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An Unusual Manifestation of Calcineurin Inhibitor-Induced Pain Syndrome in Kidney Transplantation: A Case Report and Literature Review

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Conflict of interest: None declared

Patient: Female, 23
Final Diagnosis: Calcineurin inhibitor-induced pain syndrome
Symptoms: Back pain
Medication: —
Clinical Procedure: Supportive treatment
Specialty: Transplantology

Objective: Unusual clinical course

Background: Calcineurin inhibitors (CNI) are the mainstay immunosuppressive drugs for kidney transplantation. Although they provide excellent allograft and patient outcomes, adverse effects are frequently encountered. Calcineurin inhibitor-induced pain syndrome (CIPS) is a rare adverse effect of CNI. Previous case reports with CIPS diagnosis involved incapacitating pain in the lower extremities.

Case Report: In this article, we report the first case of CIPS with severe back pain as the presenting symptom, which was correlated with a high tacrolimus trough concentration due to a drug interaction with clotrimazole troche. Magnetic resonance imaging (MRI) of the spine showed bone marrow edema, which is consistent with previous case reports. The patient's symptoms resolved within 3 weeks of the onset of pain. Treatments were symptomatic care and lowering the tacrolimus trough concentration. Pain was improved significantly with pregabalin but not with nifedipine.

Conclusions: We reviewed the literature of kidney transplant cohorts with CIPS to ascertain prevalence, pain characteristics, and treatment outcomes. Apart from our case, all patients experienced lower extremities pain and were pain-free during the follow-up period, without any residual abnormalities. CIPS is a benign but adverse effect of CNI. Counselling patients about the disease's natural history and supportive care remain the best treatment.

MeSH Keywords: Back Pain • Calcineurin • Kidney Transplantation

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Background

Calcineurin inhibitors (CNI) are currently the mainstay of immunosuppression for kidney transplantation. Both cyclosporine and tacrolimus improve allograft and patient outcomes relative to the previous era. However, the adverse effects from these medications remain problematic. Common CNI adverse effects include tremor [1], hypertension [2], post-transplant diabetes mellitus [3], and dyslipidemia [4]. Calcineurin inhibitor-induced pain syndrome (CIPS) is a less common CNI adverse effect but greatly impairs the patient's functions and abilities. CIPS symptoms include deep aching pain, usually occurring symmetrically in the lower extremities, and are associated with high levels of CNI [5]. The plain x-ray is normal, but bone scintigraphy will show increased tracer uptake in the affected bones and joints. MRI also shows patchy edema of the bone marrow. This syndrome is relatively uncommon, with a prevalence of 0.8–5.8% among kidney transplant patients [5–9]. CIPS is diagnosed by exclusion; other more common causes of musculoskeletal, neuropathic, and ischemic pain must be ruled out. In this article, for the first time, we report non-lower-extremity pain as a presenting CIPS symptom in a kidney transplant patient.

Case Report

A 23-year-old Thai woman with end-stage renal disease from lupus nephritis was on hemodialysis twice per week for 6 months at King Chulalongkorn Memorial Hospital, Thailand. She had received a kidney allograft from a 41-year-old head trauma donor in October 2017. The human leukocyte antigen (HLA) mismatches were 2-1-1 with 3% panel reactive antibodies (PRA) and crossmatch positive for B cell IgM. The perioperative period was uneventful. The induction regimens were basiliximab and methylprednisolone. She was discharged at postoperative day 10 with serum creatinine (Cr) at 1.2 mg/dl. The medications at discharge were tacrolimus 8 mg/day (tacrolimus trough concentration 4.6 ng/ml), mycophenolate mofetil 1.5 g/day, prednisolone 30 mg/day, cotrimoxazole, and acyclovir. On postoperative day 41, she visited another clinic for a systemic lupus erythematosus (SLE) follow-up and received clotrimazole troche 3 times a day for oral candidiasis prophylaxis. After taking clotrimazole troche for 2 days, she developed a severe dull aching back pain from thoracic to lumbar level, with a pain score of 10/10. The pain was aggravated by back extension and relieved with back flexion and lying down. When sitting, pain in the coccyx region was also aggravated. There was no radiation of the pain beyond the midline of the back. Painkiller medications, including acetaminophen, orphenadrine, and tramadol, were not effective. There were no neurological deficits, skin changes, or vasomotor abnormalities by physical examination. Due to the severity of her back pain and the unresponsiveness to medications, she was admitted for further investigation on postoperative day 49. She had no fever during the admission. Her laboratory investigations are shown in Table 1, and the clinical course is shown in Figure 1. The tacrolimus trough concentration was 28.2 ng/ml, rising from 9.1 ng/ml 2 weeks previously. There were no other adverse effects from tacrolimus such as tremor

Table 1. Laboratory investigations.

