Calcineurin Inhibitor Pain Syndrome

The Distribution & Severity of Pain

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Introduction

- Calcineurin is a phosphatase enzyme dispersed throughout all mammalian tissues with unique roles in both the immune and central nervous systems.[1] Its primary role in the human immune response is indirectly activating lymphocytes via its dephosphorylation of nuclear factor of activated T cells (NFAT).
- Due to its role in the cell-mediated immune response, Calcineurin has been a targeted protein of immunosuppressants in the setting of organ transplant to prevent transplant rejection.[2]
- Two drugs, cyclosporin A (CSA) and tacrolimus ([TAC] FK-506) have been developed to specifically target calcineurin and prevent the activation of T cells during organ and hematopoietic transplant.[2]
- Due to calcineurin's additional effects involving both pain modulation and vascular tone, the inhibition of the enzyme can lead to pain crises in patients taking CSA or TAC, referred to as Calcineurin Inhibitor Pain Syndrome (CIPS).[1]

Case Report

The patient is a 35-year-old Asian-Indian female receiving her second kidney transplant. Pertinent past medical history includes T2DM that was diagnosed at the age of 18, leading the complication of diabetic nephropathy diagnosed in *Feb 2016*. The reason for initial transplant was end-stage renal disease due to diabetic nephropathy. Patient received her first live kidney transplant in December 2016. Patient received her second transplant on April 25th, 2021.

On POD#2 patient complained of upper extremity weakness and numbness from elbow to fingertips. On POD#8 it was noted that the patient experienced sudden onset of severe diffuse joint tenderness (including jaw, shoulders, hip, upper and lower extremities) and muscular aches with extremely limited mobility secondary to pain. The pain worsened upon active or passive manipulation of joints alongside the generalized pain. Slight palpitation anywhere resulted in a strong pain response, especially when in accordance with joints.

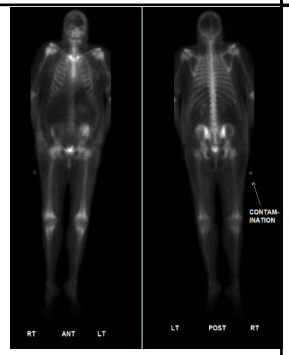

Figure 1.0: NM Bone Scan – Whole Body

Extensive workup was undertaken, in which NM Bone Scan (refer to Fig 1.0) showed abnormal rise in radioactive uptake in the shoulders, elbows, and knees. Combination of the presentation and workup, made CIPS the most plausible diagnosis. On POD #9 TAC was held, and patient was monitored. About 24 hours post discontinuation of tacrolimus, patient had much improvement, especially with jaw and upper extremity pain, while lower extremity pain persisted. Patient's pain was scaling down, but still present. On POD#13, 4 days post TAC discontinuation, the pain had completely subsided with return of full range of motion for the patient. Patient was able to complete activities of daily living independently. In order to maintain immunosuppression patient was transition to cyclosporin on POD #12 and continued to tolerate it well.

Discussion

The aim of this case report was to present an unique manifestation of CIPS. There are three key points of this patient that challenge our current understanding of the syndrome.

- Distribution of the pain: Classically, CIPS affects bilateral lower extremities primarily below the knees. Our patient had widely diffuse pain involving joints from the jaw to large joints such as the shoulder and hips. This is the first written report to mention CIPS affecting large joints as well as the involvement of upper extremities.
- Onset of the pain: The current understanding of CIPS onset is 1-3 months, whereas our patient experienced CIPS pain POD#8.
- Toleration of cyclosporine: Present literature indicates that CIPS is often associated with cyclosporine over tacrolimus, with 1-17% of renal transplant patients with on cyclosporine experience such phenomena. This patient was diagnosed with CIPS secondary to tacrolimus use, but she was able to tolerate cyclosporine well. This introduces individual level differences in the responses to cyclosporine vs tacrolimus.

Conclusion

This case report demonstrates that while CIPS is not unheard of, much is still to be understood. The case challenges the current understanding on clinical presentation of CIPS and pathophysiology. It highlights an unusual presentation of early onset of CIPS, wide involvement of joints aside from lower extremities, and toleration of cyclosporine over tacrolimus in a CIPS patient.

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