

Liver Transplant Recipient with Calcineurin-inhibitor Induced Pain Syndrome: A Case Report

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ABSTRACT

Setting: University Hospital

Patient: 65-year-old female status-post liver transplant secondary to cirrhosis.

Case Description: Prior to the rehabilitation consult on post-operative day 42, she had an episode of acute rejection requiring rapid escalation of cyclosporine dosage, later changed to high dose tacrolimus for immunosuppression, resulting in high blood levels of both calcineurin inhibitors. She then complained of paroxysms of 10/10 pain over her entire body not relieved by opioids despite escalation in medication by the acute pain service. She was not participating in a rehabilitation program because of pain. Examination revealed an anxious woman for whom any tactile stimulation caused profound pain, precluding a thorough neuromuscular examination. She demonstrated spontaneous movement in all four limbs with akathesias.

Assessment/Results: After a literature search and discussion with the transplant team to determine if calcineurin-inhibitor induced pain syndrome (CIPS) was a likely cause for her pain, the patient's immunosuppressive regimen was adjusted, as she was no longer in acute rejection. Tacrolimus was stopped, and cyclosporine dosage was gradually increased over several weeks. After her calcineurin inhibitor levels dropped, she had relief of pain such that she no longer required opioids, and could participate fully in an inpatient rehabilitation program. After less than two weeks on our inpatient service, she was discharged at a supervision level for household ambulation with a rolling walker.

Discussion: CIPS has been described as a cause of disabling pain after organ transplantation. In our patient, treatment of CIPS resulted in improved function. Reducing the blood levels of calcineurin inhibitor is the preferred treatment in the literature, as with our patient. In cases where this is not possible, calcium channel blockers have been used for pain relief.

Conclusions: Recognition and treatment of calcineurin-inhibitor induced pain syndrome improves functional outcomes in the transplant patient.

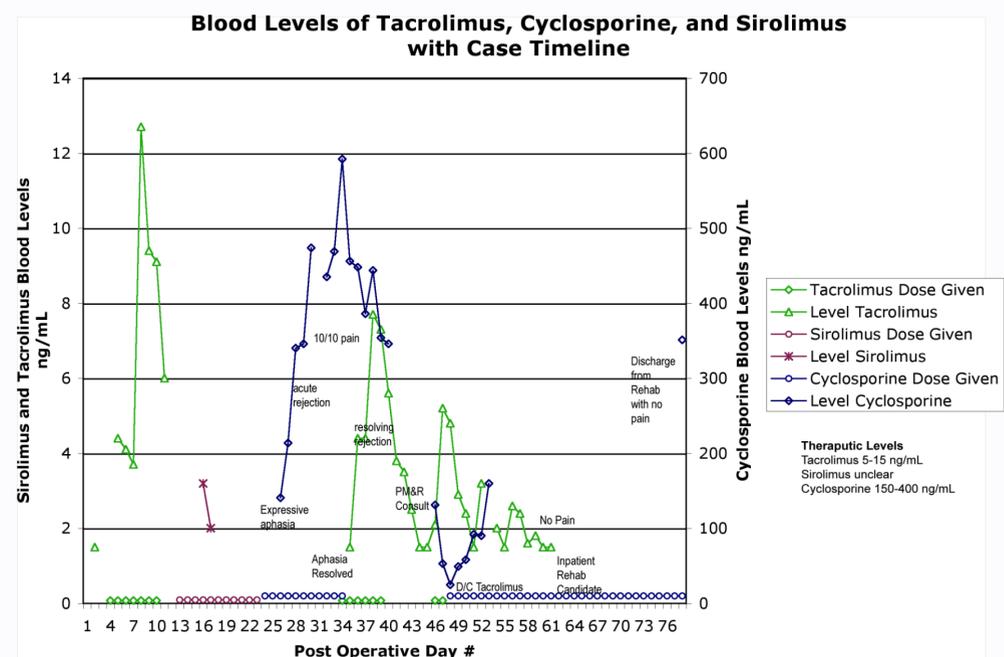


Figure 1: Blood levels of and days patient was given tacrolimus, sirolimus, or cyclosporine with case timeline.