Labs	Values at postoperative day 35	Values at back pain presentation (postoperative day 49)	Normal range
Creatinine	1.2	1.4	0.5–1.0 mg/dl
Sodium	138	128	136–145 mEq/L
Potassium	3.8	4.3	3.5–5.5 mEq/L
Chloride	107	96	95–105 mEq/L
Bicarbonate	19	20	22–26 mEq/L
Hemoglobin	15.0	15.5	12–15 g/dl
Tacrolimus trough concentration	9.1	28.2	7–10 ng/ml
Alkaline phosphatase	64 (post-op day 10)	126	40–120 U/L
Parathyroid hormone	–	47	15–65 pg/ml
Total vitamin D (25 OH)	–	14	30–80 ng/ml
Creatinine phosphokinase	–	59	25–170 U/L
Amylase	–	85	20–100 U/L

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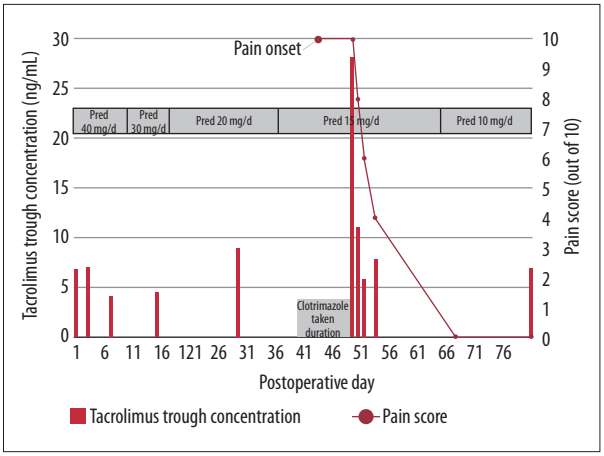

Figure 1. Clinical course.

or hypertension. Serum creatinine had risen slightly from the previous laboratory results (1.4 *vs.* 1.2 mg/dl). Plain x-ray of the back from thoracic to lumbosacral level showed neither fracture nor osteoblastic/lytic lesion. MRI of the spine revealed hypersignal intensity T2 lesions in the S4 vertebra. Faint hypersignal intensity T2 lesions were also present in T3, T4, S2, and S3 vertebrae (Figure 2). There was no fracture, osteoporosis, or osteonecrosis on the MRI. The intervertebral discs, spinal ligaments, spinal cord, nerve roots, muscle, and aorta were all normal. Although the pain site was unusual, these MRI findings along with the severe musculoskeletal pain and very high tacrolimus concentration raised suspicions of CIPS. The treatments were mainly supportive and symptomatic care. Nifedipine was given but provided no relief from the pain in her back. Subsequently, pregabalin was prescribed. The response was positive and the pain score decreased to 3/10 within 30 min after the first dose. The highly elevated tacrolimus concentration was thought to have resulted from the interaction between the clotrimazole troche and tacrolimus [10,11]. After the clotrimazole troche was discontinued, the trough concentration of tacrolimus was maintained at around 6–7 ng/ml. The patient's symptoms slowly improved and the pain was completely absent 3 weeks after onset. The patient has remained symptom-free after discharge.

Discussion and Literature Review

We report an uncommon manifestation of a rare condition. CIPS is an uncommon but debilitating adverse effect from CNI. Patients usually suffer from pain symmetrically in the lower extremities (the weight-bearing areas), particularly the feet, ankles, and knees [12]. We reviewed the literature in MEDLINE from 1966 to December 2017 and found 7 cohorts of kidney transplantation recipients with CIPS (Table 2) [5–9,13,14]. Studies with no clear CIPS diagnosis were excluded. The onset of pain usually occurs within 6 months after the use of CNI. Pain is severe and disables patients from working or performing their normal daily activities; most patients cannot walk when they have symptoms in their lower extremities. Blood CNI concentration can be elevated or within the normal range at the onset of pain. A common laboratory abnormality

