

## Interstitial pneumonitis associated with sirolimus

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### ABSTRACT

This report describes a case of pulmonary toxicity associated with use of sirolimus in a kidney transplant recipient.

The patient was a 53 year-old male with a first renal transplant under immunosuppression with tacrolimus and sirolimus. One year post-transplant he presented progressive dyspnoea, non-productive cough, chest pain and low-grade fever for 3 weeks. He had chronic allograft dysfunction with a serum creatinine of 1.8 mg/dl. After exclusion of most common causes, a computed tomography and bronchoscopy were performed. Computed tomography showed bilateral interstitial opacities predominantly in the lower lobes and patchy ground-glass opacifications while the bronchoalveolar lavage revealed predominance of lymphocytes and high levels of eosinophils. Diagnosis of interstitial pneumonitis was made and drug-induced toxicity was suspected. Sirolimus was withdrawn, leading to marked improvement in the patient's clinical and radiological status and immunosuppression was changed to tacrolimus and prednisolone. Interstitial pneumonitis is a rare complication of sirolimus therapy with only a few cases described. Further, only a few cases of other pulmonary complications associated with sirolimus including alveolar haemorrhage, alveolar proteinosis and pulmonary lymphoplasmocytic granulomatous necrotising vasculitis have been described. Withdrawal of sirolimus is normally required to resolve these conditions.

#### Key-Words:

Immunosuppression; interstitial pneumonitis; kidney transplant; rapamycin; sirolimus.

### INTRODUCTION

Sirolimus (SRL) has been increasingly used as induction and maintenance immunosuppressive therapy in solid organ transplantation. One serious adverse reaction to SRL is pulmonary toxicity. As SRL-associated pulmonary toxicity often mimics other pulmonary disorders, it is important to know the different expressions of pulmonary adverse effects associated with it<sup>1</sup>.

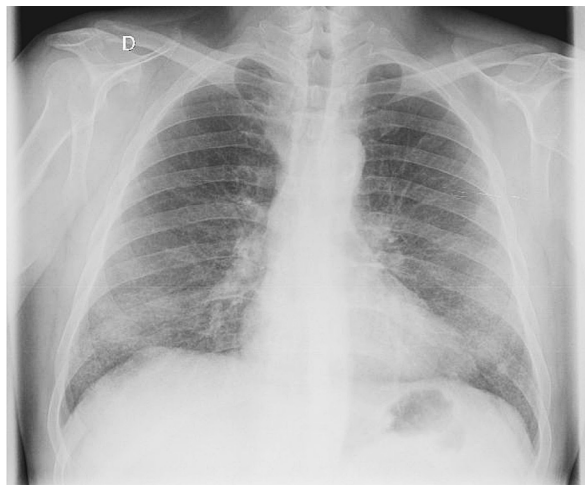
### CASE REPORT

We report a 53 year-old Caucasian male with end stage renal disease of unknown aetiology since October 2001 who received a first cadaveric renal transplant (RT) in June 2006. The donor was 50 years old, with three HLA mismatches (one in AB and two in DR), peak PRA 0%, current PRA 0% and both donor and receptor were cytomegalovirus (CMV) positive. Initial immunosuppression included ATG, tacrolimus (FK), SRL, with steroid withdrawal at day five. The post-transplant period was complicated by delayed graft function. Four haemodialysis sessions were required to achieve adequate graft function recovery. The serum creatinine stabilised at 1.8 mg/dl and patient developed post-transplant diabetes mellitus requiring treatment with oral antidiabetics.

One year after RT he was admitted with 15 days fever and fatigue. There were no pulmonary symptoms. Chest X-ray revealed diffuse infiltrates (Fig. 1) while arterial blood gas measurements were normal



