Respiratory Medicine Case Reports 7 (2012) 8–11

Contents lists available at SciVerse ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Sirolimus induced granulomatous interstitial pneumonitis

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ARTICLE INFO

Article history:
Received 7 August 2012
Accepted 18 September 2012

Keywords:
Sirolimus
Granulomatous interstitial pneumonitis
Interstitial pneumonitis
Pulmonary toxicity
Renal transplantation

ABSTRACT

Objectives: Report a case of sirolimus induced granulomatous pneumonitis.
Background: Sirolimus is used in clinical transplantation as an immunosuppressive agent. Pulmonary toxicity does occur, but only a few cases of sirolimus associated granulomatous interstitial pneumonitis have been reported.
Methods: Case report and literature review.
Results: This 53-year-old woman with ESRD from polycystic kidney disease status post deceased donor kidney transplantation presented with fever, progressive dyspnea, and hypoxia for two weeks. She had been switched to sirolimus two months before admission. A CT scan of the chest revealed bilateral ill-defined patchy ground glass opacities. Extensive investigations were negative for infection. Video-assisted thoracoscopic biopsy showed granulomatous interstitial pneumonitis. Her symptoms and infiltrates resolved after sirolimus discontinuation and corticosteroid treatment.
Conclusions: Drugs induced pneumonitis should always be considered in transplant patients after infectious or other etiologies have been excluded. Sirolimus can cause granulomatous infiltrates in the lung possibly secondary to T-cell mediated hypersensitivity.

1. Introduction

The mammalian target of rapamycin inhibitor (mTORi) sirolimus was introduced into clinical transplantation in 1999.[1] It is frequently used either in the induction phase or for maintenance immunosuppression to prevent acute and chronic rejection. Sirolimus is often used to achieve adequate immunosuppression while decreasing the dose and possible toxicity of primary agents, such as calcineurin inhibitors. Dose related myelosuppression and hyperlipidemia are the most common side effects.[1–3] Pulmonary toxicity had been reported since 2000[4] and can cause interstitial pneumonitis, organizing pneumonia, and alveolar hemorrhage.[1] To date, there have been only a few case reports of granulomatous interstitial pneumonitis associated with sirolimus. We describe a patient with polycystic kidney disease with renal transplantation who was switched to sirolimus two months before developing granulomatous interstitial pneumonitis.

2. Case report

A 53-year-old woman, a non smoker with a past medical history of hypertension and ESRD secondary to polycystic kidney disease, underwent deceased donor kidney transplantation in 2006. Her medications were changed from tacrolimus and mycophenolic acid to cyclosporine 25 mg twice a day and sirolimus 3 mg daily approximately two months before admission. She presented with fever, malaise, progressive shortness of breath, and cough with minimal sputum for 2 weeks. She did not have any other symptoms. Physical examination showed stable vital signs, O_2 saturation 96% on room air, and bilateral basilar fine crackles. Lab tests showed a Hb 8.4 g/dl, Hct 24%, MCV 77 fL, WBC 2.5 kU/l, neutrophils 55%, lymphocytes 32%, eosinophils 0.1%, platelets 141 kU/l, sodium 136 mmol/l, potassium 4.2 mmol/l, chloride 102 mmol/l, bicarbonate 22 mmol/l, BUN 15 mg/dl, creatinine 0.9 mg/dl, and normal liver enzyme. Her sirolimus level was high at 28.5 ng/dl. Urinalysis did not show pyuria or hematuria. Chest radiograph revealed bilateral thickened interstitial markings (Fig. 1). Computed tomography scan of the chest without contrast showed ill-defined patchy ground glass opacities in both lungs (Fig. 2).

Cultures were obtained, and antibiotic drugs were started to cover community-acquired pneumonia. The patient remained tachypneic and desaturated. Broad spectrum antibiotic drugs were continued with an antifungal drug (Mycamine) and trimethoprim and sulfamethoxazole. BAL fluid studies were negative for bacteria, viruses, AFB, and fungi. BAL culture for mycobacteria was also negative at eight weeks. The direct antigen for PCP was negative. She underwent video-assisted thoracoscopic biopsy which showed granulomas, interstitial fibrosis, and focal organizing pneumonia

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2213-0071
http://dx.doi.org/10.1016/j.rmcr.2012.09.002

