

Pain syndrome with stress fractures in transplanted patients treated with calcineurin inhibitors

Lindsey Gurin¹, Reginald Gohh² and Peter Evangelista³

¹Departments of Neurology and Psychiatry, New York University School of Medicine, New York, NY, ²Division of Hypertension and Renal Disease, Department of Medicine, Alpert Medical School of Brown University, Providence, RI, USA and ³Division of Musculoskeletal Radiology, Department of Diagnostic Imaging, Alpert Medical School of Brown University, Providence, RI, USA

Correspondence and offprint requests to: Lindsey Gurin; E-mail: lindsey.gurin@nyumc.org

Abstract

Bone disease remains a major cause of morbidity after renal transplantation. Post-transplant osseous complications include osteoporosis and osteonecrosis, both historically associated with glucocorticoids, and a newer syndrome of bone pain associated with calcineurin inhibitors. Calcineurin inhibitor-induced pain syndrome (CIPS) is a reversible etiology of lower extremity bone pain and bone marrow edema reported in patients receiving cyclosporine or tacrolimus after solid organ or bone marrow transplantation. While the syndrome's pathophysiology is unclear, bone insufficiency and epiphyseal impaction may play a role. We review the literature on this increasingly important post-transplant entity and describe a case illustrating the syndrome's key features.

Keywords: bone pain; calcineurin inhibitor-induced pain syndrome; renal transplantation; tacrolimus

Introduction

Bone disease, a frequent complication of all solid organ and bone marrow transplants, is of particular concern in renal transplant recipients due to the high prevalence of pre-transplant renal osteodystrophy and the difficulty of predicting this disease's course in the face of restored renal function and aggressive immunosuppressive therapy. Osteoporosis and osteonecrosis have long been the two major contributors to post-transplant bone complications and are thought to be due in large part to glucocorticoid therapy [1–4]. With the advent of newer immunosuppressive regimens offsetting decreased steroid doses with calcineurin inhibitors (CNIs), calcineurin inhibitor-induced pain syndrome (CIPS) has emerged as a third distinct etiology of post-transplant bone disease [1].

Thought to affect between 1 and 5% of solid organ and bone marrow transplant recipients, CIPS is characterized by severe symmetric lower extremity pain in the setting of cyclosporine A or tacrolimus therapy [1, 5, 6]. It generally has a sudden onset in the first 3 weeks to 14 months after transplant and resolves after a period of 3–18 months [1]. Pain is worse with walking and standing and is lessened with rest and elevation of the legs. Magnetic resonance (MR) imaging demonstrates bone marrow edema.

The pathophysiology of CIPS is not clear, but there is increasing support in the literature for a model in which a CNI-driven disturbance of bone metabolism contributes to epiphyseal impaction and stress fracture with subsequent marrow edema and pain [7–9]. Cyclosporine has for years been believed to affect bone metabolism; a similar linkage between tacrolimus and bone metabolism is suspected but less well documented [10]. We report a case of tacrolimus-

related CIPS presenting with bilateral calcaneal stress fractures in a renal transplant recipient, adding to the body of literature supporting CIPS as a disease of bone insufficiency that can be linked to CNIs as a class.

Case report

The patient is a 59-year-old woman with a history of end-stage renal disease of unclear etiology who underwent a second living donor kidney transplant on 7 December 2009. Approximately 6 weeks after transplantation, the patient complained of bilateral ankle and knee pain that had progressively worsened over the course of 2 weeks. She also reported lower extremity weakness that impaired her ability to climb stairs. Clinical examination revealed local tenderness over the lateral malleolus of the left ankle, the lateral aspect of the right knee and the medial aspect of the left knee with no associated erythema or swelling. The patient's immunosuppressive therapy included tacrolimus 1 mg twice daily, prednisone 10 mg daily and mycophenolic acid 720 mg twice daily, with a tacrolimus level of 5.6 ng/mL.

The etiology of the patient's joint pain was unclear and was managed conservatively. Her lower extremity weakness was suspected to be prednisone-related, and prednisone was decreased to 5 mg daily. Her tacrolimus dose was raised to 2 mg twice daily, with a goal of maintaining serum levels of 7–8 ng/mL.