**Figure 1**  
Bilateral alveolar infiltrates with a micronodular pattern.



**Figure 2**  
Bilateral alveolar infiltrates with a micronodular pattern more pronounced in the lower lobes.

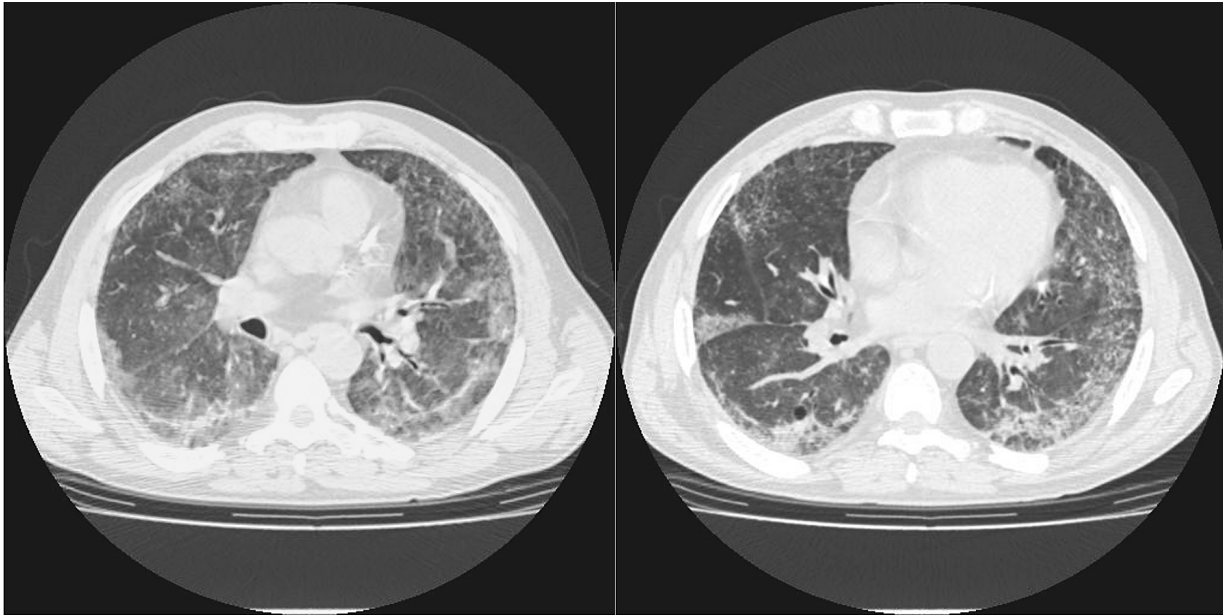
with no respiratory insufficiency. Levofloxacin 500 mg/day was initiated.

He presented to our hospital one week after the initial observation with persistent fever, non-productive cough and fatigue on minimal exertion. Physical examination revealed inspiratory crackles at the pulmonary bases and reduction of murmur bilaterally without acute distress syndrome. The remaining physical exam was unremarkable. Laboratory tests revealed leucopaenia (2200/ $\mu$ L), acute renal dysfunction with a creatinine of 2.1 mg/dl, with no other new abnormalities in blood chemistry. Reactive C-protein was 142.7 mg/L (normal  $<5.0$  mg/L). SRL and FK trough blood levels were 6.8 ng/ml and 5.20 ng/ml, respectively. Arterial blood gases with  $Fi O_2$  of 21% were pH 7.54;  $pCO_2$  15.1 mmHg;  $pO_2$  89.5 mmHg and  $HCO_3^-$  12.7 mmol/L. The patient had normal serum complement concentrations. Tests for cryoglobulins, antinuclear, antineutrophil cytoplasmic and antiglomerular basement membrane antibodies were negative. Chest X-ray revealed bilateral alveolar infiltrates in the lower lobes with a micronodular pattern (Fig. 2).

Other studies were performed to detect respiratory infection. Patient underwent bronchoscopy with bronchoalveolar lavage (BAL) on hospital day two. BAL showed no evidence of bacterial, mycobacterial, fungal, viral or parasitic infection, intra-alveolar

haemorrhage or opaque appearance (total cell count of  $6.9 \times 10^6$  with 4% neutrophils, 58% lymphocytes, 13% eosinophils and 23.6% macrophages) and was negative for malignant cells. Blood, urine and sputum cultures, CMV serology and all other investigations for virus, opportunistic fungi, mycobacteria and parasites were negative. All antibiotics were discontinued. Lung-function tests (LFT) showed marked reduction of the carbon monoxide diffusion capacity (65% less than the expected value). CT scan showed bilateral interstitial opacities predominantly in the lower lobes and patchy ground-glass opacifications (Fig. 3).

