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Successful kidney transplantation in a patient with severely compromised cardiac functions and having pre-formed donor specific antibodies

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Abstract

A young End Stage Renal Disease (ESRD) patient on maintenance hemodialysis with severely compromised cardiac functions [LVEF ~ 15%] and pre-formed Donor Specific Antibodies [DSA], who was initially not considered for transplant, underwent successful kidney transplantation after following standard treatment protocols. This case report emphasizes on two important and frequently encountered clinical scenarios. First, ESRD patients should not be denied kidney transplantation solely on the basis of compromised cardiac functions, rather be encouraged for an early transplant. Second, clinically inappropriate decisions can be taken if false positivity of DSA reports by solid phase assays are not interpreted correctly.

Keywords

Ejection fraction; donor specific antibodies; kidney transplantation; echocardiogram; luminex solid phase assay.

Introduction

Severely compromised cardiac functions with or without ischemic heart disease and pre-formed Donor Specific Antibodies have been considered relative contraindications to kidney transplantation. Here, we present a case where despite these limitations, Kidney transplantation was done successfully. Undue inhibitions and sometimes incorrect interpretation may unnecessarily limit the patient's access to best modality of Renal replacement therapy i:e Transplantation.

Case Report

A 35 years old non diabetic female with bilaterally contracted kidneys being managed with alterna-

tive Indian medicines (Ayurvedic treatment) from last 2 years presented to our hospital with uremic symptoms and volume overload with severely deranged Renal functions (serum creatinine 11.5 mg/dl; Urea 245 mg/dl). Renal Replacement Therapy (RRT) in the form of hemodialysis was initiated and kidney transplant work up was started with her mother as prospective donor.

Patient had dyspnea at rest (NYHA class IV) despite adequate dialysis dose. Echocardiogram of patient was suggestive of global Left ventricular hypokinesia with Left Ventricular Ejection Fraction (LVEF) of 15 – 20%, Grade 3 Diastolic relaxation abnormality, moderate MR, mild TR and dilatation of both atria and ventricles. Echocardiogram was performed by an experienced Cardiologist after patient achieved dry weight by optimum dose and duration of hemodialysis/ultrafiltration with adequate salt and fluid restriction. Angiography did not reveal any significant coronary artery disease. Congestive Heart Failure (CHF) was managed with adequate dose of dialysis, Beta blocker (Carvedilol), anemia management and restriction of dietary sodium (< 2 gm/day) and fluid (<1 litre/day). In view of her severely compromised cardiac status, cardiologist gave clearance for transplant surgery categorizing the patient into high risk probability of adverse cardiovascular events during perioperative period.

Complement dependent Lymphocytotoxicity (CDC) crossmatch and Flowcytometry (FCXM) HLA T & B lymphocyte crossmatch were negative. HLA DNA typing (A,B,DR) showed a 3/6 mismatch (Table1).

Table 1

Name	HLA -A	HLA -B	HLA - DR
Patient	A*02, A*23	B*41, B*50	DRB1*03, DRB1*07
Donor	A*23, A*26	B*38, B*41	DRB1*07, DRB1*13

Donor specific IgG HLA antibodies by Luminex Fluorobeads XMap (LumXm) were negative for Class 1 (HLA A,B) but weakly positive for Class 2 (HLA DRB1) [Mean Fluorescence Intensity (MFI) 580 (cutoff <500)]. She had a history of multiple blood transfusions during last 1 year which might be her possible sensitizing events. LumXm was repeated after a gap of one month which again was positive for Class 2 (HLA DRB1) (MFI 530; cutoff <500). No anti HLA Class 2 antibodies were identified by Single Antigen Bead (SAB) assay, done subsequently.

In view of weekly positive LumXm but negative CDC, FCXM & SAB assays, patient was cleared for undergoing kidney transplant surgery. Patient and her family was counselled with respect to the higher risk of graft rejection and subsequent financial burden.

Anti thymocyte globulins (ATG) was used as induction agent keeping the possibility of alloimmunization and no desensitization protocol was followed prior to transplant.

Considering her low EF, Goal directed therapy for fluid management [1] was followed for 3 days in ICU after surgery. Clinical course of patient remained uneventful in perioperative period. Patient was discharged on 8th day after surgery with serum creatinine of 0.8 mg/dl and discharge medication included Tacrolimus, MMF and Prednisolone.

