

A Young Male Heart Transplant Recipient who Developed CKD due to Cyclosporine Therapy after a Decade

Vaishnavi Chandramohan, Georgi Abraham, Milli Matthew, Ajith Mullassery, Kanchana Thirumoorthy

Abstract

We report cyclosporine-induced chronic kidney disease (CKD) in a 38-year old man who underwent cadaveric orthotopic heart transplant done 13 years ago. He was on triple immuno-suppression including micro-emulsion form of cyclosporine (neoral) with monitoring of his blood cyclosporine levels and serum creatinine. We discuss the pathophysiological mechanisms of cyclosporine toxicity in heart transplant recipients.

Introduction

Cyclosporine A (CsA)-induced nephrotoxicity is now one of the most important long-term complications in recipients of heart transplants.¹ The incidence of end-stage renal disease requiring dialysis or transplantation is 4-5% in large transplant centers.²

Moreover, 78.5% of patients develop chronic renal insufficiency after being on the therapy five years after transplantation.³

Altering the dose of cyclosporine does not avoid chronic nephrotoxicity in recipients of heart transplants although the incidence of renal failure is considerably less.

In a study done at the Heart Center North Rhine-Westphalia, the dosage of cyclosporine was halved in group A patients, with the addition of mycophenolate mofetil and prednisolone for 6 weeks. Group B patients were maintained on the same dosage of cyclosporine which they were receiving prior to the study. Measurements of serum creatinine and blood urea nitrogen (BUN) were monitored before and after heart transplantation. Although Group A patients still had elevated BUN and serum creatinine levels only a few developed progressive renal failure as compared to Group B patients.²

An attempt to withdraw CsA and maintain patients on azathioprine and steroids in patients who developed late nephrotoxicity resulted in episodes of rejection, some fatal

in several patients thus laying emphasis on the necessity of cyclosporine A for patients of heart transplant.³

Strict monitoring of blood cyclosporine levels is essential to minimize the risk of permanent renal damage. Monitoring urine examination including protein excretion in addition to plasma creatinine may detect the onset of focal segmental glomerulosclerosis.⁴

Here we are presenting the first case from India of cyclosporine nephrotoxicity with CKD in a surviving orthotopic cadaveric heart transplant patient 13 years after the transplantation.

Case Report

A 25-year-old vegetarian male who was a heavy smoker of 1 pack per day for more than 15 years, developed dilated cardiomyopathy and severe congestive cardiac failure with Grade 4 effort intolerance. He did not consume alcohol and has no family history of heart disease. He weighed 50 kgs, and serological work up for hepatitis B, hepatitis C, Epstein-Barr virus and HIV was negative. He was put on the deceased donor waiting list for a heart transplant. He underwent a deceased donor heart transplant in December 1995 at the Madras Medical Mission hospital from a 40-year-old male road-traffic accident victim who was brain-dead and on a ventilator. He was immunosuppressed with prednisolone 50mg od, azathioprine 125 mg od and a micro-emulsion form of cyclosporine (neoral) 125 mg bd. He had undergone protocol biopsies of the heart and there was no evidence of rejection. He stopped smoking, and he continued a very active life and took part in Transplant Olympics in Sydney, Australia. The serum creatinine and blood cyclosporine levels along with the dosage taken is given in Table 1 below.

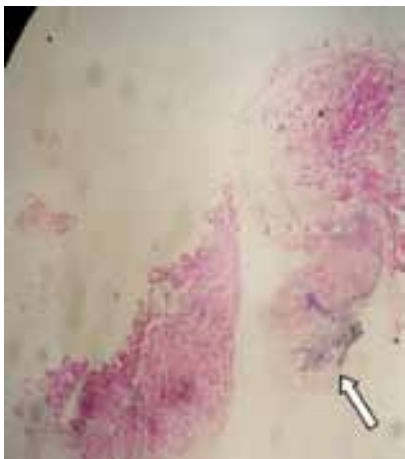


Fig. 1a : Heart- Endomyocardial biopsy showing resolving rejection

Madras Medical Mission Hospital, Chennai; Pondicherry Institute of Medical Sciences, Puducherry

