Radiology Case Reports 19 (2024) 4024–4028

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Case Report

Calcineurin inhibitor-induced pain syndrome (CIPS) affects the hips in a renal transplant recipient: A case report ☆

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ARTICLE INFO

Article history:
Received 26 January 2024
Revised 31 May 2024
Accepted 3 June 2024

Keywords:
Calcineurin inhibitor
Calcineurin inhibitor-induced pain syndrome
Renal transplant
Immunosuppression

ABSTRACT

Calcineurin inhibitor-induced pain syndrome is a rare but debilitating complication of organ transplantation. This case report describes a man in his forties who developed bilateral hip pain, an atypical presentation of calcineurin inhibitor-induced pain syndrome, after undergoing renal transplantation. Initially, avascular necrosis was suspected as a potential cause of pain. The initial radiographs revealed no abnormalities. However, high trough levels of calcineurins and subsequent magnetic resonance imaging of the hip revealed bilateral symmetric bone marrow edema, which was consistent with calcineurin inhibitor-induced pain syndrome.

Adjustments made to the immunosuppressive regimen and multidisciplinary management resulted in an improvement in the patient's symptoms. This case report emphasizes the importance of adopting a comprehensive approach to post-transplantation pain management. Moreover, this report emphasizes the importance of considering the diagnosis of calcineurin inhibitor-induced pain syndrome while investigating and managing post-transplantation patients presenting with hip pain. Clinicians need a high index of suspicion for calcineurin inhibitor-induced pain syndrome, thereby contributing to enhanced post-transplantation care and outcomes while improving the quality of life of transplant recipients experiencing musculoskeletal pain.

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Case report

A man in his forties developed end-stage renal disease due to chronic glomerulonephritis and started undergoing hemodialysis in June 2009. A baseline liver biopsy performed before transplantation revealed chronic hepatitis B virus infection with normal liver histology. The patient also had a history of hypertension, gastroesophageal reflux disease, and gouty arthritis in the ankle and wrist, with the last

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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https://doi.org/10.1016/j.radcr.2024.06.015

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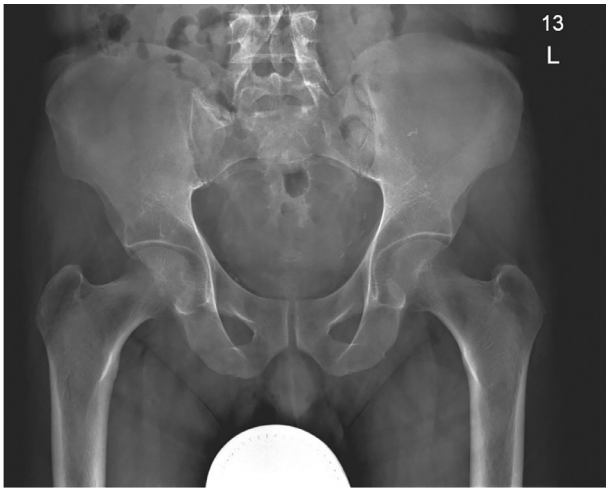

Fig. 1 – Anteroposterior radiograph of the pelvis showing normal alignment of the bones with no acute fracture or dislocation. Joint spaces and articular margins are maintained. No radiographic evidence of vascular necrosis of the femoral heads is observed.

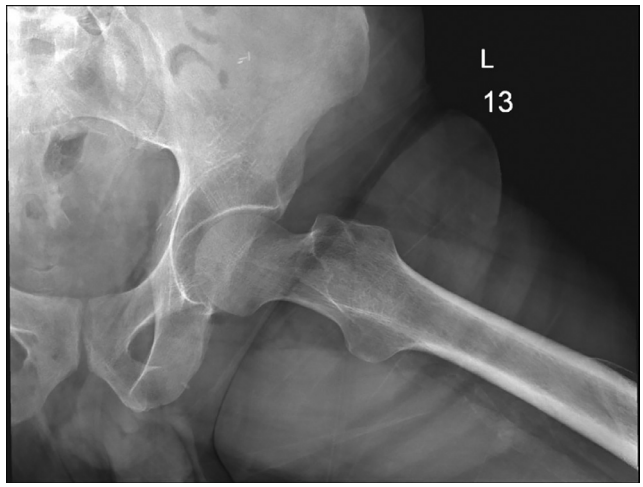

Fig. 2 – Lateral view of the left hip showing a normal alignment of the bones with no acute fracture or dislocation. No radiographic evidence of vascular necrosis of the femoral heads can be observed.

