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# A Challenging Case of Liver and Kidney Transplantation-Our Experience

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**Abstract**

In multiple solid organ transplantation, one of the main concerns is the complex immunological and clinical management of transplanted recipients with the result of the graft rejection prevention. Selecting the personalized immunosuppressive regimens in such cases is also challenging. A too low dose of immunosuppressive drug may lead to de novo anti-HLA antibodies appearance with progressive graft loss, while too high doses may lead to drug toxicity primarily affecting the organs involved and the metabolism. Calcineurin inhibitors treatment failure makes the patient to return on the waiting list. We present the case of a liver transplanted female patient in whom the nephrotoxicity induced by post transplantation tacrolimus led to the need for kidney transplantation in order to save her life.

**Keywords:** Multiple solid organ transplantation; ACE gene polymorphisms; Graft rejection; Anti-HLA; Calcineurin inhibitors

**Abbreviations:** HLA: Human Leukocyte Antigens; CNI: Calcineurin Inhibitors; ACE: Angiotensin Converting Enzyme

## Past Medical History

The 25 years old female patient, known with neonatal hepatitis of unknown etiology from birth was diagnosed with liver cirrhosis at the age of 4. Liver transplantation was performed from an unrelated brain death cadaveric donor in 2011, with incomplete matches at HLA-A, -B and -DRB1 loci. The transplant procedure was complicated with biliary anastomosis stenosis for which stent dilatation was needed. To prevent acute liver rejection, she received the following immunosuppressive combination: Prograf (5 mg/day=2.5 mg+2.5 mg), Myfortic 180 mg × 4/d and Prednisone 5 mg/d. She was clinically very well until 2013 when the signs of kidney failure appeared. The renal insufficiency with this treatment was documented by both clinical and laboratory tests as a result of drug toxicity (calcineurin inhibitor nephrotoxicity-tacrolimus). In January 2016, finally, the diagnostic was established as stage IV chronic kidney disease with proteinuria and small bilateral kidneys. Several months after that she was put on kidney transplantation waiting list. Fortunately, in the same year, she underwent kidney transplantation procedure from her mother, with haploidentical HLA. The histocompatibility assessment revealed:

- Donor and recipient were ABO and Rh compatible.
- Donor's HLA A30, A32, B13, B51, DR4, DR7.
- Receptor's HLA A1, A30, B13, B40, DR7, DR10.
- Anti-HLA antibodies: class I-negative and class II-positive (DQ2, DQ4, DQ7, DQ8, DQ9).
- Cross-match negative for class I and class II.

Post transplantation evolution was improved with no surgical, immunological or infectious complications. Laboratory analyzes showed urine output=2500 ml, creatinine=1.05 mg/dl, Hb=7.8 g/dl, tacrolimus concentration in whole blood level was 13.2 ng/ml. No proteinuria was detectable anymore in urine.

She was released with the following recommended medication: Prograf 10 mg/d=5 mg+5 mg, Myfortic 540 mg × 2/d, Prednisone 10 mg/d after meal, Omeran 20 mg/d, Biseptol 1 tb/d for 6 months post-transplantation, Valgancyclovir 450 mg/d (180 days), Betaloc Zok 50 mg × 2/d, Methionine 1.5 g/d.

One year later she was admitted to the hospital for marked physical asthenia, fever (38.3°C), diarrhea (3-4 episodes/d), nausea and vomiting started 3-4 days before admission. During admission, the patient presented chills, leukopenia 1.390/mmc, thrombocytopenia 35,000/mmc, high levels of procalcitonin (14.68 ng/mL), tacrolimus=8.6 ng/ml (Prograf 10 mg/day=5 mg+5 mg), creatinine=2.56 mg/dl and negative hemoculture. There was a suspicion of sepsis with origin in the gut. She was recommended to start empirical treatment with Meronym, Linezolid, Ecalta and Levofloxacin. Antibiotic and antifungal treatment was given for 10 days associated with a decrease in the dose of Prograf to 4 mg/d and temporary withdrawal of Myfortic. The evolution was favorable both clinically and biologically. At discharge, she had no more fever or inflammatory syndrome and creatinine=1.34 mg/dl.

In 2017, she applied for a regular check-up. The clinical evaluation showed fever, asthenia, nausea and fatigue. All these symptoms started one week before. Laboratory tests showed normocytic normochromic anemia, hypolipidemia, significant inflammatory syndrome, nitrogen retention (creatinine=1.66 mg/dl), frequent miction with fungal infections, positive hemoculture with *Klebsiella pneumoniae*, high level of plasma BKV viremia and *de novo* anti-HLA antibodies: class I (B8) and class II (DR57, DR58, DQ2, DQ4, DQ7, DQ8, DQ9). All of these de novo anti-HLA antibodies are not donor specific. Antifungal treatment with Mycamin and Levofloxacin with the decreasing daily Tacrolimus doses (Prograf=3.5 mg/d) resulted in favorable evolution. One-month later BKV become undetectable with stable anti-HLA antibodies identified and no other symptomatology.

## Discussion

Tacrolimus is a reliable immunosuppressive drug given after many solid organ transplantations such as heart, lung, liver, pancreas, kidney (recommended by KDIGO guideline [1]) or combined organ transplantation [2].

Thölking et al. demonstrated, in a study of 311 patients who underwent a renal transplantation, that tacrolimus metabolism rate influences both renal function and frequency of BKV infection in renal transplantation. The tacrolimus metabolism rate is defined by the ratio between the level of tacrolimus blood level and the daily dose of tacrolimus received by the transplanted patient [3]. Thus, a low level of tacrolimus metabolism is associated with lower eGFR values, higher rates of CNI nephrotoxicity [4], a higher incidence of BKV nephropathy (BKN) and infections [3].

