Clinical Imaging 53 (2019) 174–178

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Musculoskeletal and Emergency Imaging

Calcineurin-inhibitor induced pain syndrome – Magnetic resonance imaging and scintigraphic findings illustrated through two cases

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ARTICLE INFO

Keywords:
Calcineurin-inhibitor induced pain syndrome
CIPS
Post-transplant pain syndrome
Magnetic resonance imaging
MRI
Scintigraphy

ABSTRACT

Calcineurin-inhibitor induced pain syndrome (CIPS) is a condition characterized by lower extremity pain in patients receiving tacrolimus or cyclosporine therapy following organ transplantation. Through two cases, we demonstrate key imaging findings in CIPS with bone scintigraphy and magnetic resonance imaging (MRI), which are those of increased scintigraphic activity and marrow edema in the lower extremities, respectively. CIPS is an important condition that has characteristic imaging findings, but is unfortunately underappreciated in the radiology literature. To our knowledge, this is the first article in the radiology literature presenting two cases of CIPS, as well as the first to present both scintigraphic and MRI findings in this condition.

1. Introduction

Calcineurin-inhibitor induced pain syndrome (CIPS) is a condition describing reversible lower extremity pain in patients following organ transplantation. This entity was first described in 1989 based on symptoms in transplant patients treated with cyclosporine [1]. The term CIPS was introduced by Grotz et al. in 2001, who recognized that tacrolimus also played a role in pathogenesis [2]. We now know that CIPS occurs following both solid organ and bone marrow transplantation in patients treated with either tacrolimus or cyclosporine [3]. Estimates on frequency of CIPS following transplantation vary, with a range of 1.5–14% suggested [4].

CIPS was introduced to the imaging literature by Chapin et al. in 2013 [5]. Awareness of this condition across the radiology community, however, is still not widespread. We present clinical features, bone scintigraphy, and magnetic resonance imaging (MRI) findings of CIPS through two cases in an effort to promote a more advanced understanding of this entity. To the authors' knowledge, this is the first article in the radiology literature to highlight two cases of CIPS, and the first to discuss imaging findings with bone scintigraphy in addition to MRI.

2. Case 1

A 58-year-old male underwent orthotopic heart transplantation for sarcoidosis with cardiac involvement in April 2013. Approximately 10 months following transplantation, he began to experience debilitating bilateral foot pain, worse in the left foot. An infectious and rheumatologic work up was negative (rheumatoid factor and uric acid levels were normal). The immunosuppressive regimen included tacrolimus. At the onset of symptoms, trough levels peaked at 35.5 ng/dL (normal = 5–15 ng/dL). Bilateral ankle and foot radiographs were normal. An MRI of the left foot (General Electric Medical Systems, Milwaukee, WI) one month after onset of symptoms showed altered marrow signal within the bases of the third and fourth metatarsals with a superimposed fracture in the proximal aspect of the third metatarsal shaft accompanied by soft tissue edema (Fig. 1). A whole body bone scan two weeks later showed increased activity in both the flow and delayed phases situated around the tarsometatarsal joints bilaterally with additional areas of uptake in the second and fourth toes of the right foot (Fig. 2). A subsequent MRI of the right foot (General Electric Medical Systems, Milwaukee, WI) confirmed marrow signal abnormality in the medial and intermediate cuneiform bones, bases of the first and second metatarsals, as well as within the second and fourth toes, with soft tissue edema seen around the tarsometatarsal joints (Fig. 3). Treatment was initiated two months after the onset of symptoms through dose reduction of tacrolimus, concurrent transition to everolimus, and amlodipine (5 mg). Over the next five months, the patient experienced marked improvement in symptoms. The trough levels of tacrolimus steadily decreased until a new baseline of 2.5 ng/dL was achieved.

