Rewriting Unacceptable Antigens: HLA Delisting to Permit Transplantation - A Case Report

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Abstract

Highly sensitized kidney transplant candidates experience limited access to compatible donors, prolonged waiting times, and increased mortality while on dialysis due to broad anti-human leukocyte antigen (HLA) antibody reactivity. Advances in immunologic assessment, particularly single-antigen bead assays, have enabled more precise characterization of donor-specific antibodies (DSAs) and facilitated risk-adapted strategies such as antigen delisting, in which low-level or clinically insignificant antibodies are reclassified as acceptable to expand donor compatibility. We report the case of a 67-year-old woman with end-stage kidney disease secondary to autosomal dominant polycystic kidney disease and a calculated panel reactive antibody (cPRA) of 100%, who remained on the transplant waiting list for 12 years without a suitable living donor. Following implementation of a structured delisting protocol, low-intensity class I DSAs with a mean fluorescence intensity below 2000 were reclassified as acceptable, reducing her PRA to 99.75% and enabling a successful deceased-donor kidney transplantation. Induction immunosuppression included antithymocyte globulin, tacrolimus, mycophenolate mofetil, corticosteroids, and intravenous immunoglobulin, with adjunctive rituximab given her elevated immunologic risk. Although early postoperative hypotension required transient dialysis support, no evidence of rejection was documented. Donor-specific antibodies became undetectable after transplantation, and at three months, she exhibited excellent graft function with normal creatinine and minimal proteinuria. This case illustrates that individualized antigen-delisting strategies combined with intensified immunosuppression and careful immunologic risk stratification can safely expand transplant access for highly sensitized patients, offering improved outcomes and a meaningful survival advantage compared with continued dialysis.

Keywords: Blood Group Incompatibility; Desensitization, Immunologic; HLA Antigens; Histocompatibility; Kidney Failure, Chronic; Kidney Transplantation

INTRODUCTION

The rising incidence and prevalence of chronic kidney disease pose a major economic and societal challenge. Compared with dialysis, kidney transplantation improves quality of life and confers a survival advantage. However, deceased donor kidneys remain scarce, and the available supply is insufficient to meet the demand of all patients on the waiting list. Allocation of this limited resource must therefore balance fairness, efficiency, and flexibility.[1,2] Recent revisions to organ allocation systems have aimed to enhance equitable access to the active waiting list. Although these reforms represent an important advance, they have also increased the number of listed candidates without a corresponding expansion in organ availability, creating a scenario in which more patients may be registered but ultimately remain untransplanted.[1,2]

Among candidates on the transplant waiting list, highly sensitized individuals without a suitable living donor represent a particularly complex subgroup. Many of these patients demonstrate HLA incompatibility due the presence of anti-HLA antibodies against the entire local donor pool, resulting in markedly prolonged waiting times

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for deceased-donor kidney transplantation (DDKT) and increased waitlist mortality.[3-7] In recent years, several advances within the transplant ecosystem have improved the outlook for this population. These include prioritization of highly sensitized [calculated panel reactive antibody (cPRA) >= 80%] and particularly highly sensitized (cPRA>=98%) candidates within kidney allocation systems, expansion of kidney paired donation (KPD) programs, and the refinement of desensitization protocols for incompatible living-donor kidney transplantation.[3,7]

The introduction of single-antigen bead (SAB) Luminex assays has improved the detection of donor-specific antibodies (DSA) in kidney transplantation. Preformed DSAs are now well established to be associated with early acute antibody-mediated rejection (aAMR) and long-term graft loss.[4,6] Based on immunological risk, it is well recognized that not all DSAs carry equivalent pathogenic potential. Factors contributing to graft injury include IgG subclass, antibody strength measured by mean fluorescence intensity (MFI) and complement-binding capacity.[1,4]

Desensitization strategies aim to neutralize or lower anti-HLA antibody levels to a permissive threshold so that transplantation can proceed despite their presence and have demonstrated a survival advantage compared with remaining on the waiting list for a compatible organ.[3,7]

