Abstract:
Calcineurin inhibitors (CNI) have revolutionized transplantation of non renal organs including heart, liver, lung, and pancreas. We report cyclosporine-induced renal failure in a 61 year old man who underwent deceased donor orthotopic heart transplantation in April 2010. He was started on triple immunosuppression including cyclosporine, mycophenolate mofetil (MMF) and steroids. Fourteen months later he had developed renal failure which was proved to be due to chronic cyclosporine nephrotoxicity. We discuss the pathophysiological mechanisms of cyclosporine toxicity in cardiac transplant recipients and measures to reduce the toxicity.

Keyword: Key words Calcineurin inhibitors heart transplantation cyclosporine nephrotoxicity

CASE REPORT ON CHRONIC CYCLOSPORINE TOXICITY IN A CARDIAC TRANSPLANT RECIPIENT

CASE REPORT A 61 year old male a not a known diabetic or hypertensive, non smoker had developed Grade 4 dyspnea due to ischemic dilated cardiomyopathy and severe congestive cardiac failure in 2004. He underwent a deceased donor heart transplant in April 2010 at our institution from a 50 year old male road-traffic accident victim who was brain-dead. His preoperative blood pressure was 130/70 mmHg and serum creatinine was 1.0 mg/dl. Intra operative and post operative period was uneventful. His immunosuppressant drugs were prednisolone 30mg per day, MMF 500mg twice daily and micro-emulsion form of cyclosporine 150 mg twice daily. He was discharged with good cardiac function. The serum creatinine and blood cyclosporine levels along with the dosage taken regularly are given in Table 1. In January 2012, on routine examination, his serum creatinine was 1.6mg/dl and the patient was referred to Nephrology. Ultrasound of the abdomen showed normal sized kidneys with normal echoes. His urine examination was normal. He had tremors of both hands and
cyclosporine trough level was 248ng/ml. He underwent renal biopsy. The biopsy showed sixteen glomeruli. Two of them were globally sclerosed. The viable glomeruli showed ischemic changes with contracted capillary loops, wrinkled basement membranes and increase in urinary space (figure 1).

There was extensive interstitial fibrosis, tubular atrophy and tubular loss along with arteriolar hyalinosis (figure 2). Immunofluorescence staining for IgG, IgA and C3 were negative. Biopsy features are consistent with chronic cyclosporine toxicity.

Table 1:

<table>
<thead>
<tr>
<th>Time</th>
<th>Sr. creatinine (mg/dl)</th>
<th>CsA morning (mg)</th>
<th>CsA Evening (mg)</th>
<th>Clinical signs of toxicity</th>
<th>C0 Level (ng/ml)</th>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 2010</td>
<td>1.1</td>
<td>150</td>
<td>150</td>
<td>Nil</td>
<td>249</td>
<td>Nil</td>
</tr>
<tr>
<td>Jan 2012</td>
<td>1.6</td>
<td>150</td>
<td>150</td>
<td>Tremors</td>
<td>249</td>
<td>Renal biopsy was done and dose reduced to 100 mg bd</td>
</tr>
<tr>
<td>July 2012</td>
<td>1.5</td>
<td>100</td>
<td>100</td>
<td>Nil</td>
<td>223</td>
<td>Dose reduced to 100/75 mg</td>
</tr>
<tr>
<td>July 2013</td>
<td>1.5</td>
<td>100</td>
<td>75</td>
<td>Tremors</td>
<td>234</td>
<td>Dose reduced to 75mg bd</td>
</tr>
<tr>
<td>April 2014</td>
<td>1.9</td>
<td>75</td>
<td>75</td>
<td>Tremors</td>
<td>248</td>
<td>Dose reduced to 75/50 mg</td>
</tr>
</tbody>
</table>
Discussion
The increased success and availability of transplantation of non renal solid organs has resulted in a large number of patients at risk for renal complications of long-term immunosuppressive therapy (1-2). By 10 years after transplantation, approximately 12% of heart, 2 to 7% of lung, and 4% of liver transplant recipients had developed severe renal insufficiency (3-8). The most important factor in the etiology of this renal failure is the chronic nephrotoxicity of Calcineurin inhibitors (CNI)(4). An attempt to withdraw CsA and maintain patients on azathioprine and steroids had resulted in episodes of rejection(3). Risk factors for nephrotoxicity are advanced age, female gender, hypertension, diabetes mellitus, volume depletion, perioperative AKI, atherosclerosis, cardio renal syndrome, and conditions with chronic hypoxia like cyanotic congenital heart disease, cystic fibrosis and pulmonary hypertension(3-5).