The patient returned 1 week later complaining of a severe increase in her bilateral foot pain that occurred following the increase in her tacrolimus dose. She also reported increasing difficulty walking and presented to clinic in tears due to pain. Clinical exam showed tenderness to palpation of the right heel and the lateral aspect of the right knee

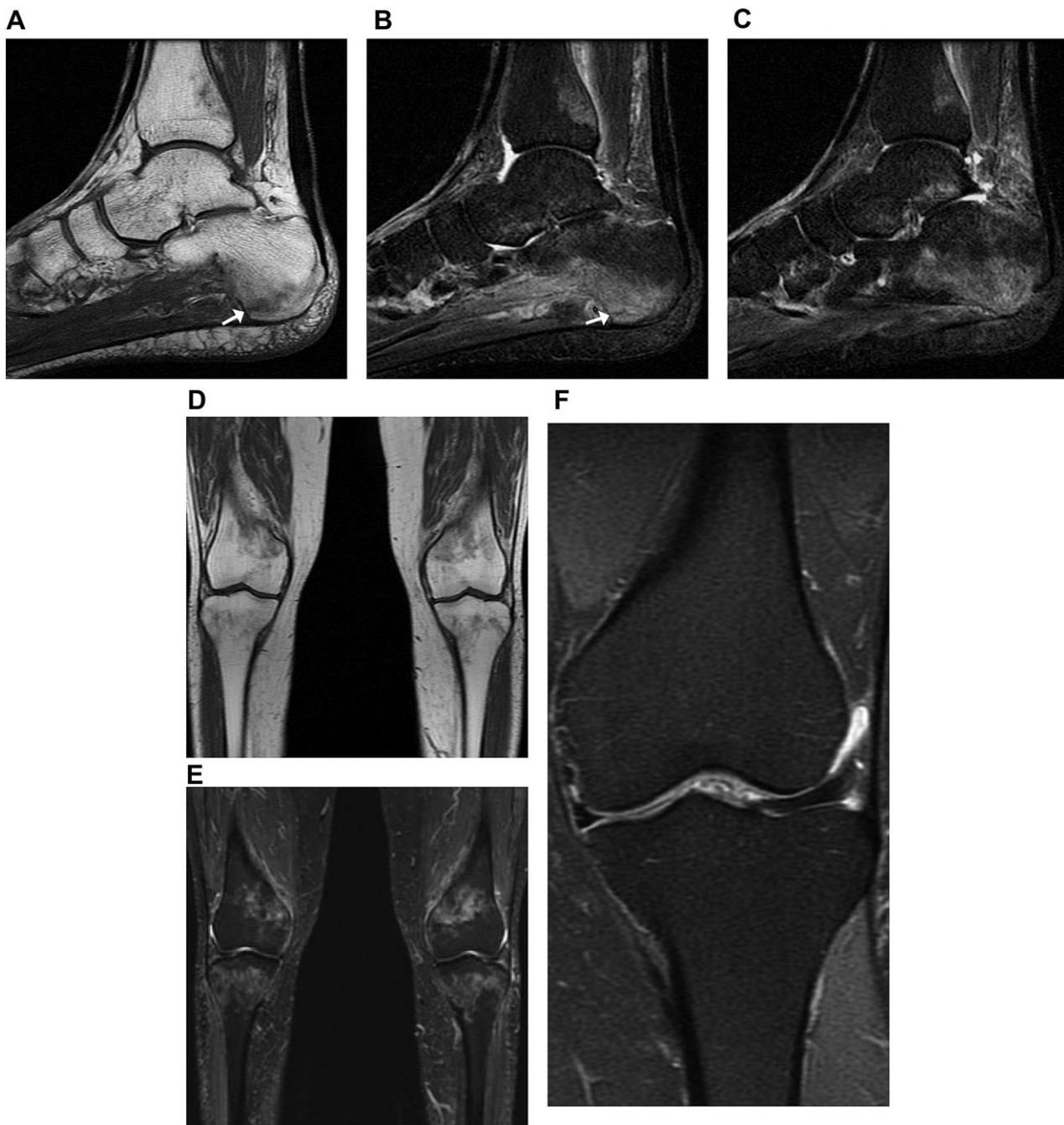


Fig. 1. A 59-year-old woman post-renal transplant with bilateral knee and ankle pain. Sagittal T1 (A) and sagittal STIR (B) of the left ankle, sagittal STIR of the right ankle (C), coronal T1 (D) and STIR (E) of the bilateral knees demonstrates patchy marrow edema in the bilateral calcanei, talus, distal femora and proximal/distal tibia. In addition, an incomplete left calcaneal stress fracture is demonstrated (arrow in A, B). A normal MR imaging of the knee (F) is shown for comparison.

and minimal tenderness of the left heel. There was no erythema or swelling. Her tacrolimus level at this time was 4.0 ng/mL; her labs were otherwise remarkable for hematuria and for elevated calcium and parathyroid hormone levels of 2.8 mmol/L (11.2 mg/dL) and 833 ng/L (833 pg/mL), respectively.

The patient's lower limb pain was suspected to be due to tacrolimus and the decision was made to convert to sirolimus.

MR imaging of the patient's ankles 2 weeks later revealed bilateral calcaneal incomplete stress fractures, in addition

to patchy areas of bone marrow edema in the medial talar head and posterolateral tibia (Figure 1A–C). MR imaging of the patient's knees also revealed patchy areas of marrow edema involving the bilateral distal femoral and proximal tibial metaphyseal regions (Figure 1D and E). These findings, in the setting of tacrolimus therapy, were consistent with a diagnosis of CIPS.

The patient showed that initial clinical improvement after tacrolimus was discontinued and sirolimus initiated for immunosuppression. Unfortunately, she suffered a massive intracerebral hemorrhage several weeks later while

receiving warfarin therapy for a history of hypercoagulability and passed away soon thereafter. No further imaging was obtained.

Discussion