Antibody delisting strategies, aim to reduce the number of unacceptable HLA antigens by reclassifying them as clinically insignificant. In this manner, antibodies which are historical but have now disappeared, very low-level antibodies, or non-complement binding antibodies may be acceptable.[4-6]

This graduated approach has demonstrated a meaningful impact on access to transplantation among long-waitlisted patients with cPRA levels of 99.9%.[4-6] More aggressive stepwise strategies can be applied according to stratified immunological risk—low, intermediate, or high—using hierarchical MFI thresholds (<5000; <10 000; and any MFI), with prioritization beginning with HLA-Cw and HLA-DP antibodies, followed by HLA-A, HLA-B, and HLA-DR, and finally HLA-DQ when necessary.[6,4]

The most significant risk associated with transplantation in highly sensitized patients is graft failure due to antibody-mediated rejection. Although large-scale randomized trials with long-term follow-up are lacking, García-Jiménez *et al*, in a cohort of 53 patients undergoing delisting and DDKT, reported an aAMR rate of 12%, supporting the effectiveness of delisting strategies in mitigating the clinical impact of DSAs.[4] With the expanding understanding of ABMR pathophysiology, the refinement of diagnostic tools, and the development of novel therapeutic agents, HLA-incompatible kidney transplantation following careful antigen delisting may represent a viable option for selected patients when no alternatives exist.[3,5,7]

Several studies have demonstrated a marked improvement in transplant access using this strategy, with up to 45% of sensitized patients achieving transplantation following delisting. This high transplantation rate has helped reduce the accumulation of highly sensitized patients on waiting lists.[5,4] Orandi *et al* demonstrated that the mortality risk following HLA-incompatible kidney transplantation is lower than that associated with remaining on dialysis while awaiting a compatible crossmatch.[7] Thus, HLA-incompatible transplantation emerges as a favorable strategy to shorten waiting times and reduce mortality.[3,7] Ultimately, this approach provides a critical opportunity to expand transplant options for highly sensitized patients and, in many cases, represents their only realistic chance for transplantation.

CASE REPORT

We report the case of a 67-year-old Caucasian woman with end-stage chronic kidney disease (ESKD) secondary to autosomal dominant polycystic kidney disease, diagnosed at 30 years of age. She had a BMI of 25.4 kg/m² and had neither diabetes mellitus nor cardiovascular disease. Her gynecologic history included three pregnancies and three uncomplicated eutocic deliveries. She developed hypertension at 49 years of age, controlled with antihypertensive therapy. She progressed to ESKD. An arteriovenous fistula was created in 2012. Renal replacement therapy was initiated with continuous ambulatory peritoneal dialysis in 2014. Her course was complicated by a peritoneopleural leak, leading to cessation of peritoneal dialysis and transition to hemodialysis. She never required blood transfusions, and her CKD-related anemia remained well controlled.

She was first referred for pre-transplant evaluation in December 2013 at 56 years of age. Vascular assessment confirmed suitability for transplantation in both iliac fossae. Urological evaluation revealed no indication for native nephrectomy. Additional pre-transplant investigations were notable for hepatic cysts; a BI-RADS 2 mammogram; and, on echocardiography, mild interventricular septal hypertrophy, left ventricular diastolic dysfunction, and preserved left ventricular ejection fraction. She was listed as active for kidney transplantation in February 2014.

Living-donor transplantation was considered. Her husband was evaluated as a potential donor. However, a positive virtual crossmatch (VXM) precluded his acceptance. The patient was subsequently enrolled in a paired-donor exchange program but did not receive any compatible offers. She was highly sensitized, with a cPRA of 100%.

After 12 years on the active waiting list, a delisting process was implemented, and multiple antibodies were reclassified as acceptable, establishing a new PRA value of 99.75%. She remained eligible for transplantation and received a deceased-donor kidney offer in October 2025. The donor was a 60 y.o male, blood group A+, with an HLA profile consisting of HLA-A*01, 33; B*14, 18; C*05, 08; DRB1*07; DRB4*01; DQB1*02; DQA1*02;

DPB1*04:01,17:01; DPA1*02. The donor was CMV IgG positive. Receptor immunological assessment showed blood group A+ and seropositivity for CMV IgG. Her HLA typing was A*25, 32; B*13, 35; C*04, 06; DRB1*07; DRB4*01; DQB1*02; DQA1*02; DPB1*02, 17; DPA1*01, 02. There were four HLA broad mismatches in ABDR: one at the A locus and two at the B locus, with no mismatches at the DR locus.

