Sirolimus-induced interstitial pneumonitis

Sir,

A 56-year-old man was admitted to the hospital with a four-week history of fatigue, dry cough and exertional dyspnoea. He had received a cadaveric renal transplant in the year 2004 for end stage renal failure due to diabetic nephropathy. Initial immunosuppression was tacrolimus and mycophenolate mofetil; tacrolimus had been replaced with sirolimus about two months prior to the onset of symptoms. On admission he was on sirolimus, mycophenolate mofetil, septrin, perindopril, felodipine, atorvastatin, aspirin and insulin. He was apyrexial but tachypneic and hypoxic (oxygen-saturation on room air 87%). His blood pressure was 158/60 mmHg, jugular venous pressure was not elevated and there was no peripheral edema. Examination of chest revealed bilateral inspiratory crepitations. Investigations showed hemoglobin 11.2 g/dL, platelets 321 x 10^9/L, white cell count 8.28 x 10^9/L and raised C-reactive protein (CRP) at 57. He had stable renal functions with creatinine 150 µmol/L and other biochemical profile was normal. Chest X-ray revealed bilateral infiltrates. A high resolution computed tomography (HRCT) scan confirmed interstitial pneumonitis with patchy ground-glass opacification and infiltration [Figure 1]. Sirolimus level at that time was 9.4 ng/ml. Auto-antibody and vasculitis screen were negative. Sputum for acid-fast bacilli and antibodies for cytomegalovirus were negative. There was nothing to suggest Pneumocystis carinii pneumonia and sputum, urine and blood cultures were sterile. Sirolimus was withdrawn and he was restarted on tacrolimus and the symptoms gradually improved over a three-week period. He had a normal chest X-ray and CRP at four months follow-up and remains well.

Immunosuppression has revolutionized organ transplantation, however, it is associated with the risk of infection and adverse effects of the drugs. Sirolimus is a new, highly potent immunosuppressant that has an inhibitory effect on the mammalian target of rapamycin (mTOR) mediated transduction pathways. It is increasingly used in renal transplant due to lack of intrinsic nephrotoxicity, reduced incidence of graft rejection and advantageous effect on arterial hypertension and posttransplantation diabetes. Nevertheless, sirolimus is associated with adverse effects like mouth ulcers, hyperlipidemia, anemia, thrombocytopenia, leukopenia and infectious and non-infectious pneumonias.[1] Our patient developed pneumonitis after he was commenced on sirolimus, the symptoms improved after withdrawing sirolimus and there was no evidence of infection or any other cause for the interstitial pneumonitis. On Naranjo’s algorithm[4] it scored 5, classifying it as a probable adverse drug reaction.

Patient with pulmonary toxicity due to sirolimus can present with cough, dyspnoea, fever, hemoptysis and eyelid edema. CRP is elevated, chest radiograph can reveal basal opacities and bronchoalveolar lavage shows lymphocytosis. Histopathology shows lymphoplasmocytic interstitial inflammation, scattered intra-alveolar epitheloid granulomas and focal organizing pneumonia. Withdrawal of sirolimus results in resolution of symptoms, radiographic opacities in chest and CRP[4].

Although pulmonary toxicity associated with sirolimus is not common,[5] with the increasing popularity and wider use of sirolimus physicians should be aware of this potentially serious but reversible complication of sirolimus.

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References