INTRODUCTION

Calcineurin inhibitors, such as tacrolimus and cyclosporine, are immunosuppressants used to prevent rejection in transplant patients. Along with sirolimus, they fall into a class of medicines used to prevent T and B cell activation.

Calcineurin is a calcium/calmodulin-dependent protein phosphatase necessary for the production of several molecules involved in T cell activation, such as interleukin-2. Calcineurin also has multiple functions in the neuromuscular system. For instance, over-expression of calcineurin in genetically engineered mice leads to more type 1 muscle fiber content. Lack of expression of calcineurin in mice creates a situation where Type 1 and Type 2A muscle fibers are not present in these mice.

Calcineurin composes over 1% of the total protein in the brain, with the highest concentrations in the hippocampus, caudate, and putamen. Calcineurin regulates ligand- and voltage-gated ion channels, neurotransmitter and hormone release, and synaptic plasticity via regulation of N-methyl-D-aspartate (NMDA) receptors. NMDA receptors are a subtype of excitatory glutamate receptors. Overstimulation of glutamate receptors is linked to neuronal cell death in ischemia, epilepsy, Huntington's disease, and amyotrophic lateral sclerosis. Inhibition of calcineurin *in vitro* leads to prolonged NMDA receptor opening to calcium influx which results in increased firing frequency of cultured rat hippocampal neurons. In addition, *in vitro*, heat nociceptive receptors responsive to capsaicin are desensitized via calcineurin.

CALCINEURIN INHIBITOR INDUCED PAIN SYNDROME (CIPS)

Calcineurin inhibitor-induced neurotoxicity is better known, but calcineurin inhibitor induced pain syndrome has only recently been described. Calcineurin inhibitor neurotoxicity can occur any time after the transplant; and in bone marrow transplant recipients, it occurs in anywhere from 3-20% of patients. There is no clear relationship between drug serum level and neurotoxicity. Risk factors for neurotoxicity include acute renal failure, acute rejection, and corticosteroid therapy. Typical clinical findings include headache, paresthesia, tremor, and akathesia. A retrospective study of the long term effects of calcineurin inhibitor neurotoxicity noted it initially presented as follows: altered mental status (70%); seizures (50%); confusion (40%); visual changes (30%) including cortical blindness; ataxia (20%); severe headaches (16%); disorientation (13%); hemiparesis and/or expressive aphasia (10%). Typical Brain MRI findings of calcineurin inhibitor-induced neurotoxicity include symmetric, non-enhancing, hypodense lesions on T1-weighted images with typical hyperintense T2 uptake. Calcineurin inhibitor-induced central nervous system toxicities often resolve clinically and radiologically with discontinuation of the drug, however, the toxicity can be permanent.

Calcineurin-inhibitor induced pain syndrome (CIPS) was first named in 2001 by Grotz, et al. Prior to Grotz, it was referred in the literature as reflex sympathetic dystrophy syndrome related to tacrolimus and cyclosporine. It has been described in kidney and bone marrow transplant recipients. Clinical characteristics include aching, severe pain that may have neuropathic characteristics, but there is no relief with any pain medication. There is increased uptake seen on triple phase bone scan along with diffuse bone marrow edema seen on MRI. It is associated with high cyclosporine and/or tacrolimus blood levels. No other neurologic or rheumatologic cause can be found. The pathogenesis is unclear. However, pain relief is experienced after reduction of calcineurin inhibitor dose. It has also been reported that administration of calcium channel blockers decreases pain.

CONCLUSION

- Development of CIPS may be related to rapid escalation of calcineurin inhibitor dose, like what happened with our patient when she underwent acute rejection.
- Diagnosis and treatment improves functional outcomes. Because of favorable prognosis and ease of treatment, and because flexibility exists in transplant medication regimens, it is important for the consulting physiatrist raise the possibility of CIPS with the transplant team.

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