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Calcineurin-Inhibitor Induced Pain Syndrome in a Heart Transplant Patient

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ABSTRACT

Calcineurin-inhibitor induced pain syndrome (CIPS) also called the "symmetrical bone syndrome" is a condition describing reversible lower extremity pain in patients after organ transplantation who are receiving calcineurin inhibitors, especially tacrolimus. We present a case of CIPS after orthotopic heart transplant complicated with concurrent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We emphasize the presentation; diagnostic evaluation, and findings. We then discuss the proposed pathophysiologic mechanisms of CIPS and conclude with discussion of management strategies. Additionally, we present a table to guide clinicians in assessing posttransplant bone pain syndromes. To our knowledge, this is the first article to describe a case of CIPS with concurrent SARS-CoV-2 infection.

CALCINEURIN-INHIBITOR induced pain syndrome (CIPS) also called the "symmetrical bone syndrome" is a condition describing reversible lower extremity pain in patients after organ transplantation who are receiving calcineurin inhibitors (CNIs), especially tacrolimus and cyclosporine. This clinical syndrome was first described in 1989 by Bouteiller et al based on symptoms in transplant patients treated with cyclosporine [1]. The term CIPS was first used by Grotz et al in 2001, who recognized that tacrolimus and not just cyclosporine played a central role in the pathogenesis of CIPS [2]. CIPS occurs in solid organ as well as bone marrow transplant recipients treated with either tacrolimus or cyclosporine [3]. The exact frequency of CIPS after transplantation is variable and unknown owing to underdiagnosis, however a range of 1.5% to 14% has been suggested [4]. Most cases are diagnosed empirically based on clinical suspicion, but a radiologic criteria for imaging CIPS was suggested by Chapin et al in 2013 [5].

Awareness of CIPS in the heart transplant literature remains poor and thus it is severely underdiagnosed.

We present a case of CIPS after orthotopic heart transplant complicated with concurrent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We conclude with a discussion of the differential diagnosis considered and management strategies.

To our knowledge, this is the first article to describe a case of CIPS with concurrent SARS-CoV-2 infection.

CASE PRESENTATION

A 51-year-old man with medical history of systemic hypertension, obstructive sleep apnea, diabetes mellitus, and neuropathy underwent orthotopic heart transplant (OHT) for end stage heart failure secondary to nonischemic dilated cardiomyopathy.

Postoperative induction therapy was with thymoglobulin, and he was started on tacrolimus and mycophenolate mofetil (MMF). He required high doses of tacrolimus up to 16 mg twice daily to maintain a target trough level of 10 to 15 ng/mL.

Posttransplant course was unremarkable with no significant acute cellular or antibody mediated rejection. Two months after OHT, he developed severe malaise, diffuse pain, and myalgias all over all over the body. He had declined the SARS-CoV-2 vaccine for unclear reasons.

He was evaluated twice in the emergency room 7 and 9 months after OHT with diffuse body aches including bilateral leg pain. During both emergency room visits he reported that his myalgias and pain were debilitating enough to interfere with daily activities. Muscles were tender to the touch and that he had associated fatigue.

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Initial rheumatologic evaluation was unremarkable including negative erythrocyte sedimentation rate and high-sensitivity C-reactive protein. Creatine kinase was unremarkable and he had negative imaging of all joints.

Atorvastatin was stopped but there was no relief; tacrolimus was suspected to be contributory, but because he was less than a year posttransplant the target level was decreased to 8 ng/mL and the transplant team felt that discontinuing CNIs was premature.

Despite these changes, he was admitted a month later (10 months after OHT) with soreness and pain worse in bilateral lower extremities, right hip, lower abdomen, and generalized myalgias. On physical examination, he had an unremarkable neurologic examination and notably full strength of his lower extremities. Laboratory findings now revealed elevated inflammatory markers—erythrocyte sedimentation rate 55 and C-reactive protein 4.5.

An x-ray of the lumbar spine showed possible right sacroiliitis. MRI abdomen and pelvis (Siemens, Germany) and SPECT (scintigraphy Technetium 99) bone scan (Siemens, Germany) were both unremarkable (Fig 1).

Rheumatology evaluation also was negative. Hydralazine induced vasculitis, drug-induced lupus, and avascular necrosis were all considered but work-up was negative.

