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LETTER TO THE EDITORS

Calcineurin-inhibitor induced pain syndrome in a lung transplant patient

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Dear Sirs,

The increasing number of transplant patients has changed the spectrum of the diseases encountered by the physicians. Calcineurin inhibitors (CIs) such as cyclosporine and tacrolimus, play a central role in the success of a transplanted organ. However, these agents are highly toxic and are associated with a variety of adverse effects including musculoskeletal pain syndrome [1–3]. CIs have recently been implicated as the causative agents for the post-transplant pain syndrome [4,5]. In 2001, Gortz *et al.* [5] coined the term Calcineurin-inhibitor pain syndrome (CIPS) for this pain syndrome. It is important to recognize this entity early, as in some patients it leads to significant morbidity in the affected patient [6]. We describe here, the first case of CIPS occurring in a post lung transplant patient.

A 34-year-old Caucasian male, after 8 years of bilateral lung transplantation for cystic fibrosis, presented with intractable joint pain of 3 months duration. Pain was severe in intensity and was present in bilateral ankles, knees, elbows, and the right shoulder. It was symmetrical, sharp, stinging, and intermittent that got worse when standing or walking, making ambulation difficult. Patient did not report any associated tingling, numbness, fever, joint edema, stiffness or rash. Examination revealed moderate distress because of pain, marked tenderness in any active or passive joint movement in ankles, knee, and hip joints. Examination of the joints had to be aborted as patient refused to cooperate because of the pain. Neurological examination revealed no obvious sensory or motor deficits. Patient was currently taking tacrolimus (3 mg in morning and 2.5 mg in evening) along with prednisone 5 mg daily as immunosuppressive therapy. In addition to cystic fibrosis, he also had pancreatic insufficiency, diabetes mellitus, renal insufficiency, gastroparesis, hypertension, depression, and sinusitis. The laboratory data revealed a normal tacrolimus trough level of 10.4 ng/ml (5-20 ng/ml). A comprehensive work to evaluate joint pain for rheumatologic diseases, porphyria, and neuropathy was inconclusive. Radiographs of the involved joints were normal. The bone scintigraphy scan showed increased tracer uptake bilaterally in the ankle, knee (along with tibial shaft), hip joints, and shoulder (Fig. 1a). The magnetic resonance imaging (MRI) of the bilateral hips and ankles revealed marrow edema that was extending into the shaft of the femora (Fig. 1b and c). A triad of unremarkable radiographs, increased uptake on bone scintigraphy, and bone marrow edema on MRI supported the diagnosis of CIPS. Along with the supportive care, pain control, the dose of the tacrolimus was reduced to the half of his current dose and amlodipine 5 mg was also started. This led to the rapid improvement in his symptoms. His repeat tacrolimus level was 7.8 ng/ml after stopping tacrolimus. Within 3 months, he was able to ambulate without any pain or residual disability.

In summary, CIPS is a rare entity occurring in 1% of solid organ transplant patients [5]. Lucas *et al.* [4] described a musculoskeletal pain syndrome for the first time after the initiation of calcineurin inhibitor therapy that disappeared after the discontinuation of cyclosporine in renal transplant patients. This pain syndrome remained uncharacterized until Grotz *et al.* [5] highlighted the three typical radiological signs: (i) normal initial radiograph, (ii) increased tracer uptake on the bone scintigraphy, and (iii) bone marrow edema on MRI leading to conceptualization of CIPS. All three of these findings were observed in the patient described here. Pain in CIPS is usually symmetrical with no skin changes, episodic, and self-limiting. CIPS is reversible and is associated with CIs. Our patient developed avascular necrosis of his bilateral hip joints secondary to the prolonged corticosteroid therapy; however, at the same time he had symptoms affecting other joints along with radiological findings to support the diagnosis of CIPS.