episode reported 8 years ago. The patient underwent a living-related kidney transplantation in July 2009, which failed after 7 years. Hemodialysis was resumed in late 2016, and the patient underwent cadaveric renal transplantation in November 2022. The patient was receiving several medications, including amlodipine and furosemide for hypertension; calcium carbonate and esomeprazole for gastroesophageal reflux disease; tenofovir for hepatitis B; and mycophenolate mofetil, prednisone, and tacrolimus (1.5 mg Q12H) for immunosuppression.

The patient reported experiencing intense bilateral hip and thigh pain more toward the left and myalgia approximately 4 months after the recent transplantation. A clinical examination conducted by his primary care physician revealed bilateral intense pain during movement; however, edema, redness, pyrexia, and cutaneous trophic alterations were not observed. Avascular necrosis was suspected; therefore, radiographs of the hip were acquired; however, no radiographic findings consistent with the patient's symptoms were observed (Figs. 1 and 2). Magnetic resonance imaging (MRI) of the hip revealed bilateral extensive symmetric bone marrow edema-like changes in the femoral head and neck region with a left subchondral insufficiency fracture (Fig. 3).

Initial laboratory workup revealed mild anemia (hemoglobin, 114 g/L) and an elevated alkaline phosphatase (ALP) level (175 U/L). The remaining laboratory results were within the normal ranges, including urinalysis and inflammatory marker levels.

Calcineurin inhibitor-induced pain syndrome (CIPS) was suspected based on bilateral extensive symmetric bone marrow edema-like changes, with transient osteoporosis of the hip included in the differential diagnosis. Septic arthritis, osteomyelitis, reflex sympathetic dystrophy syndrome (RSDS), and inflammatory arthritis were considered unlikely due to the absence of typical clinical features.

Blood tests revealed markedly elevated tacrolimus serum levels (17 ng/mL) (laboratory reference range 3 ng/mL considered normal low and 14.9 ng/mL normal high, above 15 ng/mL considered critically high). Since the abnormal, marked elevation of the serum trough level, a diagnosis of CIPS was made based on the patient's history, which correlated with the laboratory findings of the elevated levels of ALP and tacrolimus, as well as the MRI findings.

The immunosuppressive regimen was modified to a lower dose (0.5mg Q12h) with close trough monitoring. A multidisciplinary approach, including physical therapy and pain management via the administration of acetaminophen and physical modalities, was used to alleviate the symptoms and improve the patient's functional status.

The patient's symptoms improved significantly with management within a few weeks after the reduction in the dose, with close trough monitoring along with pain medication. The primary care physician determined that follow-up imaging was unnecessary.

Discussion

Organ transplantation, a life-saving procedure for individuals with end-stage disease, aims to extend the lifespan of patients and improve their quality of life. However, musculoskeletal pain is a common complication reported by approximately one-third of patients undergoing renal transplantation [1–3]. Pain can significantly impair the post-transplantation functioning and overall well-being of patients. Various factors, including hyperparathyroidism, polyneuropathy, bone deformities, and gout, contribute to post-transplantation musculoskeletal pain [1,4]. However, a primary cause of post-transplantation pain is using immunosuppressants, such as corticosteroids and calcineurin inhibitors (CNIs). Cyclosporine and tacrolimus are examples of CNIs administered to these