Mechanism of renal injury
Calcineurin inhibitors are potent vasoconstrictors that profoundly affect both afferent glomerular blood flow and promotion of systemic hypertension. The hemodynamic and nephrotoxic effects of CNI are mediated through inhibition of nitric oxide and alterations in the RAAS, (8-11). Angiotensin II is a potent vasoconstrictor that promotes interstitial scarring in the kidney. (12-13). Aldosterone increases sodium and water retention and, in the presence of ATII, also upregulates the expression of plasminogen activator inhibitor-1, which may directly lead to glomerular injury. Calcineurin inhibitors also promote the activity of other profibrotic and thrombotic cytokines, such as platelet-derived growth factor, thromboxane, and transforming growth factor-beta 1 (14-16). The latter has been shown to cause interstitial renal scarring in murine models of kidney injury and likely plays a part in chronic allograft nephropathy. (17-19). Increased intrarenal expression of additional profibrotic substances, such as collagen, fibronectin, osteopontin, and matrix metalloproteinases 2 and 9, have also been shown in patients exposed to CNI.(18-19)

Pathology
Acute toxicity causes acute afferent arteriopathy (endothelial swelling/vacuolation; necrosis and in early-stages hyaline replacement of individual myocytes), tubulopathy (small, evenly distributed vacuoles, mainly in the proximal straight tubule) and Thrombotic microangiopathy (rare). In chronic toxicity, the common finding is that of interstitial fibrosis accompanied by tubular atrophy. This is often associated with an obliterator vasculopathy, characterized by arteriolar hyalinosis, with myocyte necrosis, nodular hyaline deposits, and mucoid intimal edema. The glomeruli show changes suggestive of ischemia and collapse, with some global sclerosis. The other lesions seen more frequently in non-renal transplant patients are that of focal segmental glomerulosclerosis (FSGS) (20). In our patient there was extensive interstitial fibrosis, tubular atrophy and tubular loss along with arteriolar hyalinosis with two glomeruli were globally sclerosed.

Recommendations of International Society of Heart and Lung Transplantation for the care of heart transplant recipients (2010) on CNI usage and in minimizing the drug toxicity.
1 Calcineurin inhibitor-based therapy remains the standard in immunosuppressive protocols used after cardiac transplant (IIB).

2 The use of the microemulsion formulation of CsA is recommended because it is associated with more favorable pharmacokinetic features compared with the oil-based compound. (IIB).

3 The results of clinical trials suggest that Tacrolimus(TAC) -based regimens may be associated with lower rejection rates but not with superior survival than CsA -based regimens. (IIB).

4 Immunosuppressive induction with polyclonal antibody preparations may be beneficial in patients at high risk of renal dysfunction when used with the intent to delay or avoid the use of a CNI. (IIB).

5 Cyclosporine withdrawal can be successfully achieved 3 to 6 months after cardiac transplant in many low-risk patients (those without circulating anti-HLA antibodies, non-multiparous women, those without a history of rejection, and older HT recipients). (IIB).

6 Cyclosporine avoidance, early weaning, or very low dose maintenance therapy are all acceptable therapeutic approaches. (IIB).

7 If used, Cyclosporine weaning should be attempted if there are significant side effects and no recent rejection episodes (eg, within 6 months). (II C).

8 Lower levels of CNI in cardiac transplant recipients should be sought when CNI are used in conjunction with MMF (compared with AZA) because with this combination lower levels are safe and associated with lower rejection rates as well as improved renal function. (I B).

9 A Proliferation signal inhibitor may be substituted for CNI later than 6 months after to reduce CNI-related nephrotoxicity and in low-risk recipients. (IIC).

10 In Cardiac Transplant recipients, substitution of PSI for MMF for the specific purpose of lowering CNI exposure to reduce CNI-related nephrotoxicity is not recommended due to the interaction between CNI and PSI, which enhances CNI nephrotoxicity. (III C).

11 Measurement of 12-hour trough Cyclosporine concentration is the recommended form of therapeutic drug monitoring for routine clinical use. The target levels are dependent on the method used (high-performance liquid chromatography [HPLC] vs enzyme multiplied immunoassay technique [EMIT] vs cloned enzyme donor immunoassay method [CEDIA]), concomitant immunosuppression, toxicity risks, and time after cardiac transplant. In general, when used in conjunction with azathioprine (AZA) or a mycophenolic acid (MPA) preparation, the average CYA trough concentration target using the Abbot TDX assay (or equivalent) is 325 ng/ml (range, 275–375 ng/ml) for the first 6 post-operative weeks, 275 ng/ml (range 200–350 ng/ml) for Weeks 6 to 12, 225 ng/ml (range 150–300 ng/mL) for Month 3 to Month 6, and 200 ng/ml (range 150–250 ng/mL) from Month 6 onwards. (IIC).
Measurement of 12-hour trough concentration for twice-daily tacrolimus (TAC) and a 24-hour trough concentration for once-daily TAC is the recommended drug monitoring method for routine clinical use. The therapeutic range of TAC levels varies depending on concomitant drugs, toxicity concerns, and time after HT. In general, when used in conjunction with AZA or a MPA preparation, TAC trough concentration targets range between 10 and 15 ng/ml during the early post-operative period (Days 0–60), between 8 and 12 ng/ml for the next 3 to 6 months, and between 5 and 10 ng/ml in stable patients 6 months after HT. (IIC).

Conclusions:
This case report highlights the importance of close monitoring of CNI levels in non renal solid organ transplant recipients. Multidisciplinary team approach including transplant surgeon, cardiologist and nephrologists is required to monitor and assess long term immunosuppressive therapy.

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