All CNI's side effects could be explained by different DNA genotypes. A number of genes like the renin-angiotensin system (RAS) genes and cytokine-encoding genes have been associated with calcineurin inhibitor-induced nephrotoxicity [5]. One of the components of the RAS is ACE with gene I/D [6]. Galon et al. demonstrated that an increased risk of CNI-induced chronic nephrotoxicity could be found in liver transplant recipients with ACE gene D [7]. Known ACE genotypes and other renin-angiotensin system genes could identify liver and other organ transplant patients who are at risk of developing CNI nephrotoxicity.

Early infections with nosocomial pathogens, opportunistic pathogen and late infections tend to appear at predictable time intervals after transplant [8]. Opportunistic pathogen infections usually appear in case of high level of CNI [8].

In the presence of cellular immunodeficiency status, BK virus (BKV) could be reactivated causing hemorrhagic cystitis and nephritis [9,10].

BKV nephropathy affects up to 10% of kidney transplant recipient and can lead to graft's loss [11]. Reduction in immunosuppression results in a clearance of BKV viremia, and stabilization of graft function [12].

In our case, the Tacrolimus metabolism rate was 0.79 ng/ml, with tacrolimus-induced chronic kidney disease after the first year post liver transplantation. Also, it led to the appearance of a detectable BKV viral replication levels. By reducing the dose of Tacrolimus in approximately one month the BKV viremia has become undetectable. Unfortunately, the reduction of tacrolimus dose in a haploidentical donor-recipient HLA matching probably led to de novo anti-HLA antibodies appearance. Because of the development of *de novo* HLA antibodies it was raised the suspicion of acute antibody-mediated rejection [13,14]. Screening and identification of anti-HLA antibodies were done using Luminex 200 analyzer, LabScreen Mixed kit and LABScreen Single Antigen. A positive anti-HLA antibody was defined by a background-adjusted MFI cut-off of 1500 or greater.

To diagnose a rejection of renal allograft it is essential to evaluate the renal allograft biopsy [15]. By analyzing the kidney biopsy, in antibody-mediated allo-response can be identified an accumulation of C4d along peritubular capillaries (Figure 1) [16].

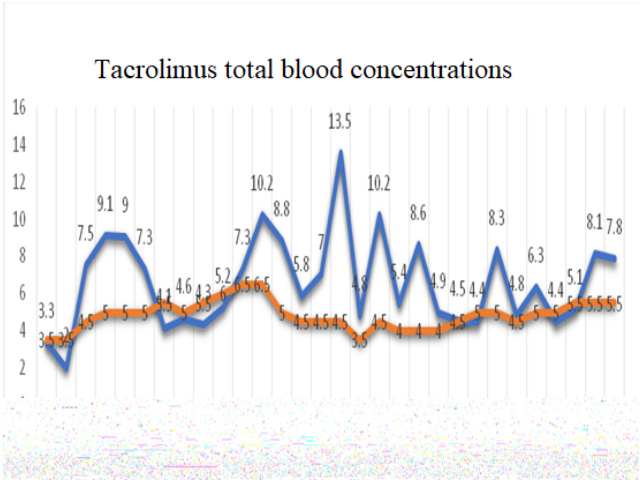


**Figure 1:** Tacrolimus total blood concentrations.

In liver organ transplantation recipients with 2 complete mismatches at either the HLA-B or -DR locus is associated with inferior graft survival according to a study published by Shin et al. [17].

In our experience, the liver graft has a tolerogenic capacity with resistance to cell-mediated as well as antibody-mediated rejection through its ability to absorb or neutralize allo-antibodies directed against HLA antigens, but protection against allo-immunity is not complete [18]. So, after liver transplantation, the patients receive immunosuppressive drugs in order to prevent the appearance of anti-HLA donor's specific antibodies which could lead to late acute rejection [19] or chronic ductopenic rejection [20]. Also, the liver has the ability to reverse ongoing rejection of other transplanted organs [21]. In patients with liver transplantation, Lee et al. showed that there are some factors which are involved in the development of the chronic kidney disease such as pre-transplantation hepatorenal syndrome, pre-transplantation proteinuria and high level of CNIs [22,23]. In patients with a history of liver disease tacrolimus could cause hepatotoxicity [24].

## Conclusions

In liver and kidney transplantation follow up it is essential. By systematically monitoring we could efficiently prevent acute rejection and we could identify the side effects of immunosuppressive therapy (tacrolimus, cyclosporine).

The choice of immune-suppressants should be made according to the particular feature of transplanted patients.

After liver transplantation, the patients should receive low doses of immunosuppressive drugs because of liver's ability to neutralize anti HLA antibodies [18].

The blood levels of immune-suppressants could be affected by co-administration of other drugs. So, it is necessary to check if there are any drug interactions before indicating any immunosuppressant combinations.

Therefore, regular concentration measurements of CNIs is mandatory in order to prevent side effects like nephrotoxicity,

hepatotoxicity, emergence of some infections and cancers that may be associated with an increased risk of rejection.

There is a need for personalized immunosuppressive protocols for patients with high and low bioavailability of tacrolimus or cyclosporine to reduce the incidence of graft rejection.

Anti-HLA antibodies should be monitored regularly. From this point of view, studies should be designed to have anti-HLA antibodies assessments always when changes in immunosuppression drug regimens are made. The impact of anti-HLA antibodies monitoring will be the prevention of early humoral and/or cellular mediated rejection.

Also, it is very important to look at HLA matching because the renal graft is a continuous source of HLA antigens against which the anti-HLA antibodies are directed.

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