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Acute Rejection Associated with Donor-Specific Anti-MICA Antibody in a Highly Sensitized Pediatric Renal Transplant Recipient

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Abstract

Allograft rejection in HLA identical transplant recipients and in patients without detectable donor specific anti-HLA antibodies has lead to the identification of non-HLA antigens as targets of the alloimmune response. Major Histocompatibility Complex class I-related chain A (MICA) antigen has been recognized as an important non-HLA target in renal transplantation. Recent studies have shown that anti-MICA antibodies are associated with acute renal allograft rejection and failure. Current cross match procedures using donor lymphocytes fail to detect MICA antibodies. Transplant candidates are not routinely tested for pre-sensitization to MICA antigens nor are transplant donors typed for MICA alleles. Optimal classification and treatment of acute rejection associated with MICA antibody remains unknown. In this case report, we are the first to describe the clinical course and treatment of donor specific MICA antibody associated with both Banff type II A acute cellular rejection (ACR) and antibody mediated rejection (AMR) in a highly sensitized pediatric renal re-transplant recipient. This case also emphasizes the importance of pre-transplant screening for donor specific MICA antibody especially in highly sensitized renal transplant patients..

Keywords

Antibody Mediated Rejection; donor specific anti-MICA antibody; anti-MICA antibody; highly sensitized patient; non-HLA antibody

Introduction

Acute rejection after renal transplantation is known to be a major risk factor for chronic allograft dysfunction and graft loss (1, 2). Recently, alloimmune responses to non-HLA targets have gained recognition for their role in renal allograft rejection and graft failure (3). Allograft rejection in HLA identical transplant recipients and evidence of humoral rejection in patients without detectable donor specific anti-HLA antibodies has lead to the identification of non-HLA antigens and their importance in allograft rejection. These include

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platelet specific antigens, angiotensin II type 1 receptor, glomerular basement membrane protein agrin, endothelial cell antigens and especially MICA antigen (3, 4).

MICA encodes a 62 kd cell surface glycoprotein that is thought to have a role in both innate and adaptive immunity (5, 6). MICA is highly polymorphic with over 60 alleles and is encoded within the major histocompatibility (MHC) gene complex on chromosome 6. Although the diversity of MICA is high, it appears to have limited variation across racial groups. In Caucasians and African Americans, the most common MICA allele is MICA*008 which accounts for 43% of the population, followed by MICA*002 at 14.1%, MICA*004 at 7.5%, MICA*009 at 7%, MICA*010 at 5.8%, and MICA*007 at 5%. (7)

MICA is a stress-induced molecule that is associated with immune surveillance. Ischemia reperfusion injury and cytokines such as IL-2, IL-4 and IL-15 can up regulate the expression of MICA on the endothelium or epithelium of the graft (8). Furthermore, the polymorphic nature and pattern of cellular expression of MICA on epithelial cells, keratinocytes, fibroblasts and endothelial cells suggests that it may be a target of the alloimmune response in transplant recipients (6). It has been shown that anti-MICA antibodies can be cytotoxic in the presence of complement and therefore could play a role in AMR (9, 10). Importantly, MICA is not expressed on T or B lymphocytes and therefore, current cross match procedures using donor lymphocytes do not detect antibodies to donor MICA (3).

Multiple studies have shown that MICA antibodies are associated with renal allograft dysfunction, rejection and failure (3, 10-12). The importance of MICA antigen in renal transplantation was first established by Stastny et al. who found that sera of transplant patients with rejection contained anti-MICA antibodies to non-self MICA alleles (5). Furthermore, anti-MICA antibodies were found to occur more frequently in sensitized patients with prior transplants compared to healthy controls as well as in patients with rejected transplants compared to those with functioning grafts (12). Moreover, the presence of preformed MICA antibodies has been associated with irreversible rejection in kidney transplant recipients without anti-HLA antibodies (11, 13). However, a limitation of these studies is that they did not distinguish between donor-specific and nonspecific MICA antibodies or follow MICA antibody levels post transplant. Recently, Marquez et al. described donor-specific MICA antibodies in 2 of 19 renal allograft recipients with C4d positive AMR, but whether the patients had concomitant ACR was not stated (2). Therefore, the pathogenesis and treatment of anti-MICA antibody in allograft rejection remains unclear. In this case report, we are the first to describe the diagnosis, clinical course and treatment of AMR and type IIA ACR associated with serial monitoring of donor-specific anti-MICA antibody levels in a highly sensitized pediatric renal re-transplant recipient.