Echocardiogram was repeated by same cardiologist after regular intervals after transplant and her Cardiac functions improved significantly as shown in Table 2.

Table 2

Echocardiogram Parameter	Prior to Tx	1 month post Tx	3 months post Tx	6 months post Tx
LVEF	15-20%	30%	45%	55%
MR	MODERATE	MILD	MILD	MILD
DRA	GRADE 3	GRADE 1	GRADE 1	GRADE 1
CHAMBER DILATATION	LA,LV,RA,RV	LA,LV	LA DILATED LV HIGH NORMAL	LA,LV HIGH NORMAL

Tx: Transplant; LVEF: Left Ventricular Ejection Fraction; MR: Mitral Regurgitation; DRA: Diastolic Relaxation Abnormality; LA: Left Atrium; LV: Left Ventricle; RA: Right Atrium; RV: Right Ventricle.

Discussion

Low EF and positive DSA by solid phase assays have been considered relative contraindications to renal transplantation. This case report emphasizes on the relevance of these two frequently encountered clinical scenarios.

Increasing evidence points to shared pathophysiological milieu in patients with concomitant cardiac and renal dysfunction. Patients with Heart Failure (HF) as primary syndrome can experience secondary kidney disease (Cardio renal syndrome) and vice-versa, the distinction between which disease is primary and which secondary is often challenging. The presence of one condition appears to accelerate the progression of other. As severity of Chronic Kidney Disease (CKD) increases, so does the prevalence of HF. An estimated 44% of patients on hemodialysis have HF [2]. Overt HF in the setting of End Stage Renal Disease (ESRD) portends a dismal outlook with three years mortality of 50% after diagnosis and 80% after hospitalization for HF [3].

Several studies have suggested that patients with CKD, as compared to non renal patients, are less likely to receive adequate (guidelines based) treatment for HF. This is because of many reasons which include higher risk of adverse events (hyperkalemia, hypotension, loss of kidney function etc) with drugs (ACEi, ARBs, MRA, Beta blockers) commonly used to treat HF, lack of data and studies in CKD population, relative control of HF symptoms by dialysis itself and non compliance amongst CKD patients due to polypharmacy, the prevalence of which is upto 50%.

Approximately 87% of patients with ESRD have major abnormalities on echocardiogram before initiating treatment with dialysis. Both pressure and volume overload present in CKD contribute to cardiac structural and functional abnormalities [4]. Exact etiology of dilated cardiomyopathy with low cardiac output frequently seen in CKD patients, as seen in our case also, without Ischemic Heart Disease (IHD) is not known. Certain uremic molecules (exact nature of which is not yet determined), Sympathetic over activity and Autonomic neuropathy associated with Uremic status have all been postulated to exert cardio toxic effects.

There are arguments for and against kidney transplant in ESRD patients with significantly decreased systolic functions, as in our case because of high risks of surgical and cardiac complications in perioperative period. HF at the time of transplant particularly those with LVEF <40% are at higher risk of all cause

mortality, cardiovascular events and Graft failure [5]. However, both prospective and retrospective studies have also shown significant improvement in cardiac functions and uneventful perioperative clinical course after kidney transplant even in cases of severely compromised cardiac functions [6] as happened in this case too. Expectations of improvement of cardiac functions after transplant are low in patients with long dialysis vintage [6]. In our case dialysis vintage was less than 6 months.

Pre transplant HF has also been identified as a strong predictor of post transplant recurrence, graft loss and risk factor for HF hospitalizations. The incidence of post transplant de-novo HF is ~ 18% at 3 years. De novo HF is also associated with lower patient and graft survival [7].

Cardiac functions improved significantly (Table 2) in our patient post transplant with complete resolution of symptoms. Since echocardiogram can give false values in presence of volume overload, imaging should be carried out when patients on dialysis are close to their dry weight. As a result of intensive dry weight and blood pressure control with frequent and prolonged hemodialysis, this patient was not volume overloaded at the time of transplant. Furthermore, her body weight never decreased rather increased after transplant suggesting absence of volume overload at the time of transplant.

CKD has been associated with increased levels of inflammatory markers such as TNF-alpha, IL-1 & IL-6. Lower inflammatory markers as well as elimination of "yet undefined uremic toxins that cause myocardial depression", Improvement in the level of anemia and volume status may all potentially explain the improvement in cardiac functions post kidney transplant. Despite few reports showing some improvement of LVEF with hemodialysis, this procedure may not eliminate these undefined uremic toxins as efficiently as done by kidney transplant.

