Case Report

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Reflex sympathetic dystrophy in a renal transplant patient
treated with sirolimus

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Introduction

Severe osteoarticular problems are common after solid organ transplantation. More specifically, unilateral foot pain can be induced by gout, fractures, avascular necrosis (due to corticosteroid treatment), foot deformities and exostosis. Bilateral foot pain after transplantation can be caused by polyneuropathy, osteoporosis and persistent hyperparathyroidism after transplantation. Recently, reflex sympathetic dystrophy as a rare complication of treatment with calcineurin-inhibitors has also been described as a cause of bilateral foot pain.

Case

A 46-year-old male renal transplant patient presented with severe pain in the left tarsus in November 2005. The primary renal disease was chronic glomerulonephritis. The first two renal transplants failed (repetitive episodes of acute rejection in the first, persistent thrombotic microangiopathy related to calcineurin inhibitor intake in the second) and were removed. In August 2002, a third deceased donor kidney transplantation was performed, using corticosteroids (CS, methylprednisolone, Medrol®, David Bull Laboratories Pty Ltd, Mulgrave, Australia), myco-phenolate mofetil (MMF, Cellcept®, Hoffmann-LaRoche, Basel, Switzerland), sirolimus (SIR, Rapamune®, Wyeth, Bershie, UK) and basiliximab (Simulect® Novartis, Basel, Switzerland) as induction immunosuppressive therapy. Maintenance immunosuppressive therapy consisted of CS (methylprednisolone 2 mg/day), MMF 1.5 g/day and SIR 3 mg/day, with adequate graft function (serum creatinine between 1.5 and 1.8 mg/dl, corresponding to a creatinine clearance of 45–55 ml/min and without proteinuria).

In November 2005, he first reported severe pain in the left tarsus, with great difficulty in walking. There was also a notable increase in sweat production of the left foot. He reported no trauma or injury in the recent past, and no changes in the immunosuppressive or concomitant medication was made. Clinical examination revealed soft tissue swelling of the left tarsus and the left ankle and a painful palpation of the left tarsometatarsal joints, but there were no other clinical signs of arthritis in one of more joints of the foot. There were no changes in skin colour and there was a normal articular mobility.

Laboratory test showed following results: serum creatinine 1.84 mg/dl, urea 80 mg/dl, total calcium 9.4 mg/dl (normal range 8.4–10.5), phosphate 3.0 mg/dl (normal range 2.4–4.5), parathormone 90 pg/ml (normal range 15–65), uric acid 9.1 mg/dl (normal range 3.4–7), C-reactive protein 7.2 mg/dl (normal range 0–0.7), sirolimus pre-dose level 9.1 μg/l, testosterone 329 ng/dl (normal range 230–1000), cortisol 16.4 (normal range 3.5–20), ACTH 11 pg/ml (normal range 10–60). There were no clinical or biochemical signs of thrombotic micro-angiopathy, microbial infection, endocrinopathy or systemic disease activity. Since gout could not be excluded completely on clinical and biochemical grounds, empirical treatment was started using colchicine. But even combined with allopurinol (Zyloric®, SMB Laboratories, Brussels, Belgium) 2 weeks after starting colchicine, this did not result in improved symptoms or clinical findings, despite a drop in serum uric acid level to 5.4 mg/dl.

Plain radiography of the left foot showed no fractures, albeit osteoporosis of the central tarsus. Therefore, Magnetic Resonance Imaging (MRI) was performed, showing a hyperintense signal in the tarsal
bones, the surrounding fat and muscle groups at T2-weighed images, with signal inversion at T1-weighed images (Figure 1A and B). These findings correspond with diffuse oedema of the central tarsus and the surrounding fat and muscle groups, suggesting disuse or reflex sympathetic dystrophy (RSD). There were no signs of recent fractures or avascular necrosis. A triphasic bone scintigraphy revealed increased uptake of 99mTc-Oxidronate (99mTc-HDP) in both the vascular and osseous phases in the left distal tarsus, confirming further the diagnosis of RSD (Figure 2A).