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https://doi.org/10.1016/j.clinimag.2018.10.022
Received 14 August 2018; Received in revised form 22 October 2018; Accepted 24 October 2018

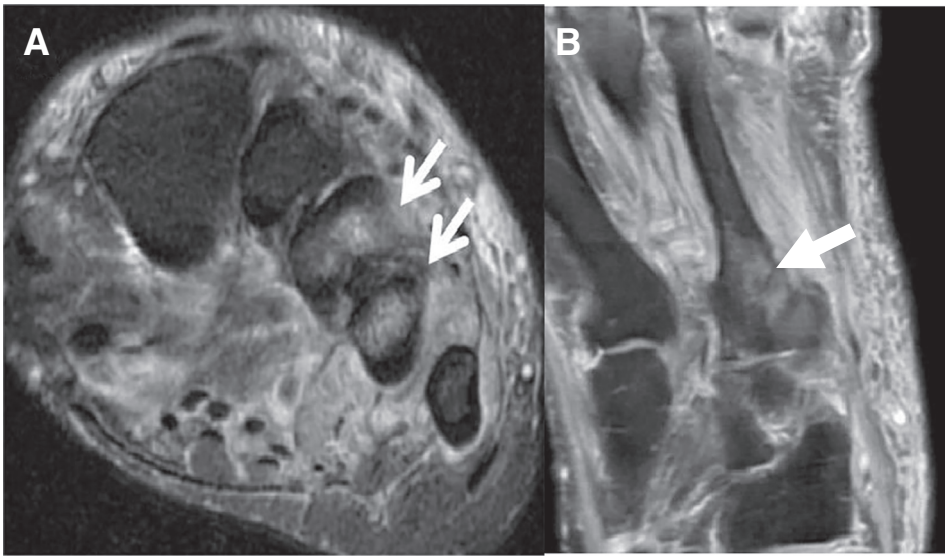

Fig. 1. Case 1 - a short axis STIR image of the left foot shows marrow edema in the bases of the 3rd and 4th metatarsals (arrows). B Long axis STIR image of the left foot reveals a fracture line proximally within the third metatarsal shaft (white arrow). Soft tissue edema accompanies marrow edema in both images.

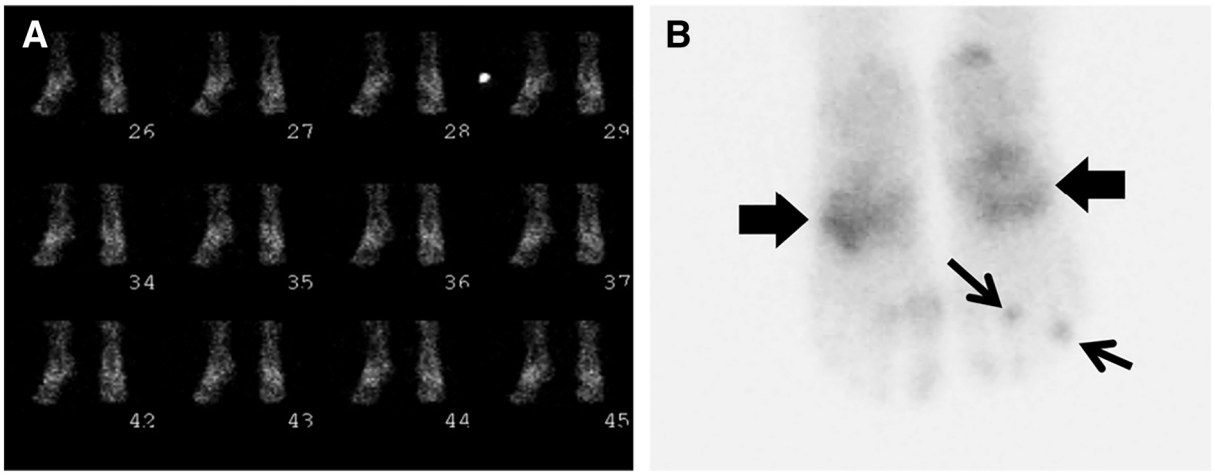

Fig. 2. Case 1 - a sequential flow images of both feet show symmetrically increased uptake around the tarsometatarsal joints. B Single planar image of both feet from the delayed phase shows symmetrically increased midfoot uptake (large arrows). Additionally, there is increased activity within the second and fourth toes of the right foot (thin black arrows).