Cyclosporine as a possible etiology of post-transplant bone pain distinct from osteoporosis and osteonecrosis was first described in 1989 [11]. Cases of distal limb pain in organ transplant recipients treated with cyclosporine were reported throughout the 1990s [9, 12, 13], and the first case linked to tacrolimus was reported in 1999 [6, 14–18]. The syndrome has since been documented in patients receiving cyclosporine or tacrolimus for bone marrow and stem cell transplants, in addition to solid organ recipients [5, 19–21]. Several cases have also been reported in patients receiving CNI therapy for reasons other than allograft transplantation including psoriatic arthritis [22], Crohn's disease [23] and ulcerative colitis [24].

The syndrome is so named for its apparent association with cyclosporine and tacrolimus, but not with azathioprine or mycophenolate [8]. CNI trough levels may be high or normal, and pain was correlated to elevated trough levels in some studies [8, 14] but not in others [10, 25]. Most patients experience symptomatic improvement with reduction of CNI levels [6]. Some authors have reported success alleviating CIPS pain with dihydropyridine calcium channel blockers [3, 8], though other studies have failed to confirm this effect [10].

The classic radiologic signs of CIPS include patchy osteoporosis on radiographs (though they are often normal); patchy bone marrow edema on MR imaging and increased uptake on radionuclide bone scintigraphy, particularly involving the knees, ankles and feet [3, 6, 8]. While the pathophysiology of CIPS is not yet entirely known, some authors have posited bone insufficiency and impaction of epiphyseal cortical bone as an etiology of these reversible radiologic findings [7, 9]. In this model, high bone turnover induced by CNI therapy leads to impaction or fracture with accompanying marrow edema [16].

The issue of whether or not CNIs truly play a significant role in bone remodeling is somewhat controversial, though it is generally accepted that cyclosporine does have some direct effect on bone metabolism [10]. Gain- and loss-of-function experiments in gene-modified mice and rats suggest a critical role for calcineurin in osteoblast and osteoclast formation [26]. Early studies showed an association between elevated blood alkaline phosphatase levels and cyclosporine-based, but not azathioprine-based, immunosuppressive regimens, and a more recent study demonstrated a correlation between elevated alkaline phosphatase and likelihood of developing CIPS [25]. These data are supported by animal models demonstrating a link between CNIs and high-turnover bone disease. Other studies, however, have not shown a link between CNIs and increased bone turnover, and the relationship remains to be further defined [25].