Case Report

A 14 year old female with Branchio-Oto renal syndrome underwent re-transplantation with a HLA cross match negative deceased donor kidney. She lost her first kidney transplant to chronic rejection at the age of ten and underwent allograft nephrectomy. Since she was highly sensitized with a panel reactive HLA antibody of 94% to class I antigens and 66% to class II antigens, she remained on dialysis for five years. In order to improve her chance for transplantation, she underwent desensitization with high dose intravenous immunoglobulin (IVIG; 2g/kg once a month for four months) and Rituximab (750mg/m2 × two doses). Two months later, she received a deceased donor renal transplant. The pre-transplant cytotoxic and flow T and B lymphocyte crossmatches were negative with the donor. Furthermore, pre-transplant HLA antibody testing by solid phase luminex testing showed no anti-donor HLA antibodies. She was induced with anti-thymocyte globulin (ATG; 1.5mg/kg/day for seven days) and was maintained on prednisone, tacrolimus and mycophenolate mofetil. Graft

function was monitored with serial serum creatinine levels. She had a pre-transplant serum creatinine of 10.7 mg/dl and a discharge creatinine of 0.7 mg/dl on post-operative day seven.

The patient maintained good allograft function until post-operative day ten when she presented with fever and anuric renal failure with a creatinine of 3.3 mg/dl. She was treated with a solumedrol pulse (10mg/kg for three days), IVIG (2g/kg over 2 days), Rituximab (750mg/m2) and was started on plasmapharesis given the suspicion of AMR. Serial biopsies were performed for clinical suspicion of rejection and for follow-up and were classified by the modified Banff 97 criteria. The initial biopsy revealed Banff type IIA ACR and AMR as diagnosed by histological characteristics and C4d positivity (Figure 1A, Table 3). Serial HLA and MICA post-transplant antibody testing was performed using single antigen Luminex technology (One Lambda, Canoga Park, CA) and the relative strength or level of the antibodies were represented as median fluorescence intensity (MFI). Donor and recipient were typed for HLA-A, B, DRB, DQB1 and MICA alleles using sequence specific oligonucleotide hybridization. We used reagents purchased from One Lambda, Canoga Park, CA. The recipient was mismatched from the donor for 2 HLA-B, 2 HLA-DR and 1 MICA alleles (Table 1). There were no donor specific antibodies (DSA) against HLA class I (A, B, C) or class II (DR, DQ, DP) antigens found pre-transplant or at the time of rejection. Antibodies to non-MICA anti-endothelial cell antigens were also negative pre and post transplantation (Table 2). The only antibody found was donor specific MICA antibody, specifically directed against MICA*012 (Table 2). Evaluation of the pre-transplant serum revealed pre-formed MICA*012 antibodies with levels that were elevated both before transplant (MFI=15,782) and at the time of rejection (MFI=15,743) (Figure 2). The renal transplant biopsy could not be stained for the MICA antibody due to the lack of reagents. The type IIA ACR was treated with anti-thymocyte globulin and the patient was maintained on plasmapharesis followed by IVIG (2g/kg) for AMR.