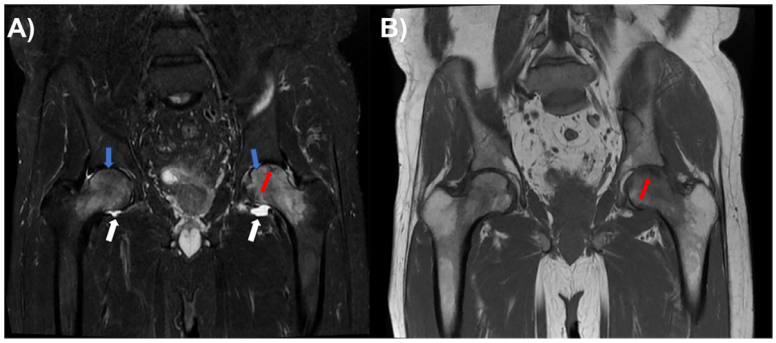

Fig. 3 – (A) Coronal short-tau inversion recovery [STIR] and (B) T1-weighted magnetic resonance images (T1WI) showing a bilateral extensive symmetric bone marrow edema-like signal within the femoral head and neck on STIR and T1WI (blue arrows). A linear hypo-intensity can be seen on the femoral head subchondral surface (red arrows) in keeping with subchondral insufficiency fracture. No flattening/collapse of the articular surface can be observed. Bilateral small hip joint effusion is higher on the left side (white arrows).

patients. These medications directly impact the metabolism and turnover of bones, leading to complications such as osteoporosis and osteonecrosis [5,6].

Corticosteroids have been widely implicated in the incidence of osteonecrosis [7,8]. CNIs are crucial immunosuppressive agents that prevent organ rejection in renal transplant recipients. Although these medications improve post-transplantation outcomes, they are also associated with bone health-related adverse effects. CIPS, a significant adverse effect of these medications, is relatively uncommon, with a prevalence of 0.8%-5.8% among patients undergoing renal transplantation [9]. Moreover, CIPS is characterized by deep aching pain that predominantly occurs symmetrically in the lower extremities and is associated with high CNI concentrations. The desired therapeutic window for tacrolimus is usually between 4 and 8 ng/mL [1]. Diagnostic imaging techniques, such as bone scintigraphy and MRI, can help identify CIPS-related changes in the affected bones and joints.

This case report presents an unusual manifestation of CIPS, a debilitating side effect linked with the use of cyclosporine and tacrolimus. CIPS is a distinct post-transplant pain syndrome; however, its underlying mechanism is not fully understood. The incidence of CIPS has been attributed to the intraosseous vasoconstrictive effect of CNIs, which increases marrow pressure and edema [9,10]. The onset of pain usually occurs within months after initiating the administration of CNIs. Severe pain prevents patients from working or performing normal daily activities, and most patients with lower extremity symptoms are unable to walk. Blood CNI concentrations may be elevated or within the normal range at the time of pain onset. However, a common laboratory finding is an elevation in ALP levels [1]. In our case, the patient presented with elevated levels of blood CNI and serum ALP.

Patients with CIPS usually experience bilateral and symmetrical pain in the lower extremities, particularly in the feet, ankles, and knees. The pain characteristically affects the distal extremities of the lower limbs [2,11]. A previous report suggested that trophic skin changes or signs of vasomotor instability are not observed in patients with CIPS and that the pain typically does not involve the hips or spine [10]. However, an unusual presentation of CIPS was reported in 2018 wherein the patient presented with severe back pain, along with a high tacrolimus trough concentration. MRI of the spine revealed bone marrow edema consistent with the findings of CIPS [9].

CIPS is characterized by a normal radiographic appearance of the affected bones, an increased tracer uptake in the affected bones and joints on bone scintigraphy, and patchy edema of the bone marrow and periarticular soft tissue visible on MRI [10]. Our patient presented with severe bilateral asymmetrical hip pain, which was more pronounced on the left side, with a normal radiographic appearance and significant bilateral symmetrical proximal femoral bone marrow edema. The left hip also showed a subchondral insufficiency fracture, which may have correlated with the increased intensity of pain on that side. To the best of our knowledge, all previous case reports, and reviews of CIPS in patients who have undergone renal transplantation involved bones around the knees or feet [12–14]. However, Li et al. reported the incidence of CIPS in 4 out of 11 patients presenting with hip pain following liver transplantation [15].

Clear guidelines or criteria have not been established for diagnosing CIPS. Therefore, it is recommended that patients receiving CNIs who present with musculoskeletal pain should undergo laboratory investigations to determine the blood CNI concentration and serum ALP levels, in addition to undergoing radiographic examinations of the hip, followed by an MRI of the pelvis and hips without intravenous contrast. Our MRI protocol included Cor STIR, Ax T1WI, and AxT2FS of the entire pelvis, with additional dedicated sequences of the symptomatic side, if required.