3. Case 2

A cadaveric renal transplant was performed in April 2015 on a 43 year-old woman for failure of a previously transplanted kidney, which was originally placed in 2005 for glomerulonephritis. One month following surgery, the patient complained of progressive pain in both feet and ankles. An infectious and rheumatologic work up was negative (rheumatoid factor and uric acid levels were normal). At this time, tacrolimus levels ranged from 8.3–11.1 ng/dL. Radiographs were normal. Bilateral ankle and midfoot MRI studies (Siemens Healthcare) demonstrated symmetric marrow signal abnormality with the talus, navicular, cuboid, cuneiforms, and metatarsals (Fig. 4). Over the next several months, tacrolimus dosing was gradually decreased with concurrent introduction of sirolimus. Symptoms improved dramatically with near resolution 6 months after surgery, at which time tacrolimus levels were 3.9 ng/dL.

4. Discussion

Calcineurin-inhibitor induced pain syndrome (CIPS) is a well-known entity in the transplant literature describing reversible lower extremity pain occurring in patients following organ transplantation. Pain typically presents symmetrically, most commonly in the knees, ankles, and feet in post-transplant patients treated with either tacrolimus or cyclosporine [4]. Symptom onset can occur as soon as several weeks following transplantation or as late as 14 months following surgery and can be debilitating [5]. The frequency of CIPS is thought to range from 1.5–14% [4]. This condition was first described in 1989 based on clinical symptoms in three renal transplant patients and one cardiac transplant patient treated with cyclosporine [1]. The term CIPS was introduced by Grotz et al. in 2001, who recognized that tacrolimus also played a role in pathogenesis [2]. CIPS was first discussed in the radiology literature by Chapin et al. in 2013 [5]. Further understanding and awareness of this condition are critical for radiologists, who may be the first to suggest this diagnosis.

Two mechanisms for CIPS have been proposed: the first being increased vascular permeability resulting in increased osseous pressure and marrow edema, and the second related to alterations in bone metabolism with increased bone turnover [2]. The former theory is plausible, as essentially all documented cases of CIPS to date have occurred