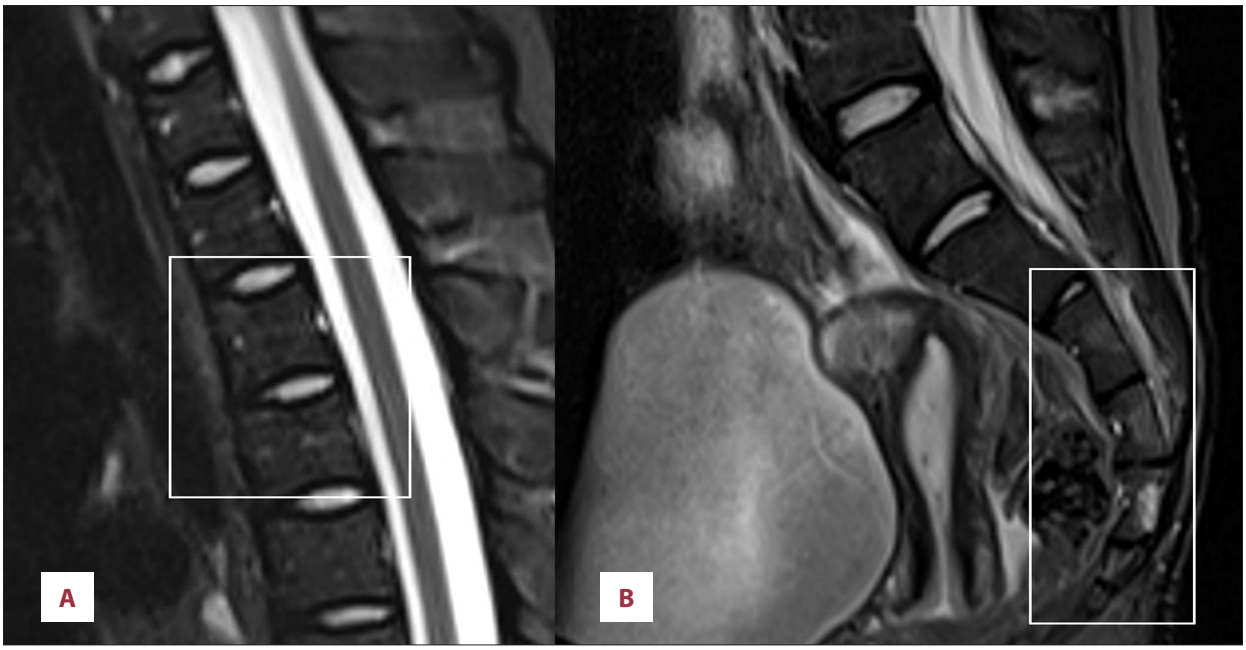

Figure 2. MRI of the thoracolumbosacral spine. (**A**) Fat-suppression T2 MRI of the thoracic spine showed faint hypersignal intensity at T3 and T4 vertebrae. (**B**) Fat-suppression T2 MRI of the lumbosacral spine showed strong hypersignal intensity at S4 vertebra and faint hypersignal intensity in S2 and S3 vertebrae.

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Table 2. Review of the kidney transplant cohorts with CIPS.

Author, year	CIPS cases/ total kidney transplant patient	CNI used	Trough concentration of CNI at pain onset (mean ± standard deviation)	Onset of lower limb pain after transplantation (mean ± standard deviation)	Treatment	Outcome
Stevens, 1995	4/386 (1%)	Cyclosporine	Not mentioned	Median 12 (8-112) weeks	Reduction of cyclosporine dose	Asymptomatic at 9±3 months post-pain onset
Grotz, 2001	8/637 (1.4%)	7 cyclosporine, 1 tacrolimus	235±25 ng/ml, 11 ng/ml	18.4±19.9 weeks	Physical rest, reduction or withdrawal of CNI, CCB	Symptoms improved after 9±5 months post- pain onset, CCB relieved pain in 2 out of 3 patients administered
Coates, 2002	4/134 (3%)	cyclosporine	240±56 ng/ml	4 weeks	Reduction of cyclosporine dose	Completely asymptomatic at 3 months post-pain onset
Goffin, 2003	5/101 (5%)	tacrolimus	9±3 ng/ml	12.4±5.3 weeks	Physical rest	Completely asymptomatic
Collini, 2006	2/243 (0.8%)	1 cyclosporine, 1 tacrolimus	168 ng/ml, 5–10 ng/mL	24 weeks, 4 weeks	Continued cyclosporine, withheld tacrolimus	Completely asymptomatic (7 months and 8 months after pain onset, respectively)
Hetzel, 2000 and Tillman, 2008	37/639 (5.8%)	30 cyclosporine, 7 tacrolimus	147±26 ng/ml, 8.8±1.7 ng/ml	23.2±19.2 weeks	Physical rest, CCB, switched cyclosporine to tacrolimus	All patients were asymptomatic at 51.6±26.6 months follow-up, switching cyclosporine to tacrolimus was not effective, 23 patients received CCB without response

