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CASE REPORT

Imaging findings in a child with calcineurin inhibitor-induced pain syndrome after bone marrow transplant for beta thalassemia major

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Abstract Calcineurin inhibitor-induced pain syndrome is an entity recognized in patients on immunosuppressive therapy after transplantation. Diagnosis is characterized by onset of pain beginning in the setting of an elevated calcineurin-inhibitor trough level. Reducing the medication dose relieves symptoms. Imaging findings can be nonspecific, including bone marrow edema and periosteal reaction. We present the unique case of calcineurin inhibitor-induced pain syndrome in a child and review the imaging findings.

Keywords Bone marrow transplant · Calcineurin inhibitor-induced pain syndrome · Child · Magnetic resonance imaging · Radiography

Introduction

Calcineurin inhibitor-induced pain syndrome causes musculoskeletal pain in post-transplant patients. Musculoskeletal pain is commonly caused by osteonecrosis or steroid-induced osteoporosis, which can predispose to insufficiency fractures. In the post-transplant setting, calcineurin inhibitors, such as tacrolimus or cyclosporine, are used as immunosuppressive agents to allow the transplant to be effective. Calcineurin is a protein phosphatase that activates and stimulates growth of the T cells of the immune system. Calcineurin inhibitors suppress T cell growth and differentiation preventing the native immune system from attacking the transplant.

Calcineurin inhibitors have been shown to affect bone metabolism. Hypothesized causes of calcineurin inhibitor-induced pain syndrome include medication-induced vascular changes within the bone, causing abnormal perfusion and permeability, ultimately leading to intraosseous vasoconstriction and resultant bone marrow edema. Other proposed mechanisms include upregulating bone turnover by osteoclasts and osteoblasts, which can cause the pain seen in calcineurin inhibitor-induced pain syndrome.

We present the case of a 2-year-old girl who developed calcineurin inhibitor-induced pain syndrome after a bone marrow transplant for beta thalassemia major. Imaging characteristics of this entity will be described, as this has not been discussed in the literature to the best of our knowledge.

Case report

A 2-year-old girl, who had undergone a matched sibling bone marrow transplant for beta thalassemia major, presented to the hospital with decreased oral intake, irritability, bilateral leg pain, progressive weakness and refusal to bear weight. Her past medical history was significant for transfusion dependent beta thalassemia requiring bone marrow transplant with resulting complications including veno-occlusive disease of the liver, cytomegalovirus reactivation, and *Escherichia coli* (*E. coli*) sepsis approximately 60 days post transplant. The cytomegalovirus reactivation was initially treated with Ganciclovir induction therapy followed by continued maintenance therapy. The girl was admitted to the intensive care unit for *E. coli* sepsis, where she was treated with ceftriaxone. As part of the normal post-transplant course, she was started on immunosuppressive therapy with tacrolimus and

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mycophenolate mofetil. Approximately 101 days post transplant, routine labs showed a supratherapeutic tacrolimus trough level of 22 ng/ml (normal therapeutic range: 5-20 ng/mL). Her tacrolimus dosing was adjusted, and the trough level normalized over the next 2 weeks.

She presented at 117 days post transplant (16 days after supratherapeutic tacrolimus levels) complaining of bilateral leg pain and weakness, with refusal to bear weight. Physical examination was significant for tenderness to palpation of the bilateral lower extremities and discomfort while ambulating. Lower extremity reflexes could not be elicited. Normal strength was elicited in all four extremities, although individual muscle group testing was limited by the child's inability to fully cooperate with the exam in the setting of discomfort. Pertinent laboratory values showed normal erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), alkaline phosphatase and creatine phosphokinase (CPK). The girl was sensitive to touch causing pain, which was not responsive to pain medications, including opioids or gabapentin.

Radiographs of the bilateral lower extremities were obtained, which showed focal periosteal reaction bilaterally (Fig. 1). Growth arrest lines were also present. There was no evidence of fracture or additional osseous abnormalities. Given the sole findings of periosteal reaction, an MRI of the lower extremities was performed to evaluate for occult fracture or other causes of pain. MRI confirmed the presence of bilateral focal periosteal reaction. In addition, T2-weighted images showed edema of the surrounding soft tissues and musculature, which enhanced on the postcontrast images. (Fig. 2). Focal bone marrow edema was seen in the right tibia and manifested as abnormal low signal on T1-W images and high signal on T2-W images, with associated abnormal enhancement (Fig. 3). Additional diagnostic testing performed included MRI lumbar spine and nerve conduction studies, which were normal. Given the recent history of elevated calcineurin inhibitor levels, lack of additional laboratory abnormalities to suggest another etiology, and no evidence of fracture on imaging, calcineurin inhibitor-induced pain syndrome was the presumed diagnosis. The calcineurin inhibitor was tapered off and the child was started on steroids, with interval resolution of the symptoms within 1 month off tacrolimus while she continued steroid taper.