HLA mismatches were evaluated at the level of broad antigens, in accordance with Portuguese legislation, which defines compatibility assessment based on HLA broad specificities. However, it is recognized that patients may develop anti-HLA antibodies directed against split antigens, even when these belong to the same broad specificity.

Current DSA were A1 (MFI 1119 in the last serum), A33 (MFI 1150 in the last serum), both of which were reclassified as acceptable in the delisting process, as showed in Fig. 1. Low intensity was confirmed in the day of the transplant (lower than 2000 MFI). There was also a historical DSA DPB1*04:01 (MFI 1343), present for the last time six years before.

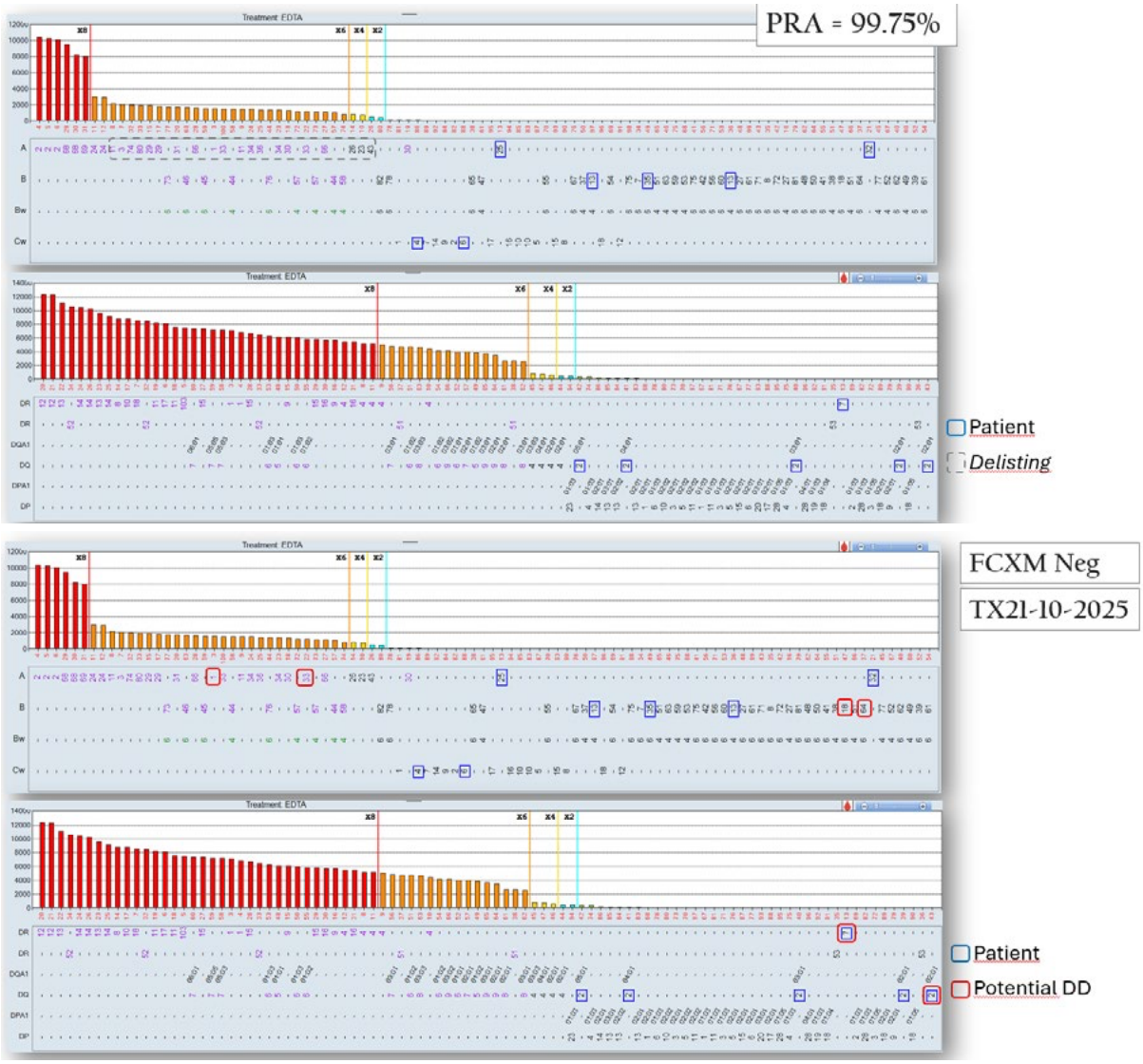

Figure 1. Single-antigen bead assay (One Lambda, Inc), highlighting the delisting process.

Both complement-dependent cytotoxicity and flow cytometry crossmatches were negative.

Induction immunosuppression included lymphocyte-depleting therapy with antithymocyte globulin (ATG), mycophenolate mofetil, tacrolimus, and methylprednisolone, complemented by immunomodulation with intravenous human immunoglobulin. Infectious prophylaxis was maintained with trimethoprim–sulfamethoxazole, valganciclovir, pantoprazole, and nystatin.

The DDKT was performed on 21 October 2025. The right donor kidney was implanted into the right iliac fossa and had a single artery and a single vein; venous reconstruction

with a vena cava patch was required, without intraoperative complications. During anesthesia, the patient developed hypotension requiring ephedrine.

On the first postoperative day, she developed persistent hypotension and sustained oligoanuria despite fluid resuscitation, later accompanied by altered mental status. She was transferred to the intensive care unit, where she remained for 24 hours. Because slow low-efficiency dialysis (SLED) was required, central venous catheters were placed in the right internal jugular and right femoral veins. Following a SLED session, her blood pressure stabilized, and her hemodynamic status improved.