CIPS or diabetic neuropathy exacerbated by tacrolimus was suspected. We started weaning tacrolimus to run a lower target level and added sirolimus with a combined goal therapeutic level of 10. MMF was decreased owing to leucopenia and thrombocytopenia with SARS-CoV-2 and bacterial super infection (Table 1). Home diltiazem was switched to amlodipine and gabapentin dosing was increased.

Owing to atypical features of green productive cough, diarrhea, and myalgias, he tested positive for SARS-CoV-2. Computed tomography chest revealed bilateral infiltrates left worse than right likely from SARS-CoV-2 infection. He also had a secondary infection with M*oraxella pneumonia* and completed a 5-day course of ceftriaxone. Because he did not become hypoxic and never required supplemental oxygen throughout hospitalization, he was not treated with dexamethasone or remdesivir.

Pain improved but did not resolve and he was discharged home on a short course of analgesics. He eventually had to be taken off tacrolimus and continued sirolimus and MMF for immunosuppression in addition to amlodipine. Table 1 shows the immunosuppression strategies employed. He has not had any more pain episodes or admissions 3 months after discharge.

Table 1. List of Agents Used for Immunosuppression Induction and Maintenance Post Heart Transplant

Time Post-OHT	Immunosuppression Agents
OHT	MMF 500 mg IV q12H, IV methylprednisolone 1000 mg followed by 125 mg every 8 h for 3 doses
1 day	Methylprednisolone 25 mg IV, MMF 500 mg IV q12H, IV ATG 125 mg (1.5 mg/kg)
2 days	Methylprednisolone 25 mg IV, MMF 500 mg IV q12H
3 days	Methylprednisolone 25 mg IV, MMF 500 mg IV q12H, IV ATG 125 mg
4 days	Methylprednisolone 25 mg IV, MMF 500 mg PO BID
1 month	MMF 1000 mg PO BID, prednisone 20 mg PO daily, tacrolimus 8 mg PO BID
2 months	MMF 1000 mg PO BID, prednisone 15 mg PO daily, tacrolimus 8 mg PO BID
3 months	MMF 1000 mg PO BID, prednisone 5 mg PO daily, tacrolimus 8 mg PO BID
6 months	MMF 1000 mg PO BID, tacrolimus 9 mg PO BID
10 months (discharge)	MMF 500 mg PO BID, tacrolimus 3 mg PO BID, sirolimus 2 mg PO Daily
11 months	MMF 500 mg, sirolimus 3 mg PO Daily, tacrolimus OFF

ATG, CD3-guided antithymocyte globulin, BID, twice a day, IV, intravenous, MMF, mycophenolate mofetil, OHT, orthotopic heart transplantation, PO, by mouth, SL, sublingual.

DISCUSSION

CIPSis a well-known syndrome in posttransplant patients that presents with reversible lower extremity pain. The pain typically presents bilaterally and symmetrically in weight-bearing joints, commonly in the knees, ankles, and feet after organ transplantation in patients treated with tacrolimus or cyclosporine [4].

The pathophysiology of CIPS remains unclear but potential mechanisms have been described. The first mechanism involves, increased vascular permeability resulting in increased osseous pressure and marrow edema. This is thought to be similar to the effects of CNI in posterior reversible encephalopathy syndrome, and the proposed pathophysiologic mechanism includes autoregulatory failure, hypertension, and endothelial dysfunction leading to vasogenic edema typically with subsequent abnormalities in the posterior brain on MRI. These effects on vasculature could manifest in the bone marrow in CIPS as well. The second mechanism is related to alterations in bone metabolism with increased bone turnover [2]. Thirdly, the role of CNIs as nociceptor modulators, which can induce facilitation of pronociceptive processes by interrupting glial function and by inhibition of nuclear factor-activated T-cells, has been postulated [6]. Fourthly, the manifestation of CIPS-like symptoms in patients with human herpes virus 6 reactivation [7] suggests a possible role for human herpes virus 6 in the pathogenesis althogh this has not been confirmed.

Diagnosis of CIPS is usually confirmed by MRI or a radionuclide bone scan that identifies areas of marrow edema or hyperemia often associated with soft tissue swelling and joint effusions [2]. However, as was seen in our index patient, some cases of CIPS have normal radionuclide scans [8]. Possible reasons for the negative imaging include the fact that the pain syndrome was present for 4 months before imaging and/or that tacrolimus dose and target level was already being reduced before imaging.