is elevated alkaline phosphatase [7], which was present in our case. Imaging of the affected areas presents 3 classical findings: normal plain radiographs, increased radiotracer uptake in the affected bones and joints, and patchy areas of marrow edema on the MRI [5,15]. Our patient had severe back pain to the same degree reported for the lower limbs in the literature. The normal neurological examination, vascular examination, absence of vasomotor instability, and trophic skin changes ruled out neuropathy, vascular insufficiency, and reflex sympathetic dystrophy syndrome (RSDS), which is also related to CNI [16]. In our patient, MRI showed a strong hypersignal intensity T2 lesion in the S4 vertebra and faint hypersignal intensity T2 lesions in T3, T4, S2, and S3 vertebrae, indicating marrow edema, which is consistent with the literature. There was no fracture, avascular necrosis, spondylodiscitis, or neoplasm evident in the imaging. Our patient's history, physical examination, and imaging results led to the diagnosis of CIPS. The patient's symptoms improved after supportive care involving lowering the tacrolimus trough concentration and prescribing pregabalin.

Due to the uncommon nature of CIPS, other differential diagnoses must first be ruled out. The more common causes of pain in the extremities after transplantation are polyneuropathy, peripheral vascular diseases, avascular necrosis, fracture, inflammatory arthritis and myositis (as found in many autoimmune diseases that cause end-stage renal disease), septic arthritis, and osteomyelitis and infiltrative diseases (malignancy and dialysis-related amyloidosis) [17,18]. Another uncommon cause of the lower-extremity pain is RSDS, which is also related to CNI [19,20]. RSDS and CIPS both involve lower-extremity pain and bone marrow edema evident on MRI. However, RSDS has different clinical presentations [16]; pain is usually asymmetric and signs of vasomotor instability and dystrophic skin changes are often present. Further experimental studies are needed to investigate whether these 2 syndromes are different diseases or a single disease with the same etiology but a diverse spectrum of clinical manifestations.

To the best of our knowledge, this is the first report of CIPS with back pain as the presenting symptom rather than the canonical lower-extremity pain. The pathophysiology of CIPS

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is still under investigation; the accepted theory is that the intraosseous vasoconstrictive effect of CNI results in increased marrow pressure and edema [5]. Calcineurin is also proposed to be involved in nociceptive processes by activating the nitric oxide pathway, interfering with the cation channels of nociceptive sensory neurons, and through γ-aminobutyric acid (GABA) and *N*-methyl-D-aspartate (NMDA) receptor modulation [21]. Treatments are mainly symptomatic (Table 2) and spontaneous remission can occur. Patients are advised to rest their affected parts. Tacrolimus and cyclosporine concentration should be maintained in the normal range. There are some reports of pain cessation in response to switching CNI to mechanistic target of rapamycin (mTOR) inhibitor in patients with normal CNI concentrations [22,23]. A medication with evidence of successful treatment is the calcium channel blocker (CCB) nifedipine (or nitrendipine) [24]. However, more recent studies found CCB to be ineffective for the treatment of CIPS [7]. Recently, pregabalin has been found to successfully diminish the pain from CIPS while allowing the patient to maintain the same tacrolimus dosage [25].

Conclusions

CIPS is a rare adverse effect, which can occur even at the normal CNI trough concentration. The common pain sites are the lower extremities, but it can involve the axial bones, as reported here. Other causes of bone pain must be ruled out before the diagnosis of CIPS is made. Treatment mainly involves supportive care and reducing the CNI concentration to the normal therapeutic range. CCB has been reported to be effective, but not in a more recent study. Pregabalin might be the new drug of choice.

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Conflicts of interest

None.

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