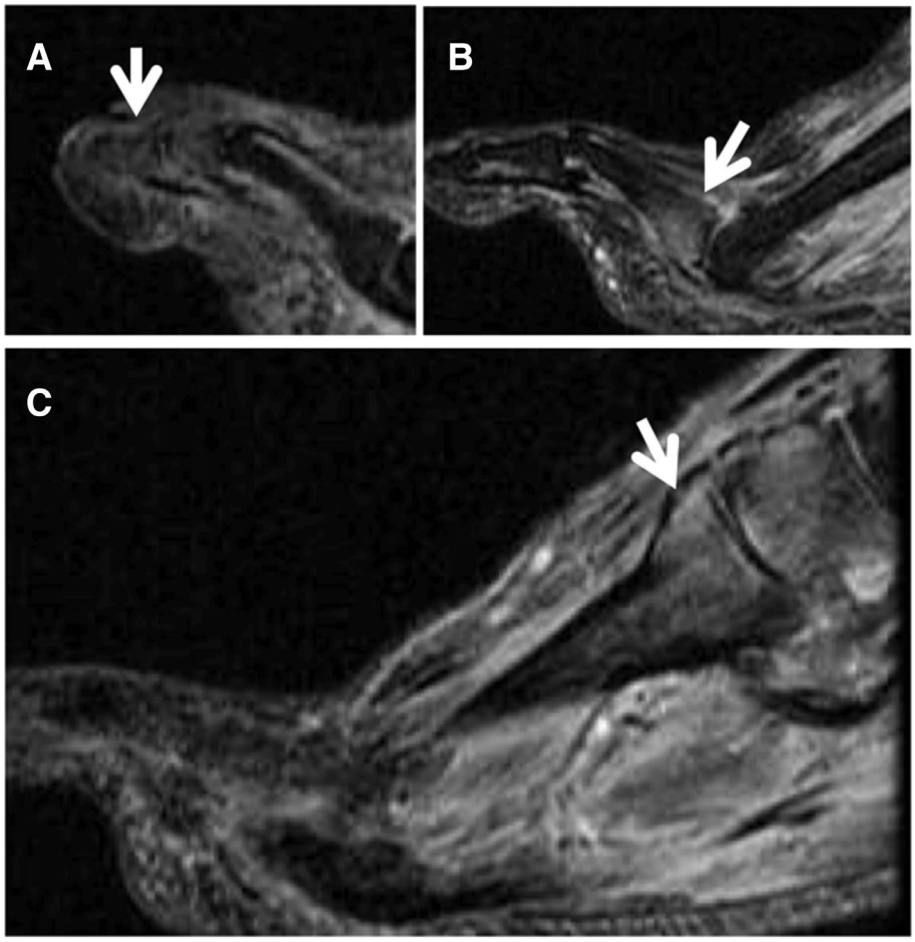

Fig. 3. Case 1 – sagittal STIR images from the right foot demonstrate marrow edema (arrows) around the fourth distal interphalangeal joint (A), within the second proximal phalanx (B), and around the tarsometatarsal joint (along with soft tissue edema) (C).

in the more distal portion of the lower extremity. The second theory is supported by a few studies that have found symptoms of CIPS to coincide with elevated levels of alkaline phosphatase [6,7]. One study documented elevated alkaline phosphatase levels in 10 out of 10 patients with CIPS over a 30-month period [11]. Alkaline phosphatase levels were not documented in our cases.

Our first clinical case of CIPS illustrates a later onset of symptoms at 10 months, which correlated with significantly elevated tacrolimus trough levels (35.5 ng/dL). Several interesting features of this case should be noted; first, the bone scan and MRI showed increased uptake and altered marrow signal, respectively, in the phalanges of the right foot. To our knowledge, no studies to date have documented imaging findings within the phalanges of the feet. Involvement of the phalanges could be explained by the proposed theory of increased vasoconstriction related to tacrolimus use and subsequent marrow congestion, which some authors suggest is more likely to occur in the more dependent portions of the lower extremity [2]. Secondly, a fracture line was also present at the base of the third metatarsal in the left foot. Superimposed fractures are not uncommon with CIPS; trabecular impaction fractures within the femoral condyles were previously reported in several cases of CIPS manifesting in the knees [6]. Additionally, before the association with calcineurin-inhibitors was elucidated, Vande Berg et al. reported on 16 renal transplant recipients with presumed epiphyseal insufficiency stress fractures [8]. Gurin et al. also demonstrated bilateral calcaneal fractures in a single case of CIPS in 2012 [7]. Lastly, our first case also demonstrates soft tissue edema accompanying marrow edema. To our knowledge, soft tissue edema in the setting of CIPS has not been discussed in depth in the literature. The presence of soft tissue edema potentially lends support to the theory of vascular permeability.

The second case illustrates an earlier onset of symptoms at 4 weeks, which is more typical of CIPS [9]. Tacrolimus trough levels in this case were normal; we now know that CIPS can also occur when tacrolimus levels are within the normal range, which is 5–15 ng/dL beyond three months following transplantation [3]. The MRI findings in this case were more typical with marrow edema centered around the tarsometatarsal joints of both feet in a strikingly symmetrical fashion.

Radiographs failed to reveal findings in our cases, which is not uncommon with CIPS. With regards to bone scintigraphy, a few studies have documented increased uptake in the delayed phase [6,10]. Our first case confirmed increased scintigraphic activity in the flow phase and delayed phase, which lends support to the proposed vascular etiology of CIPS [2]. MRI is known to be the most optimal technique for observing bone marrow changes in CIPS, which is typically relatively symmetric marrow edema most commonly seen around the knee, ankle, and midfoot [2]. This was documented in our second case.