MICA antibody levels declined with the initiation of plasmapharesis and IVIG and correlated well with normalization of renal function and resolution of ACR and AMR (Figures 2 and 3, Table 3). Subsequently, the patient developed a persistent but stable elevation in anti-MICA antibodies despite normal renal function with a MICA MFI of 6685 on post-operative day 340. Interestingly, the patient had an elevation in anti-MICA antibody level during an episode of acute gastroenteritis. A follow-up biopsy revealed resolution of AMR (C4d negative) and only low grade tubulointerstitial inflammation, not diagnostic of ACR (Figure 1B, Table 3). Serial MICA antibody levels were used to guide therapy with plasmapharesis and IVIG, which were continued and weaned off by post-operative day 340, given the MICA MFI of 6685 and the persistence of normal renal function with a serum creatinine of 0.8 mg/dl (Figure 3).

Discussion

This is the first case report to describe the diagnosis, clinical course and successful treatment of simultaneous acute AMR and type IIA ACR associated with donor-specific antibody to the MICA*012 allele in a highly sensitized pediatric renal transplant recipient. As re-transplantation becomes more common, the pathogenesis and treatment of anti-MICA antibodies will have greater relevance. Our paper details an important diagnostic and therapeutic approach when confronted by such challenging cases. To our knowledge, there is no literature on the appropriate management of allograft rejection associated with anti MICA antibodies.

This case demonstrates that donor-specific anti-MICA antibodies can be associated with both acute AMR and type IIA ACR and emphasizes the necessity of treating both humoral and cellular components of the rejection. Prior large scale studies have demonstrated the

association of anti-MICA antibodies and renal allograft dysfunction, rejection and graft failure, but did not establish donor specificity (10-12). Two recent studies by Amico et al and Marquez et al demonstrated donor-specific anti-MICA antibody associated with rejection; however, these studies focused on patients with AMR (2, 14). In our patient, donor-specific anti-MICA antibody was associated with mixed rejection, including C4d positive AMR and type IIA ACR.

Previously, classification of rejection has focused on the separation of ACR, a primarily T-cell mediated process and AMR, a complement activating dependent process. More recently, the importance of heterogeneity of cells and molecules involved in rejection, including B-cells, antibodies, cytokines and chemokines is becoming evident (4, 15, 16). It is plausible that cytokines generated during ACR contributed to the up regulation of MICA on the donor allograft and contributed to the binding of DSA to the graft leading to mixed rejection (8).

Alternatively, antibodies to non-HLA antigens such as MICA can be associated with ACR through a complement independent process while concomitantly mediating AMR through a complement dependent process (4, 16). Non-HLA antibodies binding to endothelial antigens such as MICA may up regulate expression of adhesion molecules and chemokines that facilitate leukocyte extravasation and thus mediate ACR (4, 16). Additionally, the MICA antigen itself is known to elicit a potent immunological response, especially considering that the MICA antigen is expressed at lower levels than HLA on the kidney and is less polymorphic (6, 10). Possible reasons for the powerful immune reactivity may relate to the role of the MICA antigen in innate immunity, by its ability to engage NK cells through the NKG2D receptor and exacerbate the immune response by the subsequent attraction of lymphocytes (6). The results of 14th International Histocompatibility Workshop also support the immunological potency of anti-MICA antibodies given that patients with antibodies to MICA had decreased graft survival compared to those with and without HLA antibodies at one year (17). The immunological potency of MICA compared to HLA may be a reason why some patients develop anti-MICA antibodies without donor specific anti-HLA antibodies. Further prospective studies need to be done to understand the role of the MICA antigen and the pathogenesis of anti-MICA antibodies in allograft rejection.

The exact reason for the sensitization to the MICA allele 012 in our patient is unknown, but is presumably due to prior sensitization from the first renal transplant, previous infections or transfusions. Unfortunately, we did not have cells from the prior donor to test for MICA genotyping. Our patient had an elevated level of preformed anti-MICA antibodies with an equal MFI level both at pre-transplant (post desensitization) and at the time of rejection. However, MICA antibodies are not detected by current crossmatch procedures using donor lymphocytes. Therefore, MICA antibody screening in highly sensitized individuals, and especially regraft candidates, may be important. Novel techniques are being developed to facilitate the detection of donor reactive anti-endothelial antibodies, including MICA (18). Breimer et al describe the development of their novel endothelial crossmatch technique/kit called XM-ONE using a novel flow cytometric technique incorporating donor peripheral blood endothelial precursor cells as targets (18). In highly sensitized individuals, especially regraft candidates, use of this novel endothelial crossmatch technique may allow the identification and facilitate clinical management of patients at risk of rejection due to non-HLA antigens prior to transplant.