Pain may be associated with higher trough levels of tacrolimus and improves as marrow edema recedes. Although it has been suggested that the onset of pain syndrome may correlate with the tacrolimus level, this was not present in our case. However, we saw a correlation between onset and severity of symptoms and a >5 ng/mL rise in tacrolimus level within a 24-hour period.

Table 2. Differential Diagnosis of Bone Pain in Posttransplant Patients

Diagnosis	Clinical Features	Risk Factors	Diagnostic Findings	Management
Calcineurin-inhibitor induced pain syndrome	Symmetrical bilateral reversible lower extremity pain	After solid organ or hematopoietic stem cell transplantation in patients treated with calcineurin inhibitor	MRI with areas of bone marrow edema or hyperemia at lower extremity pain site Radionuclide bone scan with increased uptake at lower extremity pain site	Dose reduction of calcineurin inhibitor and slow conversion to alternative non-calcineurin agent Introduction of dihydropyridine calcium channel blocker
Osteoporosis with fragility fractures	Pain in weight baring joints and/or extremities	Men aged ≥70 years, history of delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, chronic obstructive pulmonary disease, glucocorticoid or GnRH agonist use, alcohol or tobacco misuse Risk increases with age, greatest in postmenopausal women	X-Ray showing presence of a fragility fracture, commonly vertebral, pelvis, or wrists BMD assessment by DXA of hip and lumbar spine consistent with osteoporosis T-score ≤−2.5 SD or more below the mean of normal young white male/female individuals and presence of at least 1 fragility fracture	Oral bisphosphonate Lifestyle measures including calcium supplementation if dietary intake is inadequate, vitamin D supplementation, participation in weight- bearing activities, smoking cessation, avoidance of heavy alcohol use
Gout	Intense monoarticular lower extremity joint pain with associated skin and soft tissue inflammation	Recent trauma or surgery, high fat foods, excessive alcohol consumption, dehydration, starvation, medications that alter serum uric acid level (thiazide and loop diuretics, aspirin, allopurinol)	Diagnosis is clinical Presence of monosodium urate crystals in synovial fluid aspiration from painful joint or bursa visualized on polarized light microscopy	Oral glucocorticoids or NSAIDs, intraarticular glucocorticoid injection Lifestyle modifications including weight loss, avoidance of heavy alcohol use
Primary hyperparathyroidism	Most commonly asymptomatic Symptomatic includes bone pain, abdominal pain/flank pain, polyuria, polydipsia, gastrointestinal upset, neuropsychiatric disturbances	Increased risk with age, women, African Americans, postmenopausal, ionizing radiation in childhood, chronic lithium use, familial forms	Elevated serum calcium and elevated or inappropriately normal levels of parathyroid hormone	Parathyroidectomy
Osteonecrosis of femoral head	Groin, thigh, buttock pain with weightbearing +/− motion-induced pain +/− pain in absence of activity +/− nocturnal pain	Systemic glucocorticoids, bisphosphonates, excessive alcohol consumption, cigarette smoking. Posttransplantation, SLE, trauma, genetic disorders, HIV, spontaneous	Plain radiography of affected site consistent with osteonecrosis Gold standard: MRI of affected joint without contrast consistent with osteonecrosis	Supportive measures: Bed rest, offloading of anatomically effected area with assist devices, short term use of NSAIDs and/or opioids Surgical intervention: joint preserving procedures (eg, core decompression, bone grafting, etc), total joint replacement
CPRS				

(*continued on next page*)

Table 2 (*Continued*)