The onset of CIPS is variable. It has been d as early as 3 days following the intravenous infusion of cyclosporine [7] and as late as 8 years, as seen in our patient. Similarly, association with the trough levels of the CIs is variable too. There are reports, which showed its association with elevated trough levels of the CIs [5,8–10]; nevertheless, there is an accumulating evidence to suggest an association with the normal therapeutic levels [11,12]. A proposed hypothesis of the pathogenesis of CIPS is shown in the Fig. 1d [5,13,14]. To date, there is no specific therapy for

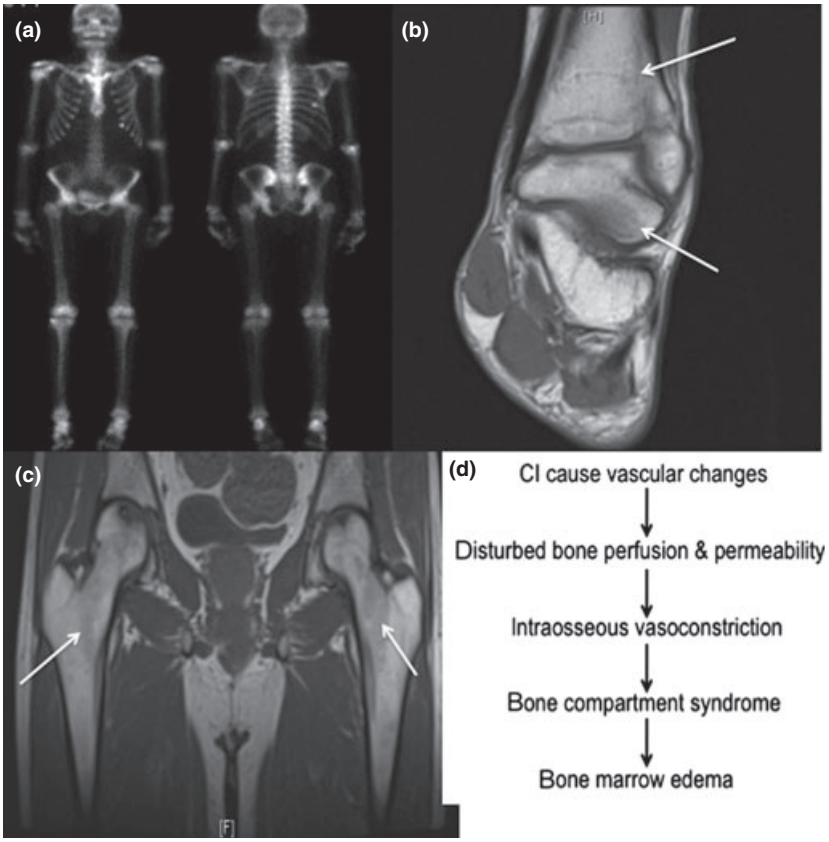

Figure 1 (a) Bone scintigraphy image showing increased tracer uptake in ankles, knees (along with tibial shaft), and hip joints. Increased tracer uptake is also seen in both the shoulders. (b) Magnetic resonance imaging (MRI) of the ankle showing increased bone marrow edema (marked by arrows) in the lower end of fibula, talus and calcaneum bone of the foot. (c) MRI of bilateral hip joints showing avascular necrosis in femora heads along with bone marrow edema in the femora neck and shaft (marked by arrows). (d) Proposed hypothesis of the pathogenesis of Calcineurin-inhibitor induced pain syndrome (CIPS) [5,13,14].

CIPS. Multiple reports with reducing or withdrawing the CI drug have shown inconsistent results. The ability of calcium-channel blockers to relieve the symptoms of CIPS is related to their ability to decrease vasoconstriction and bone marrow edema [15]. Suggested therapies for CIPS include elevation of legs, dosage reduction or withdrawal of CIs or use of calcium channel blockers. This strategy led to a resolution of symptoms in the case presented here. The responses to these therapies are, however, variable. CIPS symptoms generally improve over 2–4 months. Its pathogenesis is poorly understood and hence limited management options are available. Physicians managing post-transplant patients should keep a high index of suspicion for CIPS in post-transplant patients who present with debilitating joint pain.

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Conflict of interest

None.

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