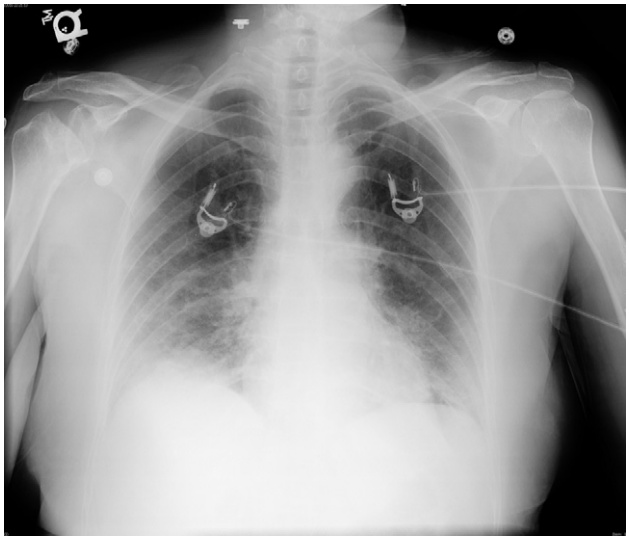

Fig. 1. Chest radiograph on admission showed bilateral increased interstitial markings.

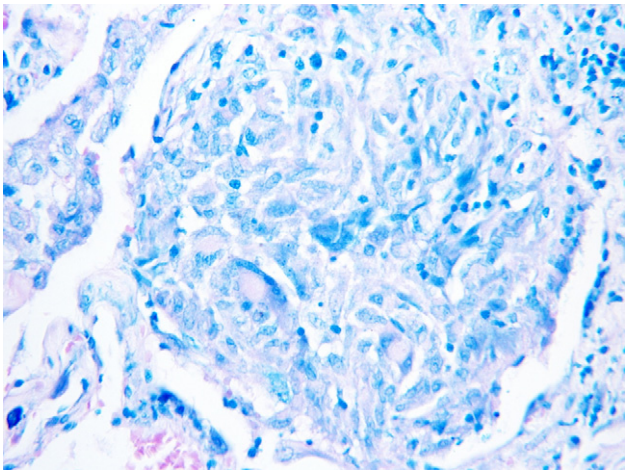

Fig. 3. Wedge biopsy showed granulomas, interstitial fibrosis, and focal organizing pneumonia.

(Fig. 3). She has a normal angiotensin converting enzyme level. The results were highly suspicious for sirolimus induced granulomatous interstitial pneumonitis, and sirolimus was stopped. The patient was started on methylprednisolone 40 mg IV every 12 h. She improved and was discharged on prednisone 30 mg/day, cyclosporine 200 mg/day, and leflunomide 15 mg/day. She was remarkably better two weeks later. Repeat computed tomography scan of the chest one month later showed near complete resolution of the previously seen interstitial lung disease, but some mild interstitial lung disease remained with peripheral interlobular septal thickening (Fig. 4).

3. Discussion

Sirolimus, initially known as rapamycin, is a macrolide antibiotic derived from the actinomycete "Streptomyces hygroscopicus".[1] It is also an immunosuppressive agent which inhibits T-lymphocyte activation and proliferation and antibody production. It binds to FK-binding protein-12 to form a complex which binds and inhibits the activation of the mammalian target of rapamycin (mTOR). The resulting inhibition of mTOR suppresses cytokine-driven T cell proliferation resulting in inhibition of progression from the G1 to the S phase of the cell cycle.[1] It was introduced into clinical transplantation and approved by the Food and Drug Administration in 1999. Since then it has been widely used as an effective immunosuppressive agent in induction or maintenance therapy. In phase III clinical trials, sirolimus caused dose dependent hypercholesterolemia and hypertriglyceridemia which are the most frequent side effects that probably result from the complex interference with lipid metabolism. Sirolimus may also alter the insulin signaling cascade and cause impaired glucose tolerance or overt post transplant diabetes mellitus.[2] Myelosuppression is another dose related sirolimus side effect. Sirolimus also has adverse kidney effects, causing acute renal toxicity by increasing the apoptosis of tubular