In our patient, MICA antibodies persisted despite pre-transplant desensitization with high dose IVIG and Rituximab and induction with thymoglobulin, with equal MFI level at pre-transplant (post desensitization) (MFI=15, 782) and at the time of rejection (MFI=15,743). The significance of the MICA antibody levels and its relation to graft outcome remains unclear and has not been well studied. Studies evaluating HLA DSA have shown that high

concentration or level of DSA can be associated with an increased risk of AMR and graft loss (16, 17, 19, 20). This has lead to the stratification of HLA DSA according to MFI levels because of the differential management that may be required to treat patients with high levels of HLA-DSA during pre-transplant desensitization or AMR. Akalin et al. found that adding peri-transplant plasmapharesis to high dose IVIG and thymoglobulin induction significantly decreased the incidence of AMR in those with strong HLA DSA compared to high dose IVIG alone (19). We do not know the threshold level of anti MICA antibodies that should be treated preemptively to avoid graft injury or rejection. Addition of peri-transplant plasmapharesis might have decreased the MICA MFI and therefore the risk of allograft injury.

Additionally, our case suggests that successful post-transplant treatment of the AMR and type IIA ACR may require plasmapharesis in addition to IVIG and Rituximab given the normalization of renal function and initial three-fold decline in MICA antibody levels (from 15743 MFI on post-operative day 10 to 5010 MFI on post-operative day 15) following the initiation of plasmapharesis on post-operative day 11. Serial levels of anti-MICA antibody were used to guide continuation of treatment with plasmapharesis and IVIG, both of which were continued until post-operative day 340. Higher levels of anti-MICA antibody (MFI above 10, 000) were associated with ongoing rejection, while lower levels of anti-MICA antibody titers (MFI 6500) were associated with resolution of rejection. Marquez et al and Amico et al also mention the use of plasmapharesis to treat AMR due to MICA DSA. As discussed previously, whether these patients had ACR was not described (2, 14). These results are consistent with previous examples in which the addition of plasmapharesis significantly improved the treatment of AMR. Lefaucher et al. demonstrated significant improvement in graft survival from 50% to 91.7% at 36 months following treatment for AMR by adding plasmapharesis and Rituximab in comparison to IVIG alone (21). Novel therapeutic agents that target treatment of AMR such as Bortezomib, Ecluzimab, and PKC inhibitor AEB071 may also provide additional options for the treatment of AMR due to MICA antibodies.

Although our patient was successfully treated, she remained with persistent MICA antibodies with a MFI of 6685. While the significance of persistent MICA antibodies is unknown, studies evaluating HLA DSA have suggested that lower concentration of DSA may be associated with accommodation (16). As described by Zhang et al, low levels of anti-HLA antibodies may promote accommodation by increasing the expression of cytoprotective proteins such as Bcl-xL through of the activation of cell survival intracellular signaling pathways including mTORC2 (16). Additionally, low levels of antibodies can also facilitate accommodation by preventing complement activation through the activation of complement regulatory proteins in the graft endothelium (16). Alternatively, the persistence of MICA antibodies may be associated with chronic rejection since MICA antibodies have been associated with chronic allograft dysfunction (12, 22). The 13th and 14th International Histocompatibility workshop demonstrated that among patients with deceased donor renal transplants, patients with anti-MICA antibodies had significantly decreased allograft survival compared to those without antibodies to HLA or MICA (17). However, the study did not include donor specificity or anti-MICA antibody levels; Therefore, the significance of anti-MICA antibody levels and its relation to graft outcome is not known. It will be important to closely monitor MICA MFI levels and allograft function in our patient. Further large scale, prospective studies need to be done to evaluate the clinical relevance of MICA MFI quantification, serial monitoring and its impact on graft outcome.