A few studies have investigated the evolution of imaging findings in CIPS. Goffin et al. followed up radiographic, scintigraphic, and MRI finding in CIPS up to one year after cessation of symptoms and found radiographic and scintigraphic findings to have resolved in approximately 50% of patients [6]. One study found marrow edema on MRI to outlast clinical symptoms in seven of ten patients [11].

CIPS must be differentiated from osteonecrosis and insufficiency fractures, which can also be a source of pain in the post-transplant setting. Osteonecrosis is most commonly seen in the hips and is related to both the daily and cumulative dosage of corticosteroids [9]. The

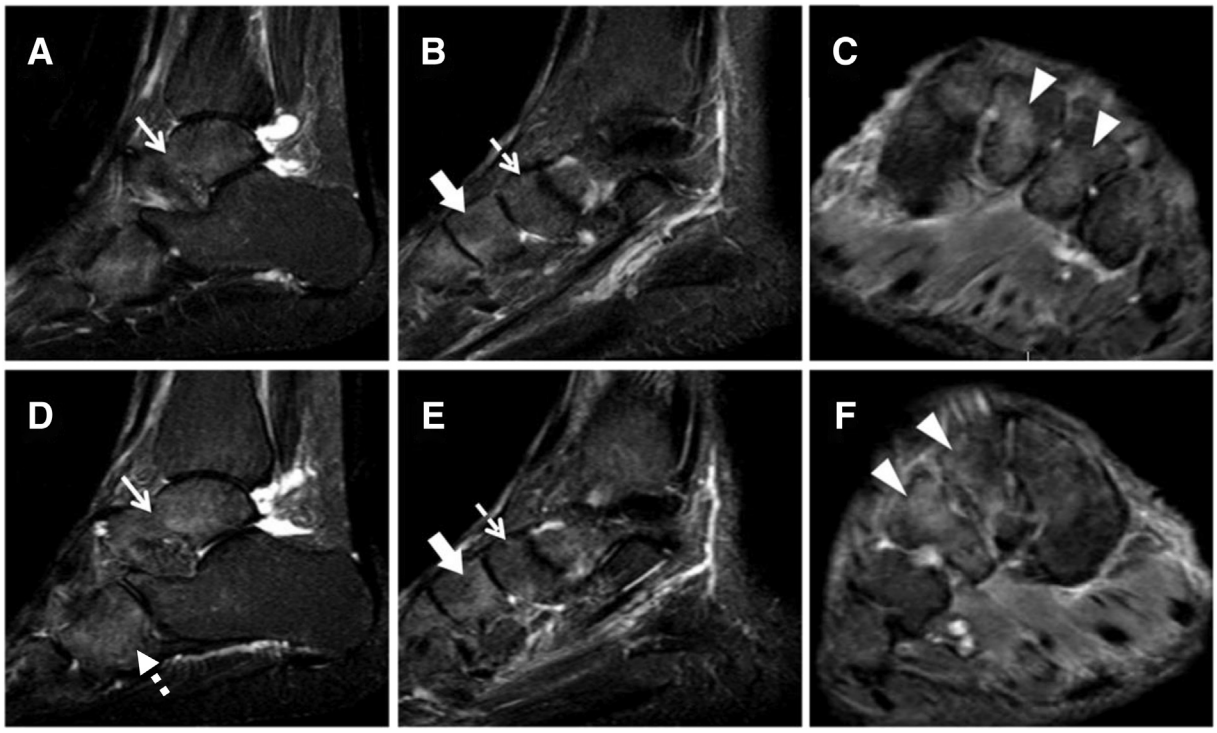

Fig. 4. Case 2 - sagittal and coronal STIR images of the left foot (A–C) and right foot (D–F) show symmetrical marrow edema in the talus (thin white arrow), navicular (dashed white arrow), medial cuneiform (thick arrow), cuboid (thick dashed white arrow), and proximal aspect of the metatarsals (arrowheads).