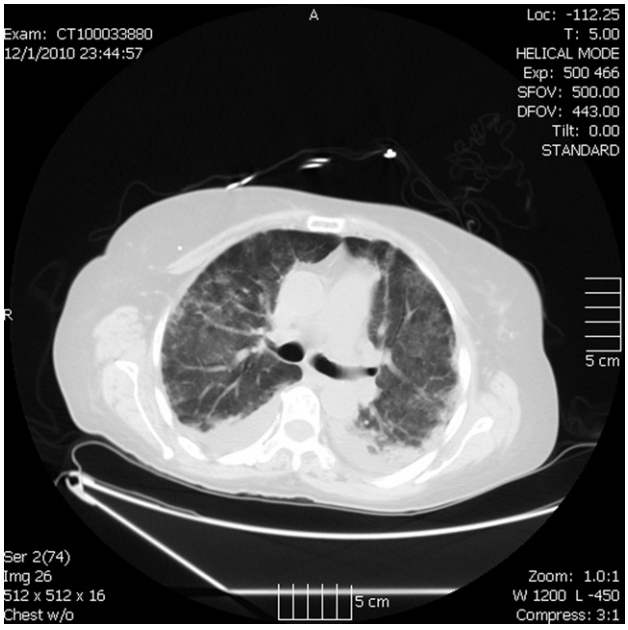

Fig. 2. Computed tomography scan of the chest on admission showed bilateral patchy ground glass opacities.

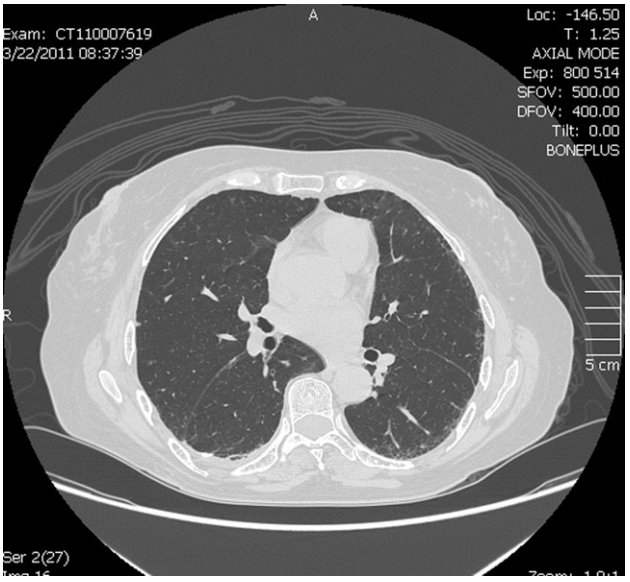

Fig. 4. Computed tomography scan of the chest performed one month after discharge showed resolution of ground glass opacities.

cells, inhibiting the regenerative response, and impairing the recovery of renal function after ischemia-reperfusion injury. Proteinuria can be found in up to 30% of patients. Severe proteinuria and high dose sirolimus induced focal segmental glomerulosclerosis have been reported. Proteinuria is usually controlled by initiating angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists and reducing sirolimus blood level to below 10–12 ng/ml.[2] Gastrointestinal side effects include mouth ulcers which are common and dose related, abdominal pain, nausea, constipation, diarrhea, hepatotoxicity, hepatic necrosis, and hepatic artery thrombosis. Other potential side effects include eyelid edema or peripheral edema that often reverses with dose reduction, poor wound healing from antiproliferative activity, arthralgia which usually resolves with dose reduction, impaired fertility, and the development of lymphoceles from antilymphoangogenic effects.[2]

To date sirolimus has been associated with a rare but serious pulmonary toxicity. The mechanism of sirolimus induced interstitial pneumonitis is still unclear. A cell-medicated autoimmune response may have a role when cryptic pulmonary antigens are exposed, and this causes lymphocytic alveolitis and interstitial pneumonitis. T-cell mediated, delayed type hypersensitivity may be another pathogenic mechanism.[3] Histologic features in our case shows granulomatous interstitial inflammation which suggests a role of T-cell medicated hypersensitivity reaction to circulating antigens or immune complexes in the lungs. T cell lymphocytes produce IL-2 and IFN-gamma which stimulate alveolar macrophages and also produce TNF- alpha and IL-1. Activated macrophages secrete several chemokines, such as monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein 1 alpha (MIP-1α), and transform into epitheloid cells and multinucleated cells contributing to cellular infiltration and granuloma formation.[5]