Diagnosis	Clinical Features	Risk Factors	Diagnostic Findings	Management
	Regional neuropathic pain, usually in distal limbs, that does not follow a dermatomal pattern, typically disproportionate to an inciting event	History of fracture, blunt trauma, crush injury, ligamentous sprain, surgery, carpal tunnel syndrome	Diagnosis is clinical based on IASP/Budapest Clinical Diagnostic Criteria diagnostic criteria [11]	Physical and occupational therapy, psychosocial/ behavioral therapy with clinical psychologist, analgesic control with NSAIDs, topical lidocaine, adjunctive medication for neuropathic pain (eg, Gabapentin, TCAs)
Undifferentiated inflammatory arthropathy	Presence of at least 1 swollen and painful joint +/− erythema	Recent urogenital, gastrointestinal, or viral infection Family history of inflammatory arthropathy, SLE, psoriasis, IBD	Laboratory testing abnormalities specific to inflammatory arthropathy. Work up includes CBC, BUN, Cr, liver function test, uric acid, TSH, ESR, CRP, RF, ACPA, ANA +/− viral panel (eg, EBV, Hep B and C) Plain radiograph of painful joint characteristic for specific inflammatory arthropathy Arthrocentesis excluding infectious or crystal disease	Treatment differs based on specific inflammatory arthropathy Typically includes starting csDMARDs (eg, MTX, SSZ) and adjunctive anti-inflammatory agents (NSAIDs or glucocorticoids)
Drug induced lupus	Subacute progressive worsening of SLE-like symptoms including but not limited to fever, arthralgias, myalgias, malaise, weight loss, cutaneous manifestations	Recent use of procainamide hydralazine (high risk for DIL), amongst others.	Laboratory abnormalities largely dependent on causative agent. ANA antibodies present (absence does not preclude diagnosis), Anti-histone antibodies present (>95% positive in high risk drugs). Elevated ESR, CRP normal or high.	Withdrawal of causative agent Severe cases may require immunosuppression (eg, glucocorticoids)
Drug-induced ANCA vasculitis	Constitutional symptoms (fever, polymyalgia, polyarthralgia, malaise) Symptoms associated with location of downstream ischemia	Recent initiation of hydralazine (most commonly), hyperthyroidism treatment (propylthiouracil, methimazole, carbimazole), minocycline	Elevated MPO − ANCA titers +/−: presence of antibodies to elastase or lactoferrin, PR3-ANCA	Immunosuppression and withdrawal of causative agent

ACPA, anti-citrullinated peptide antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; BMD, bone mineral density; BUN, blood urea nitrogen; CBC, complete blood count; CPRS, complex regional pain syndrome; Cr, ceratinine; CRP, C- reactive protein; csDMARD, conventional disease-modifying anti-inflammatory drug; DIL, drug-induced lupus; DXA, dual-energy x-ray absorptiometry; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; GnRH, gonadotrophin releasing hormone; Hep, hepatitis virus; IASP, International Association for the Study of Pain; IBD, inflammatory bowel disease; MPO−ANCA, myeloperoxidase−antineutrophil cytoplasmic antibody; MRI, magnetic resonance imaging; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; PR3-ANCA, anti-proteinase 3 antineutrophil cytoplasmic antibody; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SLE, systemic lupus erythematosus; SSZ, sulfasalazine; TCA, tricyclic antidepressant; TSH, thyroid-stimulating hormone US, ultrasound.