Discussion

Calcineurin inhibitor-induced pain syndrome was first described as "post transplant distal limb pain syndrome" in renal transplant patients and manifests as symmetrical pain most commonly affecting the lower extremities [1]. Further studies have shown that this syndrome presents in patients who have undergone other organ transplants. The term calcineurin inhibitor-induced pain syndrome was first described by Grotz et al. [2] who showed that the pain resolved with the removal of calcineurin inhibitors.

Calcineurin inhibitor-induced pain syndrome is a benign but severe cause of musculoskeletal pain in post-transplant patients. It usually presents within 1 year after the transplant with symmetrical pain that commonly affects the lower extremities. The symptoms may be present at rest but are exacerbated by standing and movement [3]. The syndrome has been commonly described in patients who have undergone a solid organ transplant, such as renal transplant, with few cases described after bone marrow transplant.

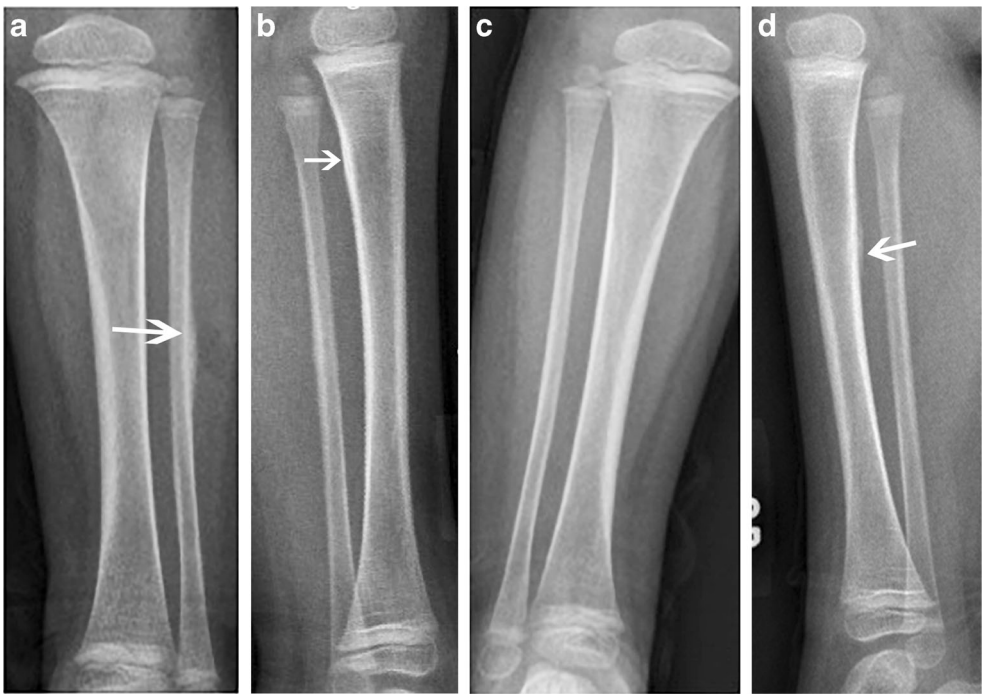

Fig. 1 AP and lateral radiographs of the left tibia and fibula (**a, b**) and AP and lateral radiographs of the right tibia and fibula (**c, d**) demonstrate smooth focal periosteal reaction along the posterior margin of the proximal bilateral tibia, and lateral margin of the left fibula (*arrows*). *Growth arrest lines* are present in the distal tibia bilaterally