Our case highlights multiple important consideration regarding MICA antibodies. Donor-specific MICA antibodies can be associated with both AMR and Banff type IIA ACR and may require treatment with plasmapharesis. Our case emphasizes the need for early

detection and screening for donor specific MICA antibodies because these are not detected using our current crossmatch procedures. Furthermore, the serial quantification and monitoring of MICA MFI levels could alter the clinical management of allograft rejection and need to be assessed in large randomized, prospective trials. In highly sensitized and regraft candidates, routine testing for donor specific MICA antibody using MFI titers could prevent allograft rejection and enhance graft survival. Further prospective trials are needed to determine the clinical relevance of the MICA antigen, routine MICA antibody screening as well as serial monitoring of anti-MICA antibodies in the prevention of graft rejection and failure.

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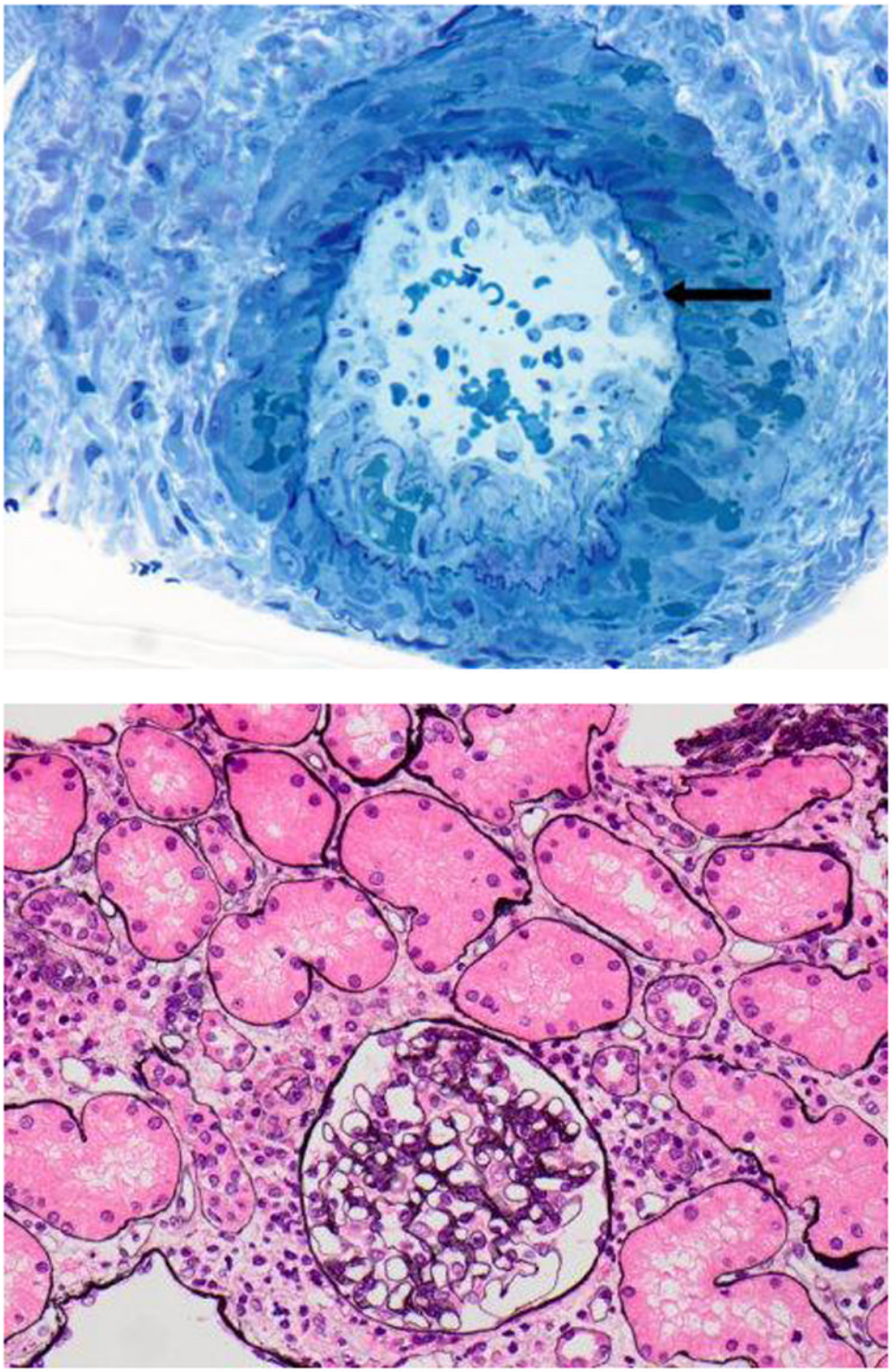