To conclude, ESRD patients should not be rejected from undergoing kidney transplant solely on the basis of compromised cardiac functions, rather be advised for early transplant as improvement in renal functions via kidney transplant might prove to be the strongest therapeutic intervention for recovery of their cardiac functions.

Another important point to be emphasized from this case report is proper interpretation of positive Donor Specific Antibodies (DSA) as clinically inappropriate decision can be taken if not interpreted correctly. HLA alloimunization is considered major histocompatibility barrier to successful organ transplantation and has been associated with an increased risk of rejection and allograft loss after transplant. In our case, Donor specific IgG antibodies by Luminex (LumXm) were negative for Class 1 (HLA A,B) but were weekly positive for Class 2 (HLA DRB1) [MFI 530; cut-off < 500] for which she was refused kidney transplant at other centers and referred to our hospital.

The first question was whether DSA were really present in our patient or the results were false positive in view of negative CDC and FCXM cross match? To confirm false positivity, a more sensitive but much costlier SAB assay was performed which did not identify anti HLA Class 2 antibodies. The LumXm incorporates a blend of Luminex beads, each with a unique fluorescent signature. Two among the beads are coated with monoclonal antibodies specific for class 1 or class 2 HLA. The LumXm detects donor spe-

cific antibodies using antigens derived from the actual donor, while Luminex single antigen assay use pre attached antigens derived by recombinant technology. False positivity has been reported on the Luminex single antigen assay and is attributed to denatured antigenic epitopes produced during processing. Case reports suggest that antibodies to the denatured epitopes do not affect the graft. Such positivity has not been reported in the LumXm assay that uses native antigens extracted from the lymphocyte membrane after membrane lysis using detergent.

There can be other causes of false positivity of highly sensitive LumXm assay like the presence of immune complexes or other immunoglobulins aggregates in sample, bacterial contamination of sample and variable amount of target HLA present on the beads. Chacko M.P et al. [8] have demonstrated that antibodies being detected by LumXm assay may be directed at an epitope uniquely present on the Luminex beads rather than HLA antigens leading to false positive values. Moreover, there is no recommended cut off values for Mean Fluorescence Intensity (MFI) positivity. Most labs set their cut off levels based on levels obtained with relevant controls and also on experience gained from clinical results. Borderline cut-off values should therefore be a guide and not rigidly enforced without careful considerations. Since Single Antigen Bead (SAB) assay which is the most sensitive test to detect HLA antibodies was negative in our patient while a lesser sensitive solid phase assay [LumXm] was weekly positive, probably the cut off MFI values (<500) set by the lab was more stringent or the result was falsely positive.

Positive DSA result is not a contraindication to renal transplant but may represent additional risk of rejection. The interpretation of positive bead based assay results in the context of negative microlymphocytotoxicity (CDC) and flow cross match is not clearly defined. The question of clinical relevance of these HLA antibodies in rejection has been reported in renal, heart and Liver transplant with mixed results [9,10]. As our patient with severely compromised cardiac status (LVEF ~15%) had a very poor prognosis on hemodialysis, a failure to identify false positive antibodies from the Luminex assays might have unnecessarily limited the patient's access to transplantation or resulted in the administration of unnecessary and costly treatment of desensitization associated with potential adverse effects of enhanced immunosuppression. The utility of money saved by avoiding unnecessary expensive treatment and tests performed and interpreted wrongly, should not be underestimated especially in developing countries like India where most of the patients are paying from their pockets. On the other hand, a failure to identify relevant HLA antibodies (false negatives) may result in the transplantation of organs with which there is an unanticipated increased risk of immunological injury that may prove detrimental to graft and recipient outcomes. So, once DSA are detected either pre or post transplant must be respected.

Conclusion

Irrespective of dialysis vintage, under careful monitoring, kidney transplant is a safe and effective procedure even in patients with severely compromised cardiac functions. There is no single perfect test till date, providing the desirable accuracy, quantitation, sensitivity and specificity to determine the immunological risk for a particular transplant recipient, so multiple imperfect assays should be used to determine true antibodies. This necessitates a personalised decision making process for each transplant recipient

with inputs from the clinicians, HLA laboratories and often the patient and their families themselves.

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