After the exclusion of infectious and immunological causes, a diagnosis of interstitial pneumonitis (IP) was made and secondary drug-induced toxicity was suspected. SRL drug toxicity was suspected and the drug was stopped. The patient was converted to immunosuppression with FK and prednisolone 30 mg/day. Discontinuation of SRL associated with corticotherapy was followed by marked improvement in the patient's clinical and radiological status. He was gradually weaned from oxygen therapy. At discharge, two weeks after admission, chest X-ray showed improvement of interstitial infiltrates (Fig. 4). One month after, LFT showed improvement of carbon monoxide diffusion capacity (40% less than the expected value).



**Figure 3**

CT showing bilateral interstitial opacities predominantly in the lower lobes and patchy ground-glass opacifications.



**Figure 4**

Chest X-ray showing markedly improved lung appearance.

Prednisolone dose was progressively tapered. After 6 months, patient has no respiratory symptoms and renal function is stable with a creatinine of 1.8 mg/dl. Current immunosuppression is prednisolone 10 mg/day and FK 10 mg/day (serum trough blood level 6.0 ng/ml).

## DISCUSSION

Lung infiltrates in renal transplant recipients have numerous causes. The most common are infectious diseases but they can also be the result of progressive underlying disease such as systemic lupus erythematosus or other vasculitis or rheumatologic diseases<sup>1</sup>. In patients receiving SRL, pulmonary toxicity is a possible cause of lung disease and this entity must be ruled out.

The use of sirolimus in solid organ transplantation was approved in 1999 by the FDA. It has been increasingly used as *de novo* therapy or as an alternative to calcineurin inhibitors in patients with renal dysfunction, graft vascular disease or malignancy<sup>2-4</sup>.

SRL is a macrocyclic lactone isolated from *Streptomyces hygroscopicus*. It blocks IL-2 post-receptor signals mediating T-cell proliferation by binding to the mammalian target of rapamycin. The downstream events that follow the inactivation of the mammalian target of rapamycin result in the blockage of cell cycle progression at the juncture of the G<sub>1</sub> and S phase<sup>5</sup>. The mammalian target of rapamycin is also involved in the proliferation of other cells, including smooth muscle cells<sup>3,5,6</sup>.

The main documented adverse effects of SRL include myelosuppression (anaemia, thrombocytopaenia), hyperlipidaemia, oedema, rash, delayed wound healing and hepatotoxicity<sup>3,5,7</sup>.

One serious adverse reaction associated with SRL is pulmonary toxicity, which has been seen after renal, liver, heart and heart-lung transplantation<sup>2,3,8</sup>. In addition to pneumonitis, other SRL-related allergic reactions such as acute interstitial nephritis, angiooedema and vasculitis have been noted<sup>9</sup>.

As SRL-associated pulmonary toxicity often mimics other pulmonary disorders, it is important to know which different expressions of pulmonary adverse effects can be SRL-associated<sup>1,10</sup>. Four different clinical entities have been described in the literature. The most frequent is IP but several cases of alveolar haemorrhage have also been published. Moreover, there are two more cases described: one of alveolar proteinosis and another of pulmonary necrotising vasculitis in patients on SRL<sup>5</sup>.

Patients with alveolar haemorrhage usually present with fever, dyspnoea and haemoptysis. Lung infiltrates are found on chest X-ray or CT scan and BAL present marked macrophage haemosiderosis<sup>1</sup>. Prashant *et al.* described one case of lymphoplasmacytic granulomatous necrotising vasculitis characterised by pulmonary infiltrates sited predominantly in the upper and middle zone with an unremarkable BAL. In this case the diagnosis was made by pulmonary biopsy<sup>5</sup>. Pedrosa *et al.* suggested another rare toxicity associated with SRL. The patient presented with progressive dyspnoea, non-productive cough, chest pain and low-grade fever of one month duration. Blood chemistry revealed slight elevation of lactate dehydrogenase levels. On CT scan, ground-glass opacification with polygonal shapes were observed and BAL had an opaque appearance with numerous macrophages. The alveolar macrophages stained positive by periodic acid-Schiff, confirming the diagnosis of pulmonary alveolar proteinosis<sup>11</sup>.

In addition, Morelon *et al.* proposed four criteria for the definitive diagnosis of SRL-induced lung toxicity: exposure to SRL preceding the onset of pulmonary symptoms, exclusion of infection or alternative pulmonary disease, exclusion of other possible offending agents and resolution of symptoms after withdraw or dose-reduction of SRL<sup>5,12</sup>.