The differential diagnosis of post-transplant pain can be challenging, as there is substantial overlap in the pathophysiology and imaging findings between conditions such as calcineurin inhibitor-induced pain syndrome (CIPS), osteonecrosis, and transient osteoporosis. These entities can all present with similar bone marrow edema patterns on imaging, and subchondral insufficiency fractures may be seen in all three [1,2,9,16]. However, certain distinguishing features can be noted. In cases involving the hip, the bone marrow edema in transient osteoporosis tends to spread into the femoral

neck region, unlike the more localized involvement of the femoral head typically seen in other conditions [17]. Additionally, the presence of geographic-shaped bone lesions is a distinctive finding of osteonecrosis [17,18]. MRI or radionuclide bone scans, which identify areas of hyperemia and marrow edema that are often associated with soft tissue swelling and joint effusions, are generally used to confirm the diagnosis of CIPS. However, radionuclide scans may appear normal in some patients with CIPS. The pain experienced by patients with CIPS is usually associated with higher trough levels of cyclosporine or tacrolimus and tends to improve with the decrease in marrow edema. Acute hip pain may be caused by transient marrow edema in patients exhibiting bone scan and MRI features similar to those of CIPS who are not receiving CNIs [18]. Ultimately, the clinical history and laboratory markers, particularly in patients receiving calcineurin inhibitors, remain the primary discriminators in differentiating these pathologies.

The treatment of CIPS includes the management of pain, administration of calcium channel blockers and intravenous bisphosphonates, reducing the dose of CNIs, and switching between different CNI classes [12]. The management of post-transplantation pain and bone health-related complications requires a comprehensive approach. This approach balances the requirement for immunosuppression by optimizing the overall well-being and quality of life of transplant recipients. Healthcare professionals should closely monitor the dosage and duration of immunosuppressive medications and consider their effects on bone metabolism. Strategies such as dosage reduction, alternative medications, and calcium and vitamin D supplementation should also be considered [1,19].

The management of CIPS focuses on addressing the assumed etiology. The primary goal is to reduce the cyclosporine or tacrolimus trough levels, which helps provide the greatest relief of pain. This is achieved by reducing the immunosuppressive regimen and compensating with higher doses of other immunosuppressive drugs. Additionally, calcium channel blockers, preferably nifedipine or nitrendipine, are recommended as they do not inhibit the metabolism of cyclosporine or tacrolimus [1].

The effect of calcium channel blockers on CIPS (calcineurin inhibitor-induced pain Syndrome) can be explained by their ability to antagonize vasoconstriction and increased intramedullary pressure caused by cyclosporine or tacrolimus [1,20,21]. This reduction in pressure within the bone marrow helps alleviate CIPS associated pain.

Non-steroidal anti-inflammatory drugs should be avoided due to their potential adverse effects on kidney function, especially in the setting of renal transplantation and high calcineurin-inhibitor levels.

The misdiagnosis of CIPS can lead to a significant reduction in quality of life, both from the pain itself and the associated anxiety. It may also result in an increased duration of analgesic drug use. Importantly, the pain syndrome is typically resolved within a few weeks after the withdrawal of cyclosporine therapy, as demonstrated in the case of our patient [1].

In conclusion, we recommend further investigation into the correlation between elevated calcineurin inhibitor drug trough levels and the onset of CIPS pain. It would be valuable to determine the specific range of drug levels at which patients start to experience pain, as well as the relationship between CIPS and elevated alkaline phosphatase (ALP) levels. A better understanding of these associations could lead to improved management strategies and preventive measures for this debilitating complication.

Patient consent

In accordance with ethical guidelines, written informed consent for the publication of the patient's case has been obtained. The patient has been provided with a clear explanation of the purpose and nature of the publication, including the potential risks and benefits involved. They have been informed that their anonymity and privacy will be maintained to the best extent possible. The patient has voluntarily agreed to participate in the publication and have provided their consent for the disclosure and publication of their identifiable information, such as medical history, radiographs, and other relevant details. The consent process included an opportunity for the patient to ask questions and seek clarification. The patient has been assured that their decision to participate or withdraw consent will not affect their current or future care. The confidentiality of the patient and their personal information will be upheld in accordance with applicable privacy laws and regulations.

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