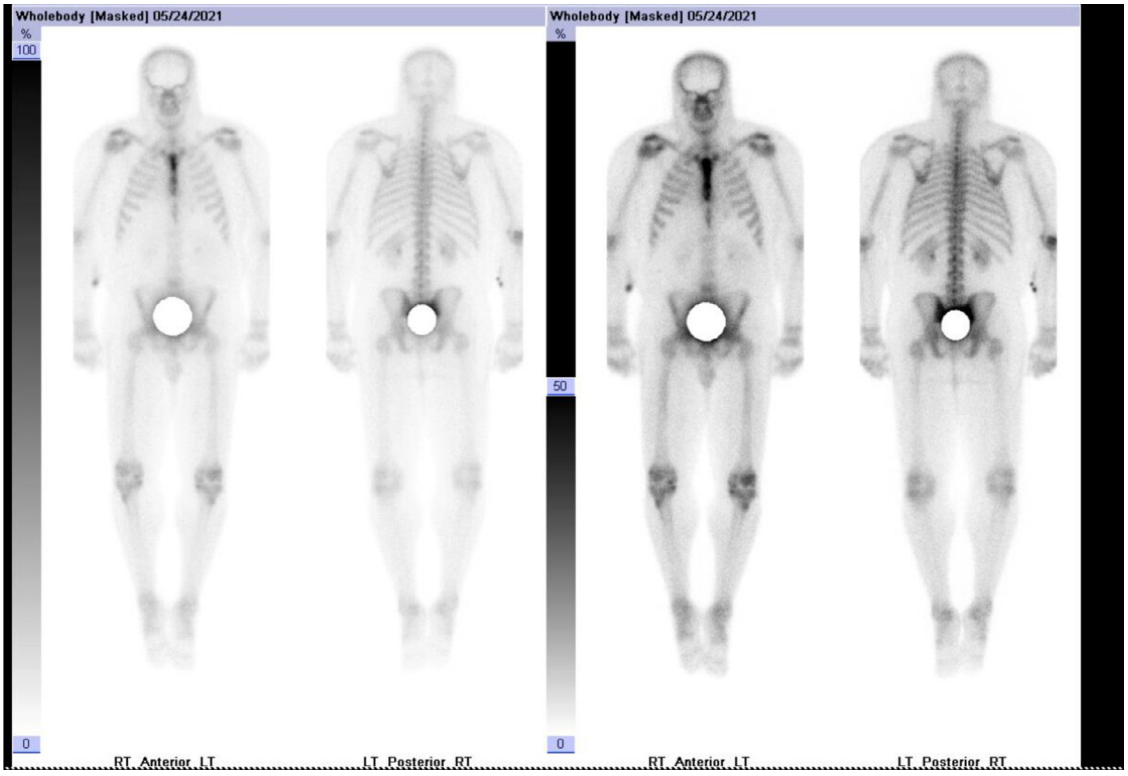

Fig 1. Whole body skeletal bone scan showing increased uptake within the sternum, consistent with sternotomy and mildly increased radiotracer uptake at wrists, elbows, shoulders, knees, and ankles.

CIPS may be sometimes difficult to distinguish from conditions such as osteoporosis with fragility fractures, gout, hyperparathyroidism, or osteonecrosis. The bilateral and symmetrical nature of the pain distinguishes it from osteonecrosis. Table 2 shows a list of important differential diagnosis of bone pain to consider in posttransplant patients.

Effective therapy for CIPS involves adjustment of the immunosuppressive regimen with reduction of CNI dose and/or target level, slow conversion to alternative noncalcineurin agent such as target of rapamycin inhibitors, and introduction of dihydropyridine calcium channel blockers such as amlodipine [9]. In our index patient, relief of symptoms was seen after reducing and eventually stopping tacrolimus and initiation of sirolimus and conversion from diltiazem to amlodipine.

Adjunctive therapies include, elevation of extremities [2], GABA analogs such as pregabalin or gabapentin, and bisphosphonates such as intravenous pamidronate [10]. The efficacy of these therapies remains uncertain, because they have almost always been used in conjunction with immunosuppression strategy change and calcium channel blocker use.

The concurrent infection with SARS-CoV-2 with bacterial superinfection was unexpected but reflects part of the growing reality of post-transplant care in the era of the coronavirus disease 2019 pandemic. Notably, the patient was transplanted 4 months after the World Health Organization declared the coronavirus disease 2019 a pandemic. Despite typical chest radiographic findings for SAR-CoV-2 infection, there was no hypoxia and indicated treatment was intravenous cephalosporin without supplemental oxygen. Owing to concurrent leucopenia and thrombocytopenia on admission with the suspected CIPS, MMF and tacrolimus was reduced but sirolimus was added. Because of the lack of hypoxia with SARS-CoV-2 infection we did not use steroids.

With an increase in the number of patients receiving solid organ and hematopoietic stem cell transplants and, hence, more CNI use, the early recognition of this syndrome is important. Pain burden associated with CIPS is severe and debilitating, responds poorly to conventional analgesics, and is responsive only to strong narcotic analgesics.

CONCLUSIONS

The differential diagnosis of severe bilateral lower extremity pain in solid organ transplant patients should include CIPS owing to tacrolimus or cyclosporine. A high index of suspicion is critical and can guide early imaging to confirm the diagnosis typically with MRI of affected extremities and bone scintigraphy. Diagnostic utility is helpful if imaging is done in the early phases of suspected diagnosis. A strategy of reducing CNI use and/or adding mammalian target of rapamycin inhibitors, augmenting neuro-modulating therapies can be life-changing for affected patients.

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