These patients usually present with fever, progressive dyspnea, dry or productive cough, and occasional hemoptysis. The common radiological findings are bilateral patchy, interstitial opacities. Consolidation or nodular opacities are less commonly seen. BAL lymphocytosis is usually associated with drug induced pneumonitis. The histopathological features from biopsies include organizing pneumonia, interstitial pneumonitis, focal fibrosis, non-necrotizing macrophagocytic granulomas, and pulmonary hemorrhage.[6,7] Risk factors of sirolimus induced pulmonary pneumonitis are not completely understood. Previous studies have reported that male gender, high dose sirolimus, and exposure to sirolimus after toxicity to other drugs may increase the risk of pulmonary toxicity. However, patients with therapeutic sirolimus levels can also develop pulmonary toxicity.[8,9]

Granulomatous interstitial pneumonitis was reported in 2001 in two adults who were S/P renal transplantation. One of the patients was initially treated with anti-tuberculosis medication for two months and improved after sirolimus was withdrawal.[3] In 2003, Avitzur et al.[10] described a case of sirolimus induced granulomatous interstitial pneumonitis in a child following liver transplantation. The child had several concurrent pathological processes: diffuse pneumonitis with alveolar proteinosis, two well-formed granulomas with multinucleated giant cells, and mucosal lymphoid

Table 1
Review of sirolimus induced granulomatous interstitial pneumonitis.

Source	Number of cases/type of transplant	Age/sex	Symptoms and duration of sirolimus exposure	Sirolimus dose/level	Radiograph	Method of tissue obtained/Histology	Outcome
Morelon et al.[3] 2001	8/kidney	4 male 4 female Mean age 56	7/8 had pulmonary symptoms 1/8 asymptomatic Not available	Dose not available Level 15–30 ng/ml	Bilateral asymmetrical infiltrates in all patients	Only 2/8 underwent transbronchial biopsy; Organizing pneumonia, interstitial lymphocytic infiltrate and nonnecrotizing macrophagic granuloma	All patients alive
Avitzur et al.[10] 2003	1/liver	8/female	Fatigue, decreased appetite 9 months of sirolimus	0.12–0.18 mg/kg/day Level 5 ng/ml	Multiple parenchymal nodular opacities	Open lung biopsy; Diffuse pneumonitis, alveolar proteinosis, granulomatous interstitial pneumonitis, PTLD	Alive
Seethamraju et al.[11] 2003	4/lung	Not available	Not available	Not available	Not available	Transbronchial biopsy; 2 patients: granulomatous interstitial pneumonitis 2 patients: pulmonary alveolar proteinosis	Alive
Howard et al.[12] 2006	1/liver	73/female	Fever, dyspnea, nonproductive cough 2 weeks of sirolimus	Dose not available Level 6.1–13.1 ng/ml	Bilateral pleural effusion, consolidation in the left lower lobe	Transbronchial biopsy; Granulomatous interstitial pneumonitis, noncaseating granuloma, organizing pneumonia	Alive
Hamour et al.[14] 2006	1/heart	59/male	Fever, fatigue, dyspnea 2 months of sirolimus	1 mg/day Level 8.8 ng/ml	Ground glass opacification and patchy consolidation in the left lower lobe	Transbronchial biopsy Lymphocytic interstitial pneumonitis with non-caseating granulomas	Alive
Robert et al.[13] 2007	4/liver	53/male	Dyspnea and cough 3 months of sirolimus	Dose not available Median level 9.7 ng/ml	Patchy ground glass change in the upper and lower lobes, bilateral pleural effusions	Transbronchial biopsy; Interstitial non-caseating granuloma, granulomatous pneumonitis	Alive
Our case	1/kidney	53/female	Fever, dyspnea, productive cough 2 months of sirolimus	3 mg/day Level 28.5 ng/ml	Bilateral interstitial infiltrates	Open lung biopsy; Granulomatous interstitial pneumonitis, focal organizing pneumonia	Alive