Figure 1.
A: Biopsy at the time of rejection revealed vascular ACR type IIA and C4d positive AMR. Interlobular artery with intimal inflammation, endothelial swelling and subendothelial lymphocytes (arrow) (Toluidine blue stain; original magnification 600×).

b: Biopsy performed post-treatment of ACR and AMR. The tubulointerstitium has mild edema and lymphocytic inflammation with only rare foci of tubulitis (periodic acid-methenamine silver (Jones) stain; original magnification 400×).

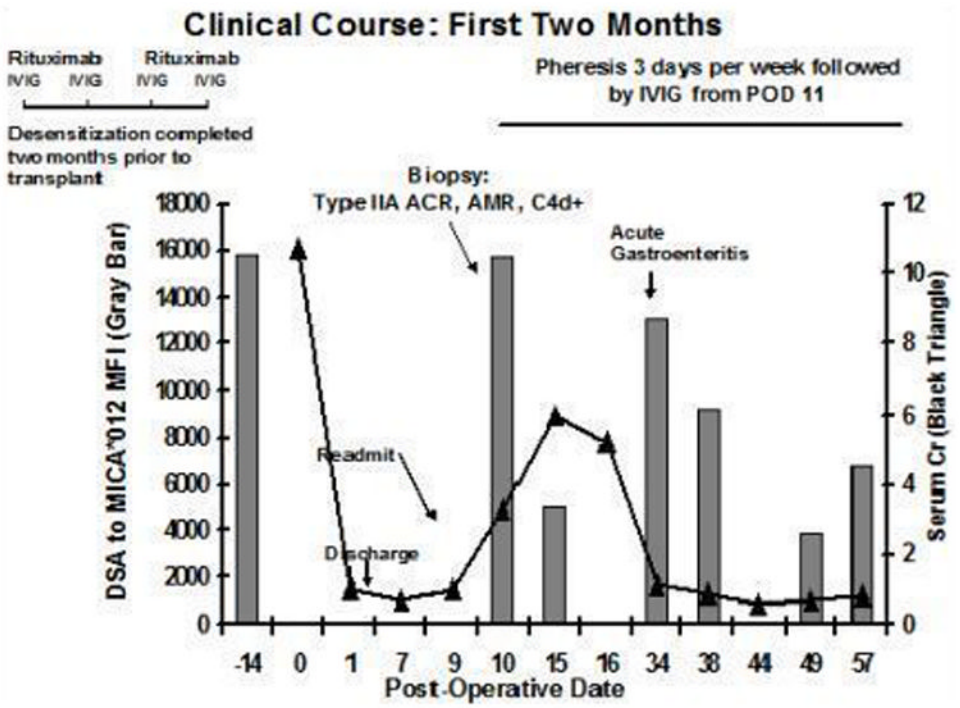

Figure 2.

Gray bars represent MFI of MICA DSA and black triangles represent the serum creatinine. MICA MFI decreased and renal function normalized following the initiation of plasmapharesis.

