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Reversible Chronic Interstitial Nephritis Induced by Tacrolimus

—Tacrolimus Chronic Interstitial Nephritis

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Abstract

Calcineurin inhibitors (CNI) are potent immunosuppressive agents in prophylaxis against graft rejection and autoimmune diseases including primary glomerulopathies. Previous research showed reversible; acute afferent arteriolar vasculopathy and irreversible chronic interstitial fibrosis associated with CNI nephrotoxicity. In this case report we describe a patient, with minimal change disease, that had developed chronic and progressive renal disease while receiving therapeutic dose of Tacrolimus. His serum creatinine had reached 537 umol/L and his nephrotic state worsened. Kidney biopsy showed chronic interstitial nephritis. Tacrolimus was discontinued and he was treated with 1 mg/kg prednisone in addition to Mycophenolate mofetil (MMF) 1 g twice daily. By the 2nd month; serum creatinine returned to normal and by the 3rd month serum albumin too. After 1 month of therapy; the dose of Prednisone was tapered down gradually till 5 mg daily by the end of 3rd month. Moreover, the dose of MMF was reduced to 500 mg X2 by the end of 3rd month. After 2 years of follow up; he remained stable and without relapse of NS or renal failure. In conclusion, reversible renal disease, due to chronic interstitial nephritis can be induced by CNI which is amenable to treatment with Prednisone and MMF.

Keywords

Calcineurin Inhibitors, Mycophenolate Mofetil, Tacrolimus, Interstitial Nephritis, Minimal Change Disease, Nephrotic Syndrome

1. Introduction

Calcineurin inhibitors (CNI) are potent immunosuppressive agents in prophy-

laxis against graft rejection viz. human kidney, liver and heart transplantation [1]. Moreover, due to their inhibition of T cell activation, they are often used off label in multiple autoimmune disorders including nephrotic syndrome [2]. Initially, Cyclosporine A was introduced in 1970 followed by Tacolimus in 1984 [3]. The latter did not have the adverse effects of hypertrichosis and gingival hyperplasia, and was associated with lower graft failure rates in kidney transplant patients when compared to Cyclosporine A [4]. Despite their structural differences; both drugs have similar mechanism of action and unfortunately acute and chronic nephrotoxicity [5]. Previous research had shown that acute CNI-nephrotoxicity is reversible and is due to afferent arteriolar vasoconstriction. On the other hand; chronic CNI-toxicity was irreversible and characterize by interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, as well as glomerulosclerosis [5]. Moreover, recent register studies have demonstrated that virtually all kidney transplanted patients develop signs of chronic CNI-toxicity within 10 years after kidney transplantation [6]. In this case report, we expand the spectrum of such toxicity with the addition of reversible chronic interstitial nephritis.

2. The Case

A 17-year-old man presented with relapse of his nephrotic syndrome in June 2020. His disease was diagnosed at the age of 2 years. He used to respond completely to Prednisone 1 mg/kg for 1 months followed by gradual tapering till discontinuation by 3rd month. Subsequently, he had 1 relapse/year and had responded to corticosteroid therapy. Ten years later, he relapses were more frequent (up to 4/year) and had received 3-months course of oral Cyclophosphamide yet without benefit. Kidney biopsy showed minimal change disease on light microscopy and lacked any immune deposits on immunoperoxidase stain. Initially, he was started on Tacrolimus 2 mg twice daily. However, as seen in **Figure 1**, his serum creatinine had increased from normal to 270 umol/L and serum albumin had decreased further from 29 to 17 g/L. At that time, 13-hour Tacolimustrough level was within therapeutic range at 2.9 ug/L (Normal: up to 7). The dose of Tacrolimus was reduced to 1 mg twice daily and Prednisone 20 mg daily was added. Moreover, Rituximab 1 g infusion followed by another one 2 weeks later was given in an attempt avoid future use of Prednisone and Tacrolimus. One month later, serum albumin had increased to 35 g/L yet serum creatinine that had decreased initially to 100 umol/L had increased gradually to 150 umol/L. Hence, Prednisone and Tacrolimus were discontinued to assess the efficacy of isolated Rituximab therapy. Unfortunately, 1 month later, he relapsed again with serum albumin at 13 g/L and serum creatinine remained high at 150 umol/L. Subsequently, Prograf 1 mg twice daily was added, as a synergetic agent, to his inefficient Rituximab therapy. Unfortunately, 1 months later, on such re-chalange and despite low serum level of Prograf, his serum creatinine had increased to 537 umol/L. Moreover, he remained edematous with serum albumin at 13 g/L. At this stage, kidney biopsy was done and had shown normal glomeruli with features

