Tacrolimus induced bone pain syndrome after kidney transplantation: case report and review of the literature

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ABSTRACT
Objective: To present a case of calcineurin inhibitor-induced bone pain syndrome. Case report: A 54-year-old Caucasian male patient underwent a haploidentical kidney transplant and, at the end of the third postoperative month, developed severe, spontaneous, symmetrical pain in his knees, ankles, and feet, associated with functional impairment, induced by calcineurin inhibitors. The diagnosis was confirmed by MRI and bone scan. Evolution: The patient presented spontaneous remission of symptoms at the end of the sixth postoperative month. Conclusion: Calcineurin inhibitor-induced bone pain syndrome is an uncommon clinical condition, but it can impair the quality of life and good evolution of transplant recipients. Correct and prompt diagnosis with MRI and bone scan is recommended.

Keywords: tacrolimus, cyclosporine, renal transplant, bone pain, calcineurin inhibitors.

INTRODUCTION
The use of calcineurin inhibitors to prevent graft rejection has increased over the last 30 years, leading to an increase of the incidence of complications.

Bone pain syndrome of the lower limbs was described in the 1990s and, initially, it was related with the use of cyclosporine in solid organs transplantation. Later, it was also described in association with tacrolimus in bone marrow transplants.

Calcineurin inhibitor-induced pain syndrome is a rare complication, and it is characterized by the development of severe, spontaneous, bilateral pain affecting the knees, ankles, and feet, and it is often associated with functional impairment, which usually develops in the first six months post-transplant.

Case report
A 54-year-old male patient, physician, with end-stage renal disease (ESRD) of unknown etiology, residing in Curitiba, Paraná, Brazil, received a haploidentical transplant from a living donor and was treated with prednisone, 0.6 mg/kg/day, sodium micophenolate, 720 mg bid, and tacrolimus, 0.13 mg/kg/day, as well as basiliximab on the first and fourth postoperative days. He was discharged on the sixth postoperative day with a creatinine level of 1.3 mg/dL and normal blood pressure levels.

At that time, the patient had a tacrolimus blood level of 26.2 ng/mL. The dose of tacrolimus was reduced to 0.10 mg/kg/day, with a reduction in blood levels to 6.6 ng/mL. The creatinine level was maintained at 1.19 mg/dL, and simvastatin, 20 mg/day, for hypercholesterolemia was instituted.

At the end of the second postoperative month, the creatinine level rose to 1.82 mg/dL and one week later it reached 2.86 mg/dL. The dose of tacrolimus was reduced once more, reaching 0.08 mg/kg/day, and the creatinine level stabilized around 1.0 mg/dL with a tacrolimus level of 8.0 ng/mL.

At the end of the third month, the patient developed pain in the left knee. After a few days, the pain became bilateral, severe, and the patient had walking difficulty, especially when climbing or going down stairs. Although the pain showed some relief with rest, it was persistent, even at night. He complained of a feeling of increased knee volume, which did not improve with regular analgesics. He then developed pain in the dorsal area of the feet and in the ankles, with greater functional incapacity. The joints did not show signs of inflammation, only pain on palpation.

Determination of C-reactive protein was normal; PTH = 159 pg/mL; LDH normal; uric acid = 5.33 mg/dL; rheumatoid factor test
normal; ESR = 5 mm; and antinuclear antibodies negative. Serum creatinine was maintained around 1.0 mg/dL, and plasma level of tacrolimus was 8 ng/mL.

Magnetic resonance imaging (MRI) of the left knee showed moderate articular effusion with subchondral damage in the medial femoral condyle (Figure 1) associated with an extensive area of edema in the adjacent trabecular bone (Figure 2). Bone scan showed an increase in isotope concentration in the medial and lateral condyle of both femurs, in the lateral aspect of the right tibial plateau, and tarsal bones (Figure 3).

Pain persisted until the middle of the fourth postoperative month, when it decreased progressively and had practically disappeared at the end of the sixth postoperative month.