A second proposed hypothesis implicates CNIs in a disturbance of the vascular supply to bones, with changes in perfusion and permeability leading to marrow edema [8, 27]. In this explanation, lower limbs and feet are preferentially affected due to the increased venous pressure resulting from standing upright; elevation of the legs relieves this pressure and subsequently lessens pain [8].

While some of the radiologic features of CIPS are also shared by osteonecrosis and reflex sympathetic dystrophy

(RSDS), these latter post-transplant bone pain syndromes differ significantly in clinical course. Osteonecrosis pain is permanent, weight-dependent and usually localized to the hips; CIPS, on the other hand, is typically reversible and preferentially affects feet and knees [8]. RSDS is distinguished clinically from CIPS by its asymmetric pain distribution, its upper limb predominance and its characteristic association with extremity edema, vasomotor instability and trophic skin changes [6, 8].

Our patient's clinical presentation of lower extremity pain that worsened after increase of her tacrolimus dose and that was accompanied by bone marrow edema on MR imaging, strongly suggests CIPS. Her bilateral calcaneal insufficiency-type stress fractures further suggest a derangement of bone metabolism.

Treatment for CIPS currently involves reducing CNI doses, even when trough levels are within the normal range [6]. Exchanging cyclosporine for tacrolimus (or vice versa) was not effective in one study [25]. Dihydropyridine calcium channel blockers have alleviated symptoms in some patients [8]. Many patients report improved symptoms at rest and with elevation of the legs, and some authors have advocated strict avoidance of physical strain as a way to avoid trauma and subsequent impaction or insufficiency fracture of fragile bone [10]; our experience corroborates this.

Conclusions

There are numerous contributors to abnormal bone metabolism in end-stage renal disease and transplant, and kidney recipients are more prone than recipients of other solid organ transplants to fractures of the appendicular skeleton and feet [28]. CIPS, however, represents a potentially reversible etiology of lower extremity bone disease in transplant recipients and as such deserves greater recognition. Our patient's experience provides further support for CIPS as a distinct post-transplant bone disease entity that may be induced by either cyclosporine or tacrolimus.

Conflict of interest statement. None declared.

References

1. Grotz W, Breitenfeldt K, Cybulla M. Immunosuppression and skeletal disorders. *Transplant Proc* 2001; 33: 992–993
2. Morales E, Gutierrez E, Andres A. Treatment with calcimimetics in kidney transplantation. *Transplant Rev* 2010; 24: 79–88
3. Elder GJ. From marrow oedema to osteonecrosis: common paths in the development of post-transplant bone pain. *Nephrology* 2006; 11: 560–567
4. Casez JP, Lippuner K, Horber FF *et al.* Changes in bone mineral density over 18 months following kidney transplantation: the respective roles of prednisone and parathyroid hormone. *Nephrol Dial Transplant* 2002; 17: 1318–1326
5. Nishikawa T, Okamoto Y, Tanabe T *et al.* Calcineurin-inhibitor-induced pain syndrome after a second allogeneic bone marrow transplantation for a child with aplastic anemia. *Pediatr Transplant* 2009; 13: 641–644
6. Collini A, De Bartolomeis C, Barni R *et al.* Calcineurin-inhibitor induced pain syndrome after organ transplantation. *Kidney Int* 2006; 70: 1367–1370
7. VandeBerg BC, Malghem J, Goffin EJ *et al.* Transient epiphyseal lesions in renal transplant recipients: presumed insufficiency stress fractures. *Radiology* 1994; 191: 403–407