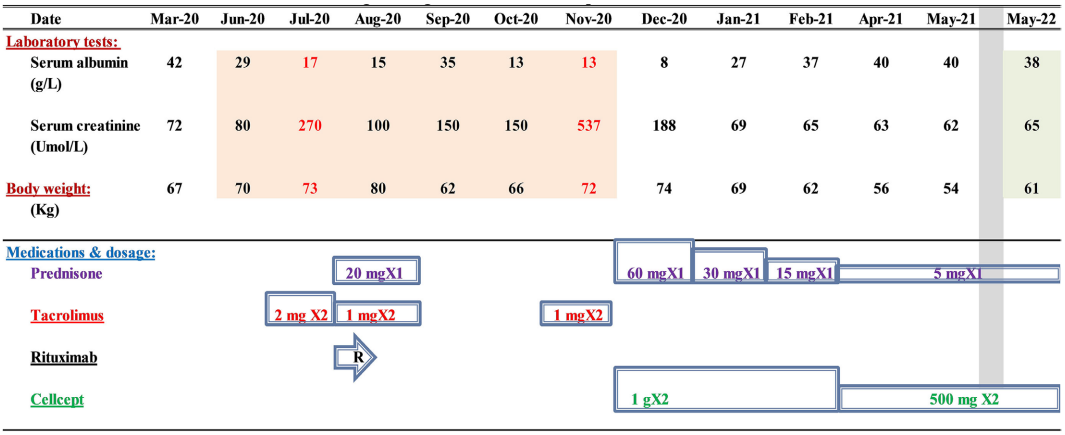

Figure 1. Flow chart of historic biochemical and weight changes with different therapies.

of active interstitial with chronic elements and fibrosis (**Figure 2**). Tacrolimus was discontinued and Prednisone 60 mg daily was added in addition to MMF 1 g twice daily. One month later, serum creatinine had decreased to normal and serum albumin had increased to 27 g/L with resolution of his nephrotic state and 5-kg weight loss. One month later, his serum creatinine remained normal and serum albumin had improved further to normal. The dose of Prednisone was reduced gradually after the first month and had reached 5 mg daily by the 3rd month. Since the patient was stable, the dose of MMF was also reduced after 3 months to 500 mg twice daily. By now, and after 1 year of the latter dose decrement, he remained stable clinically and without hypertension, proteinuria and hematuria.

3. Discussion

This case report reveals 2 important issues viz. a) Induction of interstitial nephritis, by Tacrolimus, that is reversible with Corticosteroids and MMF and b) safety and efficacy of MMF in management of frequently relapsing minimal change disease refractory to Cyclophosphamide and even Rituximab. The induction of chronic interstitial nephritis as a CNI-toxicityis a new phenomenon that has valuable future implications. It is different from; a) the vasculopathic acute toxicity sinceit will not improve with dose-decrement or drug-discontinuation, and b) the irreversible chronic interstitial fibrosis. It should be included in the differential diagnosis of chronic renal disease in native or transplanted ones in patients on CNI and diagnosis can be established by kidney biopsy [7]. In suspected cases that lacked overt etiology of graft-dysfunction; a) discontinuation of CNI, and b) therapeutic trial of Corticosteroids and MMF, may be rewarding. In our patient; MMF was a valuable tool in management of drug-refractory NS and limited long-term and high-dose exposure to Corticosteroids [8]. After its 3-months induction phase; its immunosuppression remained adequate at lower dosage. Moreover, in addition to its potent immunosuppression, it has a potent antiproliferative action via suppression of both B and T cells via stimulation of CD3/CD28 that inhibits T cell IL-17, IFN-γ and TNF-α production [9]. The

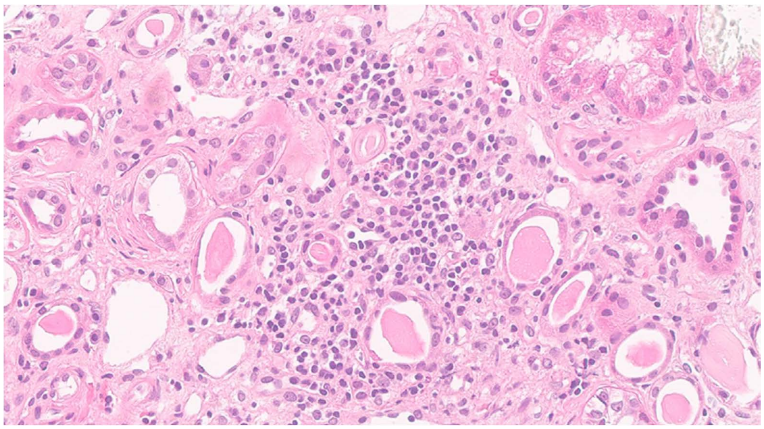

Figure 2. Photomicrograf of a kidney biopsy of patient (n: 8) showing small tubules with low cuboidal epithelium and contain pink protenacious material (thyroidization) with fibrotic interstitium filled with lymphocytes, neutrophils, eosinophils and plasma cells (H & E × 200).

latter has been shown in steroid-resistant MCD and nephritis associated with Henoch-Schönlein Purpura [10] [11].

4. Conclusion

Interstitial nephritis should be considered in patients with renal impairment following CNI-therapy. Kidney biopsy is essential for diagnosis and prognosis is favorable with proper management.

Informed Consent

Written informed consent was obtained from the patient for the publication of this clinical case, there are no images of the patient in this manuscript

Conflicts of Interest

The authors declare that they have no potential conflict of interest related to the contents of this article.

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