overall incidence of osteonecrosis following transplantation once approached 20% but has decreased dramatically to about 5% following the introduction of anticalcineurin medications [12]. With osteonecrosis, the average timing of onset tends to be later than in CIPS, usually occurring at least 18 months following transplantation [13]. Two imaging hallmarks of osteonecrosis are involvement of the immediate subchondral bone and presence of the double line sign in 65–85% of cases [14]. Important differentiating features in CIPS include a more dependent location in the lower extremity as well as relative symmetry. As discussed, insufficiency fractures can occur in the setting of CIPS; however, it is not known at this time whether these fractures precede or follow the finding of bone marrow edema. Insufficiency fractures occurring outside the setting of CIPS are usually centered within marrow edema, whereas in CIPS, marrow edema may be more extensive and even multifocal, as demonstrated in our second case.

Clinical history and imaging can also help differentiate CIPS from other entities manifesting with marrow edema on MRI, such as complex regional pain syndrome (CRPS) and inflammatory arthropathy. CRPS, also known as reflex sympathetic dystrophy (RSD), is a multifactorial condition most typically seen following trauma or surgery and can occur in the upper and lower extremities [15]. The early phase of disease usually presents with erythema and swelling of the overlying skin and soft tissues, while the chronic stage typically demonstrates atrophic changes of the skin and soft tissues [16]. In a retrospective study evaluating MRI findings in 15 patients with CRPS, marrow edema was seen in seven patients, insufficiency fractures occurred in five, and soft tissue swelling was present in a minority of cases [16]. The same study discovered marrow edema to be absent in all five cases in the chronic phase of CRPS [16]. The key differentiating features from CIPS; however, are a clinical history of surgery or trauma, occurrence in both the upper and lower extremities, and a lack of symmetry. Inflammatory arthropathy must be excluded in the work up of CIPS through serum rheumatoid factor, erythrocyte sedimentation rate, and C-reactive protein. Osseous erosions will also often accompany marrow edema in the setting of inflammatory arthropathy.

While a universal treatment for CIPS is not yet established, current strategies focus on reducing levels of tacrolimus or cyclosporine, gradual conversion to another immunosuppressant, and/or introduction of a calcium channel blocker, most often amlodipine [17]. In our first case of CIPS following cardiac transplantation, eventual relief of symptoms was seen after initiation of amlodipine. The success of this medication has also been documented in other studies [2,17], which supports the theory of altered vascular tone as the pathophysiologic cause for CIPS.

There are limitations for our study, which include a retrospective analysis, lack of a histopathological diagnosis, and no documentation of ALP levels. We acknowledge that these limitations are also present in other studies describing this entity.

In conclusion, radiologists must recognize CIPS as a cause of lower extremity pain in patients following transplantation who are treated with either cyclosporine or tacrolimus, as this condition can occur in up to 10% of transplant patients [4]. Our cases demonstrate that symptoms in CIPS may manifest soon after transplantation or may be delayed in onset. Cases may occur with elevated or normal serum levels of the implicated immunosuppressive agent [3]. Symptoms typically occur in the lower extremities, with the knees, ankles, and feet being typical locations, and are often symmetric [4]. MRI is the modality of choice in depicting symmetric marrow edema in affected areas of the lower extremities and marrow edema often outlasts the clinical symptoms [11]. Bone scintigraphy can show increased activity in both the flow and delayed phases. Therapeutic options include cessation of the offending immunosuppressant as well as initiation of calcium channel blockers [4].

Disclosures

None.

Declarations of interest

None.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Abbreviations

CIPS: Calcineurin-inhibitor induced pain syndrome
MRI: magnetic resonance imaging
ALP: alkaline phosphatase
CRPS: complex regional pain syndrome
RDS: reflex sympathetic dystrophy