Treatment with intravenous biphosphonates (Aredia®, Novartis, Basel, Switzerland) was started, but had to be discontinued after three doses of 30 mg, due to symptomatic hypocalcaemia (total calcium 7.7 mg/dl; ionized calcium 0.97 mmol/l (normal range 1.1–1.35) and gastrointestinal intolerance (vomiting and diarrhoea) without changes in clinical presentation. Subsequently, a temporary increase of CS (methylprednisolone from 2 to 8 mg/day) for 2 weeks was attempted, despite the absence of signs of adrenal insufficiency; however, no positive effects could be noted.

As no clinical changes could be observed after more than 3 months, SIR was stopped and switched to tacrolimus (TAC, Prograft®, Fujisawa GmbH, Munich, Germany) under close monitoring of tacrolimus pre-dose levels (targeted at 6–8 ng/ml) and serum creatinine. Concomitantly, the dose of CS was increased (methylprednisolone 2 to 4 mg/day), but the dose of MMF was maintained. Surprisingly, 2 weeks after this switch, the patient reported a dramatic clinical improvement with resolution of pain, swelling and sweating. A control MRI only showed minimal oedema of the left tarsus, however, of much less intensity as compared to the first MRI.

**Discussion**

RSD (also called algodystrophy, causalgia, Sudeck’s atrophy, reflex neurovascular dystrophy and more recently, complex regional pain syndrome) is a complex syndrome, characterized by neuropathic pain, hyperaesthesia, autonomic and motor disturbances. The pathophysiological mechanism is unclear and treatment remains difficult [1]. Its aetiology is multifactorial and has been related to traumatic injury, peripheral nerve injury, coronary artery disease,
hemiplegia, pulmonary tuberculosis, antituberculous drug administration and barbiturate and other anti-convulsive drug administration. In the last few years, calcineurin-inhibitors (CsA and TAC) have also been recognized as a triggering factor of RDS [2–6]. In this context, it is also called calcineurin-inhibitor-induced pain syndrome (CIPS). CIPS is usually located in the joints of lower limbs, especially knees and ankles, in a bilateral and symmetrical distribution. This is unlike other drug-induced RSD, which affects predominantly the upper limbs and is rather unilateral. The clinical symptoms of CIPS usually appear in the early phase after transplantation (usually in the first 3 months), when the plasma levels of calcineurin inhibitors are high. Greatest improvement of the symptoms is noted when drug levels are decreased. However, other therapeutic options include calcitriol, calcitonin, biphosphonates, calcium-channel blockers (nifedipine) and steroids [7].

The patient described in this report developed a pain syndrome of the left foot, 3 years after successful renal transplantation on stable doses of Cs, MMF and SIR. The clinical, radiographic and scintigraphic findings, however, were cardinal features of RSD, as assessed by Kozin’s criteria [8]. Avascular necrosis, which may cause similar radiological signs, was not probable because of associated autonomic disturbances in combination with hyperesthesia and motor dysfunctions, the low basal dose of Cs and the rapid reversibility of symptoms after switching SIR to TAC [9]. The fact that in this patient, improvement of the symptoms only appeared when SIR was interrupted, suggests a possible relation between SIR and RSD. Although recurrence of the symptoms after re-administration of SIR would be a much stronger proof of this association, this was judged not to be ethically justifiable.

Nevertheless, RSD in this patient differed from classical calcineurin inhibitor-associated CIPS in some aspects. First, symptoms were unilateral, hence it resembles more RSD related with other (non-calcineurin inhibitor) drugs. Secondly, the temporal relationship between transplantation and the onset of the RSD is long. Moreover, the patient always had rather low SIR pre-dose levels (never exceeding 15 µg/l). Thirdly, the dose of Cs was slightly increased at the time of switching SIR to TAC from 2 mg/day to 4 mg/day, in order to avoid rejection phenomena. It was judged that this could not be ethically justifiable.

In conclusion, RSD is a known complication that might appear in renal transplant patients receiving calcineurin inhibitors. To our knowledge, this is the first report of RSD in a renal transplant patient treated with SIR. Based on the findings described in this

![Triphasic bone scintigraphy at initial presentation (A) and after discontinuation of SIR (B).](https://academic.oup.com/ndt/article-abstract/22/9/2709/1843072/2711)
report, it can be speculated that in kidney transplant patients, SIR may also associated with the development of RSD. However, additional reports are warranted to support this association.

Conflict of interest statement. None declared.

References


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