As described above, IP is the most frequent pulmonary clinical picture associated with SRL toxicity. Reported in renal, liver, heart and heart-lung transplantation, it has an estimated rate of 5-11%<sup>2</sup>. The pathogenesis of SRL-associated IP is not well understood. Some authors suggest a dose dependent drug toxicity, but it is also reported to be associated with low SRL blood levels, acute CD4 lymphocytic alveolitis and eosinophils in BAL, suggesting an immune mechanism mediated by T lymphocytes<sup>3,7</sup>.

Although risk factors for pulmonary toxicity are not clearly established, they are likely to include late exposure to the drug (*i.e.* switch regimen), older age, male gender, concomitant immunosuppressive treatment and high SRL levels<sup>13</sup>. There are, however, some reports of levels of SRL in the normal range despite development of clinical disease, as occurred in our case<sup>5,14</sup>. Another suggested risk factor is the presence of severe renal insufficiency, as tolerance to SRL may be modified<sup>3,14</sup>. Our patient also presented allograft dysfunction, which could predispose to SRL toxicity.

The time course from the initiation of SRL and the onset of pulmonary complications is broad<sup>5</sup>. Symptoms onset within 1 month to 51 months after the initiation of SRL<sup>2,14</sup>. Dry cough and dyspnoea are the most common symptoms and hypoxaemia is frequently observed<sup>2,14</sup>. Other symptoms, such as fever, fatigue, weight loss and haemoptysis, may present<sup>5,14</sup>. Physical examination frequently reveals crackles and crepitus<sup>3</sup>.

Leukocyte counts vary markedly and C-reactive protein is usually elevated<sup>5,14</sup>. Most patients have moderate hypoxaemia<sup>3</sup>. Chest X-ray typically shows pulmonary infiltrates, but a normal X-ray does not exclude the pathology<sup>3,14</sup>. As in our patient, CT scans usually presents bilateral, mostly peripheral, asymmetrical interstitial infiltrates, areas of ground-glass opacification and patchy pulmonary consolidation in a peribronchial distribution (bronchiolitis obliterans – organising pneumonia-like aspects) predominantly involving the lower lobes<sup>2-3,5,14</sup>.

BAL usually shows hypercellularity with a high percentage of lymphocytes, >20% (lymphocytic alveolitis). In some cases BAL presents mild eosinophilia (<5%)<sup>2-3</sup>. In our case, BAL showed predominance of lymphocytes and higher levels of eosinophils.

BAL cultures must be negative for bacteria, fungi, parasites and viruses<sup>3</sup>. In face of non-specific symptoms, CT scan and BAL are important in identifying SRL-associated pneumonitis<sup>3</sup>. Neither antineutrophil cytoplasm nor antiglomerular basement membrane antibodies are positive. Diagnosis is made after exclusion of infectious, auto-immune and other toxic causes of lung disease<sup>14</sup>.

The exclusion of the offending drug, in this case withdrawal of SRL, is the treatment of choice for suspected SRL-induced pneumonitis. Some authors also suggested dose reduction of SRL. While this strategy resulted in initial improvement in some cases, in most of them it was inadequate, requiring later withdrawal of SRL due to recurrence of pneumonitis even with low doses of SRL<sup>3,14</sup>.

While steroid treatment has been instituted in some cases, no convincing data are available to support this strategy<sup>14</sup>. In our case we changed immunosuppression to steroids (starting with 0.5 mg/kg) concomitantly with withdrawal of SRL. This strategy was adequate, with clinical improvement of our patient in 48 hours.

The prognosis is generally good with clinical and radiographic improvement within 14-28 days in 95% of the patients with SRL discontinuation or dose-reduction<sup>14</sup>. Unusually, one case of posterior development of pulmonary fibrosis has been reported<sup>15</sup>. Three deaths were reported and all were heart transplant recipients<sup>4</sup>. After one month, our patient presented improved respiratory functional tests.

Normal chest X-ray and CT scans are generally seen within 6 months. The unexplained presence of new pulmonary infiltrates in any patient taking SRL makes bronchoscopy and BAL analysis necessary to exclude infection and to provide supportive evidence for the diagnosis of SRL-associated pulmonary disease. We should consider a trial of cessation of therapy, with expected improved clinical symptoms and radiological appearances within weeks and months, respectively<sup>1</sup>. Discontinuation of SRL effectively reversed the clinical picture here. After 6 months of follow-up this patient completely recovered.

**Conflict of interest statement.** None declared.

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