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Year	S. creatinine	Cs-A dose		Blood CS-A levels	Creatinine clearance
		am	pm		
1995		125 mg	125 mg		
1996	1 mg/dl	100 mg	75 mg	193 ng/ml*	99.2
1997	0.8 mg/dl	75 mg	50 mg	100-150 ng/ml* 500-600 ng/ml^	124
1999	1.9 mg/dl	100 mg	100 mg	93 ng/ml*	52.2
2000	1.2-1.5 mg/dl	150 mg	150 mg	210 ng/ml*	82.6
		75 mg	50 mg	190 ng/ml^	66.1
2002	1.5 mg/dl			190 ng/ml*	66.1
2003	1.8 mg/dl				55.1
2004	1.6 mg/dl			528 ng/ml^	62.0
2007	1.9 mg/dl	100 mg	50 mg		52.2

*whole blood trough level; ^c-2 level

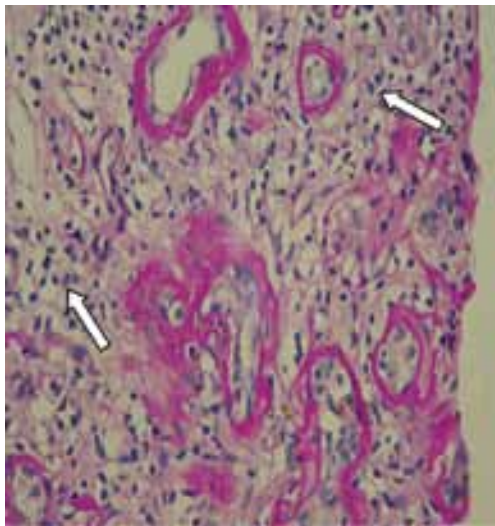


Fig. 1b : Kidney- Cytoplasmic vacuolization of tubules

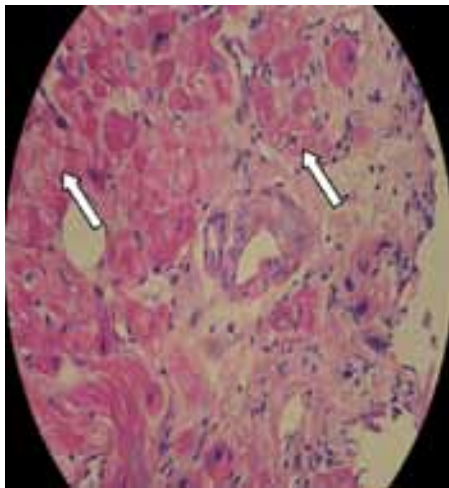


Fig. 1c : Heart – Interstitial fibrosis, perivascular with mononuclear infiltrates

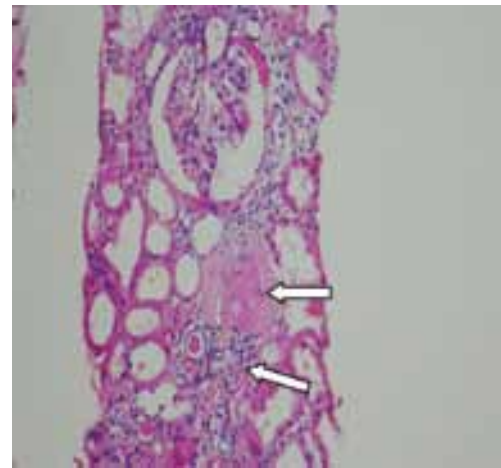


Fig 1d : Kidney-Tubular atrophy, interstitial fibrosis

He had a rejection episode in May 2000 when he presented with shortness of breath and edema and he underwent an endocardial biopsy through the right internal jugular vein.

The rejection episode was treated with injection methylprednisolone with mononuclear infiltrates inflammation with fibrosis 500 mg for 5 days and T cell depleting monoclonal antibody IO R3- 5mg intravenous for 10 days. His rejection reversed and he continued to do well. A coronary angiogram done showed normal epicardial coronaries and a renal angiogram did not show evidence of renal artery stenosis soon after the treatment of rejection episode.

In September 2002, ultrasound examination of the kidneys showed right kidney 10.4 cmx4.6cm and left kidney 9.6cmx4.6cm with normal appearance. Urine examination was unremarkable.