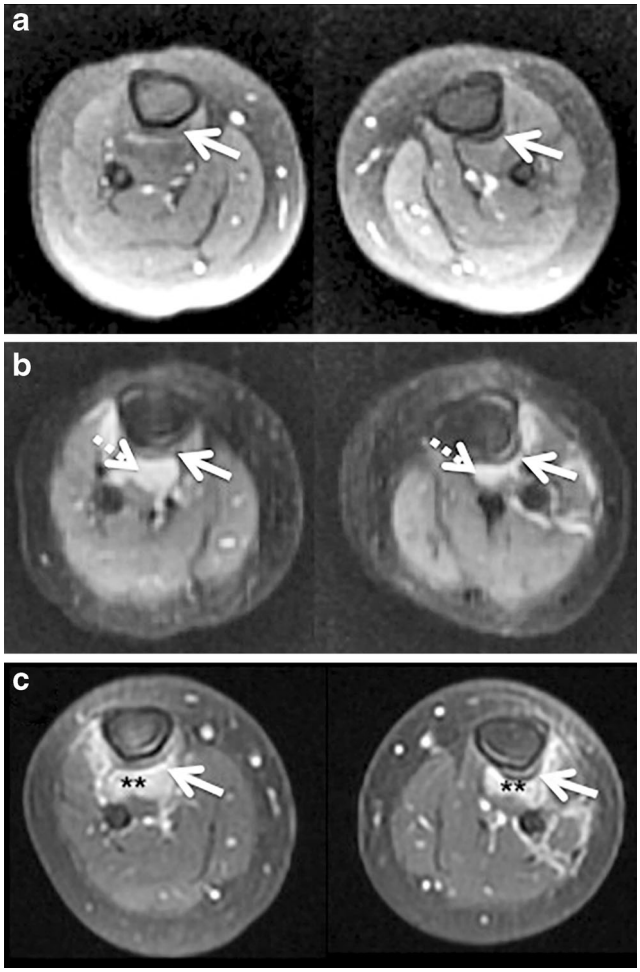

Fig. 2 Axial T1 (**a**), axial inversion recovery (**b**) and axial T1 postcontrast images (**c**). There is bilateral posterior tibial periosteal thickening (*solid arrows*) with surrounding muscular edema (*dotted arrows*). Postcontrast images demonstrate corresponding enhancement of the edematous musculature (**)

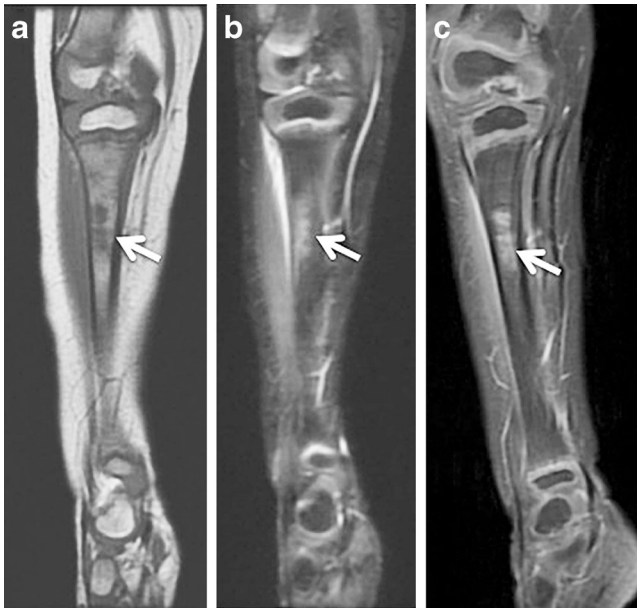

Fig. 3 Coronal T1 (**a**), coronal inversion recovery (**b**), and coronal postcontrast (**c**) show low T1 signal (**a**, *arrow*) with corresponding fluid signal (**b**, *arrow*) within the bone marrow of the right proximal tibial diaphysis. On postcontrast images, there is corresponding enhancement (**c**, *arrow*). These findings represent focal bone marrow edema

Although the etiology is not entirely clear, it has been hypothesized that calcineurin inhibitors can invoke changes in vascular permeability within the bone marrow. This leads to bone marrow congestion, which manifests as bone marrow edema on MRI. In addition, increased bone marrow turnover has been observed in these patients [4]. In the literature, the onset of symptoms has been described with variable correspondence to the calcineurin-inhibitor blood levels. In our case, the child had a supratherapeutic level 16 days prior to presentation and a normal tacrolimus level at the time of presentation. Other studies have described similar findings, with patients having symptoms in the setting of concurrent therapeutic levels [5]. One study described acute symptoms during initial infusion of cyclosporine [6]. Therefore, there is no current consensus on the time of onset of symptoms in the context of calcineurin-inhibitor levels.