8. Grotz WH, Breitenfeldt MK, Braune SW et al. Calcineurin-inhibitor induced pain syndrome (CIPS): a severe disabling complication after organ transplantation. *Transpl Int* 2001; 14: 16–23
9. Goffin E, vande Berg B, Pirson Y et al. Epiphyseal impaction as a cause of severe osteoarticular pain of lower limbs after renal transplant. *Kidney Int* 1993; 44: 98–106
10. Hetzel G, Malms J, May P et al. Post-transplant distal-limb bone-marrow oedema: MR imaging and therapeutic considerations. *Nephrol Dial Transplant* 2000; 15: 1859–1864
11. Bouteiller G, Lloveras J, Condouret J et al. Painful polyarticular syndrome probably induced by cyclosporin in three patients with a kidney transplant and one with a heart transplant. *Rev Rhum Mal Osteoartic* 1989; 56: 753–755
12. Naredo Sánchez E, Balsa Criado A, Sanz Guajardo A et al. Leg bone pain syndrome due to cyclosporine in a renal transplant patient. *Clin Exp Rheumatol* 1994; 12: 653–656
13. Jagose J, Bailey R, Hughes T. Acute bone-marrow oedema in cyclosporin-treated renal transplant recipients. *QJM* 1997; 90: 359–366
14. Villaverde V, Cantalejo M, Balsa A et al. Leg bone pain syndrome in a kidney transplant patient treated with tacrolimus (FK506). *Ann Rheum Dis* 1999; 58: 653–654
15. Malat G, Dupuis R, Kassman B et al. Tacrolimus-induced pain syndrome in a pediatric orthotopic liver transplant patient. *Pediatr Transplant* 2002; 6: 435–438
16. Franco M, Blaimont A, Albano L et al. Tacrolimus pain syndrome in renal transplant patients: report of two cases. *Joint Bone Spine* 2003; 71: 157–159
17. Goffin E, vande Berg B, Devogelaer J et al. Post-renal transplant syndrome of transient lower limb joint pain: description under a tacrolimus-based immunosuppression. *Clin Nephrol* 2003; 59: 98–105
18. Puig I, Mari JM, Martinez-Miralles E, Perich X et al. Reflex sympathetic dystrophy syndrome of the lower limbs in a renal transplant patient treated with tacrolimus. *Transplantation* 2000; 70: 210–211
19. Kida A, Ohashi K, Kobayashii T et al. Incapacitating lower limb pain syndrome in cord blood stem cell transplant recipients with calcineurin inhibitor. *Pathol Oncol Res* 2004; 10: 204–206
20. Noda Y, Kodama K, Yasuda T et al. Calcineurin-inhibitor-induced pain syndrome after bone marrow transplantation. *J Anesth* 2008; 22: 61–63
21. Lavoratore S, Navarro O, Grunebaum E et al. Cyclosporine-induced pain syndrome in a child undergoing hematopoietic stem cell transplant. *Ann Pharmacother* 2009; 43: 767–771
22. Lawson C, Fraser A, Veale D et al. Cyclosporin treatment in psoriatic arthritis: a cause of severe leg pain. *Ann Rheum Dis* 2003; 62: 489
23. Isaacs K. Severe bone pain as an adverse effect of cyclosporin therapy for Crohn's disease. *Inflamm Bowel Dis* 1998; 4: 95–97
24. Rahman A, O'Brien C, Patchett S. Leg bone pain syndrome in a patient with ulcerative colitis treated with cyclosporin. *Ir J Med Sci* 2007; 176: 129–131
25. Tillmann F, Jäger M, Blondin D et al. Post-transplant distal limb syndrome: clinical diagnosis and long-term outcome in 37 renal transplant recipients. *Transpl Int* 2008; 21: 547–553
26. Tamler R, Epstein S. Nonsteroid immune modulators and bone disease. *Ann N Y Acad Sci* 2006; 1068: 284–296
27. Breitenstein A, Stumpe K, Gnannt R et al. Calcineurin inhibitor-induced pain syndrome after kidney transplantation—a rare but disabling condition. *NDT Plus* 2010; 4: 63–66
28. Bia M. Evaluation and management of bone disease and fractures post transplant. *Transplant Rev* 2008; 22: 52–61

Received for publication: 4.7.11; Accepted in revised form: 13.10.11