. *Transplantation* 2000;69(7):1531-1532.
- Dominguez J, Mahalati K, Kibrd B, McAlister VC, MacDonald AS. Conversion to rapamycin immunosuppression in renal transplant recipients: report of an initial experience. *Transplantation* 2000;70(8):1244-1247.