Transplant International

LETTER TO THE EDITOR

Sirolimus-associated acute interstitial nephritis in a renal allograft

doi:10.1111/j.1432-2277.2009.01016.x

Sirolimus lacks the short- and long-term nephrotoxicity of calcineurin inhibitors. Nevertheless, it can cause renal problems such as prolongation of delayed graft function, proteinuria and glomerulosclerosis or thrombotic microangiopathy [1–3]. We here report on a case of acute interstitial nephritis (AIN) in a renal allograft, which was most likely caused by sirolimus.

A 55-year-old Caucasian woman suffering from ADPKD received her first renal allograft after 3 years on CAPD. Induction therapy included Campath-1H 30 mg and prednisolone, followed by tacrolimus monotherapy. 3 months later sclerosing encapsulating peritonitis was diagnosed and immunosuppression switched from tacrolimus to sirolimus and prednisolone. Two years after transplantation a ureteral stenosis was detected and a new ureteral implantation was planned. To avoid impaired wound healing, sirolimus was discontinued and immunosuppression was switched to tacrolimus. With tacrolimus serum creatinine rose from 1.4 to 1.8 mg/dl. Therefore, she was put back on sirolimus 3 months after surgery. Initially, serum creatinine decreased from 1.8 to 1.4 mg/dl. Sirolimus blood level was 7.1 ng/ml. However, 3 weeks later her serum creatinine had increased to 3.0 mg/dl. In addition, she had a painful ulcer on her tongue, fever and shivering and her CRP was 7.6 mg/dl. No eosinophilia was seen. Urinanalysis showed leukocytes and leukocyte casts. β2-Microglobulin excretion was markedly increased. Comedication consisted of pantoprazole, furosemide and metoprolol.

A transplant biopsy contained 20 normal glomeruli. Interstitial oedema was present. The interstitium showed dense mononuclear infiltration with a marked proportion of eosinophils and focal infiltration of tubuli. Vessels were normal and no endothelialitis was detected. Immunofluorescence was negative for immunoglobulins and C4d, and tubular epithelia did not express HLA-DR. Immunohistochemical staining for polyomavirus (SV-40 T antigen) was negative. These findings are compatible with the diagnosis of acute allergic interstitial nephritis. The patient was switched from sirolimus to tacrolimus, and pantoprazole was stopped. Fever subsided and CRP levels normalized within the next week, but serum creatinine remained elevated. Prednisolone was increased to 30 mg. After 2 weeks serum creatinine had dropped to 2.0 mg/dl (Fig. 1).

Acute interstitial nephritis (AIN) in a renal allograft is very rare [4–8]. Most of the cases were caused by trimethoprime sulfamethoxazole. Our patient clearly had AIN. Acute rejection or viral nephritis was excluded. In addition, elevated markers of inflammation and urinary findings such as leukocyturia and high β2-microglobulin excretion are characteristic of AIN.

The time course of reexposure to sirolimus followed by acute renal failure suggests that sirolimus was the causative agent in our patient. Other macrolide molecules such as erythromycin, clarithromycin and azithromycin have also been described to cause AIN.

Pantoprazole has been reported to induce AIN and it cannot be excluded as the causal agent. A recent review of 64 cases of proton pump inhibitor-associated AIN describes a mean exposure time of 13 weeks (range 2–52 weeks) before onset of disease [9]. Our patient had been on pantoprazole for 3½ years. This long exposure period argues against pantoprazole as the causative drug.

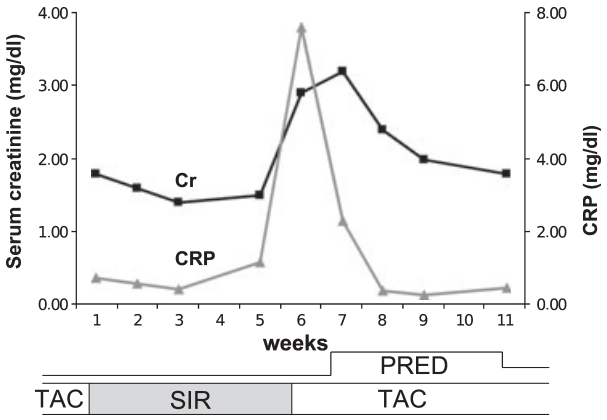

Figure 1 Time course of serum creatinine and CRP levels following the second exposure to sirolimus (beginning at week 1). 5 weeks later creatinine and CRP rose sharply. After sirolimus was stopped, CRP declined rapidly, whereas renal function only improved after the steroid dose had been increased.

There is possibly a third alternative explanation for the development of AIN in our patient. Apart from its immunosuppressive potential by restriction of lymphocyte proliferation sirolimus has strong proinflammatory effects. mTOR inhibition in macrophages and dendritic cells induces proinflammatory cytokines such as IL-12 and IL-1β, reduces the anti-inflammatory cytokine IL-10, and stimulates antigen presentation [10]. An inflammatory reaction underlies the interstitial pneumonitis frequently associated with sirolimus. T cells and eosinophils, which we also detected in the allograft biopsy of our patient, are the hallmark of that disease [11]. In addition, sirolimus can induce fever, angioedema, especially after reexposure [12], and leukocytoclastic vasculitis[13]. We speculate, that by its proinflammatory action sirolimus may have induced or aggravated an immune response directed against pantoprazole. In that scenario the combination of both drugs would be necessary to cause AIN.

Why did AIN not occur during the first exposure to sirolimus? The most likely explanation is, that during first exposure in the treatment of sclerosing encapsulating peritonitis sirolimus was combined with a much higher prednisolone dose (25 mg) compared to the second exposure (2.5 mg). Furthermore, AIN after repeated drug exposure is a well-known phenomenon, especially for the antibiotic rifampicin [14].

After discontinuing sirolimus and pantoprazole, our patient showed improved constitutional symptoms and markers of inflammation, but serum creatinine remained elevated. After a short course of a moderate steroid dose, renal allograft function rapidly improved. We therefore conclude that AIN completely resolved without causing persisting damage to the allograft.

In summary, AIN could be included in the list of renal side-effects of sirolimus. Allograft biopsy is necessary to establish the diagnosis. Elimination of the causative agent and administration of steroid treatment is able to induce full remission of sirolimus-associated AIN.

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