Sirolimus-Induced Drug Fever in a Renal Transplant Patient: A Case Report

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ABSTRACT

Herein we have described the case of a male renal transplant recipient who developed drug fever apparently related to sirolimus. He had been stable under an immunosuppressive regimen of tacrolimus and mycophenolate mofetil, but developed acute cellular rejection at 5 years after transplantation due to noncompliance. Renal biopsy showed marked interstitial fibrosis, and immunosuppression was switched from mycophenolate to sirolimus, maintaining low tacrolimus levels. One month later he was admitted to our hospital for investigation of intermittently high fever, fatigue, myalgias, and diarrhea. Physical examination was unremarkable and drug levels were not increased. Lactic dehydrogenase and C-reactive protein were increased. The blood cell count and chest radiographic findings were normal. After extensive cultures, he was started on broad-spectrum antibiotics. Inflammatory markers and fever worsened, but diarrhea resolved. All serologic and imaging tests excluded infection, immune-mediated diseases, and malignancy. After 12 days antibiotics were stopped as no clinical improvement was achieved. Drug fever was suspected; sirolimus was replaced by mycophenolate mofetil. Fever and other symptoms disappeared after 24 hours; inflammatory markers normalized in a few days. After 1 month the patient was in good health with stable renal function. Although infrequent, the recognition of drug fever as a potential side effect of sirolimus may avoid unnecessary invasive diagnostic procedures. Nevertheless, exclusion of other common causes of fever is essential.

SIROLIMUS (SIR) is a macrolide derivative that has been shown to be a potent immunosuppressant with antitumor properties.¹ Since its introduction in 1999, it has allowed the development of various strategies to provide adequate immunosuppression, while avoiding the nephrotoxic effects associated with calcineurin inhibitor therapy.²

Most SIR side effects are dose-related, including oral ulcers, delayed wound healing, lymphoceles, infections, hyperlipidemia, and myelosuppression.³ More recently, interstitial pneumonitis has been recognized as a side effect of mammalian target of rapamycin (mTOR) inhibitors that might also be related to immune-mediated toxicity.^{4,5}

CASE REPORT

Herein we have reported the case of a 45-year-old Caucasian man who was first diagnosed with IgA nephropathy in 1996. His past medical records were positive for poorly controlled hypertension and aortic stenosis for which he underwent valvuloplasty in 1998 and was treated with oral anticoagulants. Eventually he reached end-stage renal disease and started hemodialysis in 2000.

Three years later he underwent deceased donor kidney transplantation. Immunosuppression consisted of tacrolimus (FK), my-

cophenolate mofetil (MMF), and prednisone. Serum creatinine on discharge was 1.2 mg/dL and remained stable.

In February 2008 he was admitted to the hospital with impaired kidney function, namely, a serum creatinine of 3.4 mg/dL without proteinuria, which was attributed to noncompliance. Kidney allograft biopsy showed Banff grade Ib acute rejection and grade II chronic rejection. He was treated with methylprednisone pulses (500 mg/d for 3 days) and basiliximab (20 mg on days 1 and 4), as he proved to be allergic to antilymphocyte therapy. Kidney function improved slightly, and he was switched from MMF to SIR (2 mg/d), while maintaining a low dose of tacrolimus (2 mg twice a day).

One month later he was admitted to the hospital for investigation of intermittently high fever (38°C–39°C), asthenia, and diffuse myalgias of 3 weeks duration in association with watery diarrhea for the previous week. On admission, the physical examination was unremarkable except for fever and a mild systolic bruit. Laboratory

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findings included: normal blood cell count (leukocytes: 7500/ μ L; hemoglobin 12.9 g/dL; platelets 145,000/ μ L); elevated lactic dehydrogenase (LDH; 730 U/L) and C-reactive protein (CRP; 17.3 mg/L); and stable serum creatinine (2.5 mg/dL). FK and SIR blood levels were 5.4 and 9.8 ng/mL, respectively. Chest X ray was benign. After blood, urine, and fecal cultures were collected, the patient was started on empirical broad-spectrum antibiotics (ceftriaxone 2 g/d and levofloxacin 500 mg twice a day). Echocardiogram excluded infectious endocarditis. Abdominal and pelvic computed tomography (CT) did not show any infectious focus, abnormal mass, or lymphoproliferative disease. Doppler ultrasound of the transplanted kidney ruled out obstruction. Serologic tests for viruses (influenza A and B; parainfluenza 1, 2, and 3; Epstein-Barr; cytomegalovirus; Echovirus; Coxsackie A and B; HIV; hepatitis B and C), bacteria (*Chlamydia psittaci* and *C. pneumoniae*; *Mycoplasma pneumoniae*; *Rickettsia* spp.; *Coxiella burnetii*; *Brucella melitensis*), and immune-mediated diseases were negative.

In a few days, the diarrhea improved, but fever and myalgias persisted. After 12 days, antibiotics were stopped, as no clinical improvement was achieved. The patient then developed a dry cough on inspiration. Chest X ray at that time showed bilateral interstitial infiltrates and a CT scan revealed mild interstitial opacities in the lower lobes with a ground-glass appearance (Fig 1). Bronchoscopy showed no macroscopic lesions and bronchoalveolar lavage (BAL) disclosed no cellular predominance. BAL, sputum, blood, urine, and fecal cultures failed to reveal any infectious organisms.

Pharmacologic fever was therefore suspected and SIR was withdrawn. Clinical improvement was rapidly obtained as the fever disappeared in 24 hours and inflammatory markers normalized in a few days (CRP: 2 mg/L after 48 hours). Respiratory complaints also resolved. He did not undergo bone marrow aspiration.

The patient was discharged 5 days later on an immunosuppressive regimen consisting of MMF (500 mg twice a day), FK (1.5 mg twice a day), and prednisone (7.5 mg/d). One month after dis-

charge, he was asymptomatic with stable renal function (serum creatinine: 2.0 mg/dL).

DISCUSSION

This case of drug fever was related to an mTOR inhibitor.^{3,6} The causative relationship was only assumed after thoroughly excluding infection, immune-mediated disorder, and malignancy. The rapid clinical improvement with resolution of symptoms after discontinuation of SIR supported this hypothesis.

As is the case for other adverse effects of SIR, a pathogenesis has not yet been established. Although a direct toxic effect might play a role, an immune-mediated mechanism may be proposed, for it has been implicated in SIR-induced pneumonitis and anemia.^{1,2,5} In vitro and in vivo studies have demonstrated the development of an inflammatory syndrome associated with this drug, with elevation of CRP, fibrinogen, and cytokines.¹ The up-regulation of tumor necrosis factor alpha (TNF α) and interleukin (IL)-6, two potent pyrogens, and the inhibition of IL-10, which blocks the production of numerous inflammatory mediators, may explain the symptoms.^{1,7}

Given the important role of mTOR inhibitors in immunosuppressive regimens in selected transplant recipients, the recognition of drug fever as a potential side effect is essential, as it may help avoid costly and unnecessary diagnostic evaluations.

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Fig 1. Chest CT scan showing mild interstitial opacities of the lower lobes with ground-glass appearance.