There is a wide differential diagnosis of musculoskeletal pain in a patient post transplant, including osteonecrosis, insufficiency fracture, polyneuropathy or secondary hyperparathyroidism. Therefore, the evaluation of a post-transplant patient with musculoskeletal pain can be challenging. In conjunction with laboratory values and physical examination findings, imaging plays a crucial role in diagnosing these patients. In our patient, given that both lower extremities were symptomatic, imaging of the bilateral lower extremities was performed.

Initial radiographs in patients with calcineurin inhibitor-induced pain syndrome are commonly negative [2]; however, studies have shown the presence of periosteal reaction, patchy osteopenia and joint effusion [7]. MRI findings are more widely described; however, imaging findings are nonspecific and include bone marrow edema, typically in a symmetrical distribution [3]. One study has shown periosteal signal abnormality with associated bone marrow edema [6]. Bone scintigraphy can also be used for evaluation and may demonstrate bilateral symmetrical uptake in the lower extremities.

One of the first studies to evaluate MRI findings in post-transplant patients with lower extremity pain was by Vande Berg et al. [7] in 1994, who described transient epiphyseal lesions thought to be secondary to insufficiency fractures. These were described as linear areas of low signal on T1-W images, deep to and paralleling the articular surface. Additional findings described on MRI include foci of low signal likely representing "trabecular impaction" that can be seen in the areas of bone marrow edema. Bone marrow edema is the most common MRI finding seen with calcineurin inhibitor-induced pain syndrome; however, it is nonspecific

and can be seen with other entities such as transient osteoporosis and regional migratory osteoporosis [3]. Our patient did not have imaging findings involving the physis; however, bone marrow edema and periosteal reaction was present in the tibial diaphysis bilaterally. These MRI findings in a patient with bilateral lower extremity pain using calcineurin inhibitors support the diagnosis of calcineurin inhibitor-induced pain syndrome in the absence of other clinical or laboratory findings.

In post-transplant patients with lower extremity pain, common differential considerations include osteonecrosis and insufficiency fractures, which are typically unilateral processes. These patients can have long hospital courses with multiple complications, as with our patient, predisposing them to osteopenia of the bones secondary to disuse. This can be a predisposing factor to insufficiency fractures; however, in the setting of calcineurin-inhibitor use and bilateral symptoms, calcineurin inhibitor-induced pain syndrome should be considered as an etiology of symptoms. Osteonecrosis can be diagnosed with characteristic MRI findings of linear areas of low signal on T1-W and T2-W images and an inner line of high signal on T2-W images, representing active granulation tissue, otherwise known as the "double line" sign. As discussed above, imaging findings of calcineurin inhibitor-induced pain syndrome can be seen on the spectrum of insufficiency fractures; however, the clinical history, bilateral involvement and use of calcineurin inhibitors with improvement of symptoms after weaning of the treatment can support the diagnosis of calcineurin inhibitor-induced pain syndrome.

Other etiologies of bilateral musculoskeletal pain include inflammatory polyneuropathy and reflex sympathetic dystrophy. Inflammatory polyneuropathy can be associated with elevated ESR and CRP, which is normal in the setting of calcineurin inhibitor-induced pain syndrome. In addition, inflammatory polyneuropathy may affect joints other than the lower extremities, which are not typically involved with calcineurin inhibitor-induced pain syndrome. Reflex sympathetic dystrophy typically is asymmetrical in distribution, with confluent involvement of an involved portion of an extremity, differing from the findings seen in calcineurin inhibitor-induced pain syndrome.

Ultimately, the vascular abnormalities and increased bone turnover need to be addressed to effectively treat patients with calcineurin inhibitor-induced pain syndrome. The treatment of choice is decreasing calcineurin-inhibitor levels or changing immunosuppression therapy. Additional supportive measures include pain control and elevation of the legs [2]. Calcium channel blockers can also be an adjunct therapy [8].

Musculoskeletal pain can be common in post-transplant patients. In the clinical setting of a post-transplant patient on calcineurin inhibitors with otherwise negative laboratory tests, calcineurin inhibitor-induced pain syndrome is an important diagnostic consideration that should be addressed promptly. Therefore, it is important for radiologists to be aware of the imaging findings. In addition, it is important radiologists work closely with the clinicians to quickly and accurately make the diagnosis for prompt treatment of the patient.

Compliance with ethical standards

Conflicts of interest None

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