**DISCUSSION**

We reported a case of calcineurin inhibitor-induced bone pain syndrome in a patient after renal transplant. This is a rare syndrome first described in 1991 in patients with cyclosporine-induced immunosuppression.1 Severe pain in knees, ankles, and feet that improves with rest is the main symptom. Patients have normal physical exam except for pain on palpation of the affected areas, without signs of inflammation.1,5,7

The patient described here developed nephrotoxicity with elevated levels of tacrolimus before the onset of symptoms. Serum creatinine reached 2.8 mg/dL, but it returned to normal levels after reduction of the drug dose.

**DIAGNOSIS**

Bone necrosis or aseptic necrosis affecting post-transplant patients who received high doses of corticosteroids is the main differential diagnosis.10 In those cases, pain is usually proximal, and spontaneous resolution of the damage is not seen.

Neuropathic complications affect up to 20% of post-transplant patients who received cyclosporine or tacrolimus, including dizziness, tremors, dysesthesia, changes in mental status, and encephalopathy, among other symptoms.4 Similar findings can also be seen in reflex sympathetic dystrophy, but the increase in temperature in the affected areas and changes in skin color seen in those cases differentiate it from calcineurin inhibitor-induced pain syndrome. Other signs of dystrophy include dysesthesia, autonomous nervous system instability, with vasomotor and sweating changes, and it is usually unilateral.11,12

Besides the clinical presentation, MRI and bone scan are fundamental for the diagnosis.19 Bone marrow edema where symptoms began is the most characteristic MRI
finding. In our patient, the test was directed to the left knee, where symptoms started, and the femoral bone marrow was not investigated. But the results of the exam are compatible with this syndrome: intra-articular effusion and soft tissue edema. The bone scan was identical to those described in the literature: bilateral and symmetrical increased capture in the femoral epiphysis and tarsal bones,\textsuperscript{8,9} which did not leave room for diagnostic doubts.

Increased levels of alkaline phosphatase and calcium before the onset of symptoms in most patients have been reported.\textsuperscript{5,7,19}

**Pathophysiology**

The relationship between the pathogenesis of the syndrome and cyclosporine or tacrolimus is controversial,\textsuperscript{4} since similar symptoms were reported before calcineurin inhibitors were available, and its development would be related with the presence of microfractures caused by microtraumas in the weakened bone that supports greater post-transplant physical activity.\textsuperscript{16,17} However, the coincidental development of pain and increased serum levels of calcineurin inhibitors in the first few months post-transplant, and the absence of the syndrome in patients who use other immunosuppressive drugs indicate a causal relationship with calcineurin inhibitors.

Possible pathophysiological mechanisms implicated in this syndrome include drug-induced vasoconstriction leading to intraosseous ischemia followed by local accumulation of adipose cells and bone marrow edema, which contributes for the development of a compartment syndrome.\textsuperscript{13,4}

**Treatment**

In this syndrome, symptoms are frequently incapacitating and they do not respond to different types of analgesics. In all literature reports, as well as with our patient, the syndrome subsided spontaneously, without sequelae, in a few weeks to months.

It has been reported, although without consistent results, that calcium channel inhibitors interfere with the bone marrow edema, improving symptoms by antagonizing the vasoconstrictor effects of calcineurin inhibitors.\textsuperscript{13} The discontinuation or reduction in the dose of immunosuppressive medication do not influence improvement of the symptoms in most studies published.\textsuperscript{1,7,14} Non-steroidal anti-inflammatory drugs are not effective. Recent reports on the use of iloprost, a prostacyclin analogue with vasodilator action, showed that it could lead to improvement of the symptoms in a few days.\textsuperscript{20} Our patient was treated only with common analgesics and, although pain was incapacitating for some time, it resolved spontaneously after 90 days.

**Conclusion**

We emphasize that serum levels of alkaline phosphatase should be monitored in the first 6 months post-transplant in all patients treated with calcineurin inhibitor and, if they develop pain in the knee or feet, early MRI and bone scan should be done to assure the correct diagnosis.

**References**

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