Renal scintigraphy demonstrated good perfusion and radiotracer uptake with normal visualization of the excretory system and physiological urinary elimination. However, marked parenchymal tracer retention produced an ascending renographic curve, warranting continued monitoring. Doppler ultrasonography of the graft confirmed adequate global perfusion, with a patent renal artery and vein. Resistive indices were 0.85 in the main renal artery and 0.75 in the segmental branches.

Given her elevated immunological risk and the presence of DSA, a single dose of rituximab was administered on 27 October 2025 at a total dose of 600 mg (375 mg/m²). This decision was based on overall immunological risk, concern for DSA rebound, and also based on extrapolation from other desensitization strategies.

At the three-month follow-up, the patient had an uneventful clinical course. Her serum creatinine was 0.7 mg/dL, (estimated glomerular filtration rate of 92 mL/min/1.73m² using the 2009 CKD-EPI equation); Urinalysis revealed an albumin-to-creatinine ratio (ACR) of 25 mg/g and a protein-to-creatinine ratio (PCR) of 326 mg/g, with no hematuria.

On postoperative day 6, no DSA were detected, as well as at three months follow-up.

DISCUSSION

This case illustrates several key challenges in the management of highly sensitized kidney transplant candidates and highlights the potential of structured antigen-delisting strategies to expand transplant opportunities in this increasingly prevalent population.[3,5,6] Our patient had a cPRA of 100% for more than a decade, with multiple class I and class II anti-HLA antibodies and no suitable living-donor options. Despite the prolonged waiting time, she ultimately achieved successful DDKT.

Highly sensitized patients experience disproportionately long waiting times, increased waitlist mortality, and markedly reduced access to transplantation, particularly in regions with limited donor availability.[3,5] Advances in immunological assessment—most notably the adoption of single-antigen bead (SAB) assays—have enabled more precise characterization of antibody profiles and immunologic risk.[4,6] However, the increased sensitivity of SAB testing may classify some candidates as "untransplantable" despite clinically acceptable risk levels. This discrepancy underscores the importance of a rational, individualized delisting strategy, as implemented in the present case.[5,6]