On routine examination in 2007 his weight was 66kg,height 174cm and BMI 23.6 kg/m².Ultrasound of the abdomen showed normal sized kidneys with normal architecture. BP was 130/80 mmHg. Serological work up including HBsAg and anti-HCV were negative and urine examination was normal. In February 2008, he underwent an ultrasound-guided percutaneous renal biopsy, 13 years after his heart transplantation.

The histopathological features were diagnostic of chronic cyclosporine toxicity (Figure I). Immunofluorescence was

negative. Other investigations included: serum cholesterol: 208mg/dl, triglycerides 220mg/dl, HDL 40mg/dl, LDL 123mg/dl.

He was switched over to rapamycin 2mg OD while tapering and discontinuing neoral in a week. His blood trough rapamycin level was 12 ng/ml on 2 mg OD which was reduced to 1mg OD to maintain a blood level of 8 ng/ml.

Discussion

The adverse effects of cyclosporine are hyperkalemia, Type 4 renal tubular acidosis (RTA), thrombotic microangiopathy,oligoanuric acute renal failure and CKD. A rare side effect of cyclosporine is permanent renal damage. Chronic kidney disease is clinically evident in 80-100% of non-renal transplant patients who have survived 36 months after transplantation.³ The percentage of cardiac transplant recipients with stages 4 to 5 CKD is 1.9% about 12 months after transplantation,6.8% after 36 months and 10.9% 60 months after transplantation.⁶

Acute functional toxicity of cyclosporine manifests with drop in glomerular filtration rate, elevation of serum creatinine level, vasoconstriction and toxic tubulopathy which are reversible in response to lowering of the dosage of the drug. The diagnosis of arteriopathy and thrombotic microangiopathy should lead to cessation of cyclosporine administration as there is a chance of irreversible renal damage.⁵

Chronic nephrotoxicity is characterized by hyaline arteriopathy, striped interstitial fibrosis and tubular atrophy as seen in our case. The presence of glomerulopathy with focal or segmental glomerulosclerosis is also an indicator of chronic kidney damage which is irreversible. Appropriate management is dose reduction or discontinuation of cyclosporine and a switch over to alternative immunosuppressive agents.

The development of CKD in non-renal transplant recipients mandates reduction or elimination of nephrotoxic drugs including cyclosporine and tacrolimus as there is additional risk of increased frequency of hospitalizations and infectious complications. There is also a two to four fold increased risk of mortality and dysfunction of transplanted heart.⁶

The following risk factors were considered to give rise to renal disease in cardiac transplant recipients. These included drug-induced nephrotoxicity, atherosclerosis involving renal vessels, renal hypoperfusion caused by congestive cardiac failure, cyanotic congenital heart disease, hypertension, diabetes

mellitus, peri-operative acute kidney injury and advancing age. The incidence of chronic nephrotoxicity increases with time since transplantation.⁵

The mechanism of chronic nephrotoxicity is mediated by angiotensin-II and aldosterone which lead to renal vascular injury and vascular thrombosis, tubulointerstitial fibrosis and glomerulosclerosis. Chronic Cs-A use stimulates plasma renin and pro rennin activity with hyperplasia of juxtaglomerular apparatus. There is increased synthesis of TGF-beta. In advanced cases, renal scan shows normal or reduced size kidneys. Calcium channel blockers improve GFR if added to a calcineurin inhibitor(CNI) regimen because they reduce the degree of afferent arteriole vasoconstriction. Incorporating mycophenolate mofetil or mTOR inhibitor can reduce the dosage of CNI given. This patient will require renal replacement therapy in future.

From the point of view of the transplant cardiologist, it would be useful to know which patients are more likely to develop renal dysfunction when treated with CsA as age and the presence of renovascular disease may be important risk factors. This could lead to better targeted therapy, with the use of agents like mycophenolate mofetil, rapamycin and low-dose CsA from the outset in those patients at greater risk in consultation with the nephrologist.²

We conclude that to ameliorate nephrotoxicity due to

cyclosporine, renal functions should be monitored closely and periodically in orthotopic heart transplant recipients combinedly by the treating cardiologists and nephrologists. As newer least nephrotoxic immunosuppressive agents have become available, patients who are on CNI should be switched over to these newer agents to prevent long term nephrotoxicity and thereby CKD in these patients.

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