hyperplasia along the bronchiole-vascular bundles with positive EBV encoded RNA stain and positive CD-20 stain consistent with EBV positive PTLD of the benign lymphoid hyperplasia subtype. Sirolimus was discontinued, and she was treated with ganciclovir and anti CD-20 monoclonal antibody (Rituximab). Seethamraju et al.[11] also reported two cases of granulomatous interstitial pneumonia associated with sirolimus toxicity in lung transplant patients. Howard et al.[12] described an orthotopic liver transplant case who developed respiratory symptoms after two weeks of sirolimus; transbronchial biopsy showed granulomatous interstitial pneumonitis and organizing pneumonia. The patient's symptoms improved within a few days after sirolimus was replaced with tacrolimus, and the chest radiograph improved during three months later. Sirolimus is more widely used later in liver transplantation. Robert et al. reported a case series of four liver transplant patients from the center in UK who were switched to sirolimus therapy prior to their respiratory symptoms.[12,13] Two of them had granulomatous interstitial pneumonitis from lung biopsy. The other two patients had diffuse alveolar damage and mild interstitial pneumonitis. Sirolimus is also used after heart transplantation, and Hamour reported a case with granulomatous interstitial pneumonitis after two months of low dose sirolimus in a 53-year-old man with a heart transplantation for ischemic cardiomyopathy[14] (Table 1).

Granulomatous lung lesion can be secondary to infectious causes, such as tuberculosis, non-tuberculous mycobacterium, histoplasmosis, cryptococcosis, blastomycosis, and coccidioidomycosis. Non-infectious granulomatous diseases like sarcoidosis, berylliosis, Wegener's granulomatosis, Churg-Strauss disease, and even foreign body granulomatous reaction need to be considered in the differential diagnosis. The patient's immune status is important in evaluating granulomatous lung lesions so extensive investigation should be started in these transplant patients because sirolimus associated pulmonary toxicity should be a diagnosis of exclusion.

Morelon et al.[3] developed the following diagnosis criteria for sirolimus induced lung disease:

1. Exposure to sirolimus preceding the onset of pulmonary symptoms.
2. Exclusion of infection or alternative pulmonary disease, including toxicity due to other drugs, such as azathioprine, beta-blockers, fibrates, sulfamethoxazole and trimethoprim.
3. Resolution after sirolimus discontinuation.
4. Lymphocytic alveolar cellular profile and pathological findings, although nonspecific, consistent with drug-induced pulmonary toxicity.

In the case we describe the patient was switched to sirolimus two months before the onset of respiratory symptoms. Cultures and serologies did not show evidence of infection, and the patient did not improve after empiric antibiotic and antifungal therapy. The resolution of symptoms and radiographic findings after sirolimus discontinuation supported the diagnosis of sirolimus induced granulomatous interstitial pneumonitis with Naranjo score of 6 (Table 2) which means probable adverse drug reaction. Although the benefit of steroid has not been clearly documented, our patient received methylprednisone and was discharged on prednisone.

Table 2
Naranjo scale.

1. Are there previous conclusive reports on this reaction? Yes (+1) No (0) Do not know or not done (0)	+1
2. Did the adverse event appear after the suspected drug was given? Yes (+2) No (−1) Do not know or not done (0)	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? Yes (+1) No (0) Do not know or not done (0)	+1
4. Did the adverse reaction appear when the drug was readministered? Yes (+2) No (−1) Do not know or not done (0)	0
5. Are there alternative causes that could have caused the reaction? Yes (−1) No (+2) Do not know or not done (0)	0
6. Did the reaction reappear when a placebo was given? Yes (−1) No (+1) Do not know or not done (0)	0
7. Was the drug detected in any body fluid in toxic concentrations? Yes (+1) No (0) Do not know or not done (0)	+1
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? Yes (+1) No (0) Do not know or not done (0)	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Yes (+1) No (0) Do not know or not done (0)	0
10. Was the adverse event confirmed by any objective evidence? Yes (+1) No (0) Do not know or not done (0)	+1

Naranjo score 6 probable adverse drug reaction.
Scoring: >9 – definite ADR; 5–8 – probable ADR; 1–4 – possible ADR; 0 – doubtful ADR.

4. Conclusion

We describe a patient with a renal transplant for polycystic kidney disease who developed respiratory symptoms and interstitial infiltrates after the addition of sirolimus. After opportunistic infection and other autoimmune related pulmonary conditions are excluded, drug-induced pulmonary hypersensitivity should be in the differential diagnosis in these patients. Discontinuation of the culprit drug can be life saving.

Conflict of interest

The authors have no conflicts of interest. No financial support was received for this study.

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