Everolimus-associated interstitial pneumonitis in a patient with a heart transplant

Sir,

Pneumonitis is a severe complication of different immunosuppressive treatment regimens; in particular, cases of sirolimus-associated pneumonitis have been reported so far [1–3]. Here, we report for the first time a patient who developed pneumonitis as a result of an everolimus-based immunosuppressive treatment regimen.

A 71-year-old man was admitted to the hospital because of severe diarrhoea, intermittent fever and generalized malaise. Nineteen years previously, he underwent a heart transplantation and was therefore on immunosuppressive treatment with everolimus (1.75 mg twice daily), mycophenolate mofetil (500 mg twice daily) and prednisone (7.5 mg/day). Despite a target serum level of about 8–10 µg/l, the 24 h everolimus trough level was markedly increased (22.6 µg/l). Laboratory indicators of systemic inflammatory reaction were elevated at this time (C-reactive protein 271 mg/l, pro-calcitonin 7.5 mg/l). After institution of empiric intravenous antibiotic treatment (ceftriaxone, metronidazol), clinical symptoms of gastrointestinal tract infection disappeared rapidly. However, low grade fever remained and slowly developing respiratory symptoms came to the focus of our attention. The patient was tachypnoeic at rest and had fine bilateral basal cracklets on auscultation. Peripheral oxygen saturation was found to be low and even fell under exertion to 85%, blood gases showed partial respiratory insufficiency (pO2 61 mmHg, pCO2 32.7 mmHg). Acute endocarditis was excluded by echocardiography. CRP was still elevated (148 mg/l), blood cultures taken before empiric antibiotic therapy were negative for bacterial and fungal pathogens and, despite changing the antibiotic therapy to piperacillin/tazobactam, the fever increased to 40°C (see clinical course—Figure 1). The chest X-ray did not reveal pulmonary infiltrations, but in the high-resolution computed tomography of the chest bipulmonal ‘air trapping’

Fig. 1. The clinical course, serum CRP concentrations and serum trough levels of everolimus in relation to treatment. The bronchoscopy was performed on day 9.

and larger areas of ground glass opacification could be demonstrated, consistent with the diagnosis of bronchiolitis obliterans (Figure 2). A bronchoscopy with bronchial alveolar lavage was performed. The differential cytology of the bronchial alveolar lavage revealed severe lymphocyte and neutrophile alveolitis. We rapidly stopped the antibiotic therapy, treated the patient with high-dose steroids (0.7 mg/kg/day) and replaced everolimus by cyclosporine A. One day thereafter, the patient was afebrile for the first time since admission. One week later the dyspnoea had resolved completely, lung function improved, and there was no significant drop in oxygen saturation on exertion. The dose of steroids was tapered and discontinued after 6 weeks.

This first reported case of an everolimus-associated pneumonitis coincided with an extremely high serum trough level (22.4 μg/l), probably due to an increased intestinal absorption as a consequence of diarrhoea. Interestingly, in a recent report of five renal transplant recipients, sirolimus-induced pneumonitis resolved after conversion to everolimus [4], but with respect to our case report, this procedure might not be recommendable. The safest therapeutic option seems to be to withdraw the incriminated drug and to temporarily increase the steroid dose.

Conflict of interest statement. None declared.


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Fig. 2. Air trapping associated with bronchiolitis obliterans consistent with pneumonitis. (A) High-resolution CT scan obtained at end of inspiration shows mosaic perfusion with areas of different attenuation. (B) High-resolution CT scan obtained at end of expiration shows focal areas of increased attenuation in both lungs as a result of air trapping.