Our patient's antibody profile demonstrated progressive reductions in MFI over time, with both A1 and A33 DSAs measuring below 2000 MFI at the time of transplantation. Current evidence indicates that not all DSAs confer equivalent pathogenic risk; factors such as IgG subclass, complement-binding capacity, and antibody strength strongly influence clinical outcomes.[4,6] The biological behavior of donor-specific antibodies (DSAs) directed against HLA-A1 and HLA-A33 mismatches remains poorly defined. Data specifically characterizing anti-A1 and anti-A33 antibodies are limited and as a result, it is uncertain whether these mismatches predominantly induce deleterious humoral responses or generate DSAs with a less aggressive, potentially accommodating phenotype, limiting precise immunologic risk stratification and underscoring the need for functional characterization in this setting.

Studies such as those by García-Jiménez *et al* have shown that delisting strategies focusing on low-intensity antibodies can yield acceptable rates of aAMR, supporting their use when compatible donors cannot be identified.[4,5] They reported that personalized delisting of low-intensity antibodies based on longitudinal MFI trends and immunologic risk assessment can safely expand access to transplantation in highly sensitized candidates, achieving acceptable rates of antibody-mediated rejection and favourable early graft outcomes.[4] The absence of donor-specific antibodies early after transplantation in our patient—even in the presence of a transient increase in anti-HLA antibodies—further supports the notion that low-MFI preformed DSAs may be clinically manageable with appropriate immunosuppression.[4]

Another important consideration is the patient's postoperative course. Although she developed early hemodynamic instability requiring dialysis support, these complications were not suggestive of immunological graft injury. Imaging studies demonstrated preserved graft perfusion without evidence of vascular compromise or acute rejection, and her subsequent functional recovery was favorable, as reflected by stable creatinine and absence of proteinuria or hematuria at the two-month follow-up. Early postoperative hypotension is a well-known risk factor for delayed graft function, particularly with older or marginal donors; however, her full recovery suggests that the graft retained intrinsic viability.[9]

The immunosuppressive regimen—comprising lymphocyte-depleting induction with ATG, tacrolimus-based maintenance, and intravenous immunoglobulin—aligns with current recommendations. Such intensified protocols aim to reduce the likelihood of early aAMR, particularly in patients undergoing HLA-incompatible transplantation

or transplantation in the presence of low-level DSA.[3,7] The patient's stable early graft function and absence of rejection episodes support the effectiveness of this immunologic risk–adapted approach.

Donor selection also played a critical role in the favorable outcome. The donor kidney had only three HLA mismatches, negative complement-dependent cytotoxicity (CDC) and flow crossmatches, and no class II DSA, all factors known to mitigate the risk of aAMR. The absence of DR and DQ mismatches is particularly relevant, as class II DSAs are strongly associated with chronic antibody-mediated rejection and long-term graft failure.[4,6]

Ultimately, this case exemplifies how structured delisting strategies can provide a feasible pathway to transplantation for highly sensitized patients who otherwise have little realistic prospect of receiving a compatible organ.[5,6] Several cohort studies, including the work by Orandi *et al*, have demonstrated that survival following HLA-incompatible kidney transplantation exceeds that of remaining on dialysis while awaiting a compatible donor.[7] Thus, expanding the use of individualized delisting protocols and refined immunologic risk stratification may meaningfully reduce disparities in transplant access.[3,5,7]

The STAR Meeting Group report led by Carrie Schinstock also underscores that DSA interpretation, emphasizing antibody strength, functional characteristics, and temporal dynamics, rather than isolated MFI cut-offs, is key to guide clinical decision-making.[9]

This risk-adapted approach aligns closely with our strategy of longitudinal monitoring and individualized delisting.

In conclusion, this patient's successful transplantation after 12 years on the waiting list underscores the importance of flexible, evidence-based immunological management. It demonstrates that with meticulous monitoring, tailored delisting strategies, and appropriately intensified immunosuppression, selected highly sensitized patients can achieve favorable short-term outcomes despite substantial immunologic barriers. Continued research and long-term follow-up will be essential to refine delisting thresholds, improve prediction of DSA pathogenicity, and optimize outcomes in this complex and growing population.[5,6,8]

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