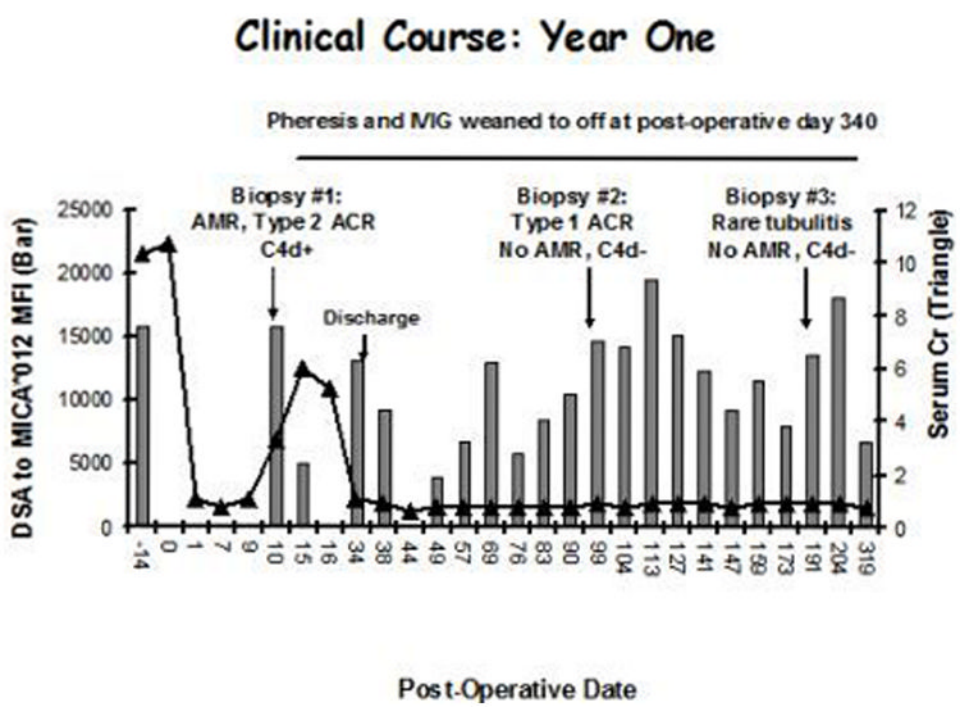

Figure 3.

Gray bars represent MFI of MICA DSA and black triangles represent the serum creatinine. Serial biopsies revealed resolution of AMR and an improvement in ACR. Renal function remained normal despite persistent MICA antibodies.

Table 1

Donor and Recipient HLA and MICA Genotyping

	HLA A	HLA B	HLA DR**	HLA DQ**	MICA Loci 1	MICA Loci 2
Recipient	1, 24	13, 45	14, 15	5,6	008	009
Donor	1, 24	**7, 55***	**1, 13***	5,6	008	**012***

Bold=mismatched alleles

* Donor and recipient are mismatched for HLA B, HLA DR and MICA loci 2, specifically the MICA 012 antigen.

** The recipient did not produce antibodies to HLA-C or DP antigens pre or post-transplant as determined single antigen luminex class I and class II antibody testing and did not require additional HLA-C or DP typing.

Table 2

HLA, Endothelial cell, and MICA Antibody Testing

	Serum Cr	Biopsy	Donor Specific anti-HLA-A, B, C, DR, DQ, DP Antibody	Anti-Endothelial Cell Antibodies**	Donor Specific Anti-MICA Antibody
Pre-Transplant	10.7		Negative	Negative	**MICA*012**
Discharge	0.7		Negative	Negative	
Re-Admission	3.3-> 6	**ACR, type II AMR (C4d+)**	Negative	Negative	**MICA*012**

** The endothelial cells in this assay do not contain MICA antigens

This assay detects antibodies to non-MICA endothelial antigens

Table 3

Biopsy Results

	Biopsy #1	Biopsy #2	Biopsy #3
Date	Post-transplant day 14	Post-transplant day 90	Post-transplant day 180
Indication	graft dysfunction; acute renal failure	Follow-up; ongoing treatment with IVIG and plasmapharesis	Follow-up; ongoing treatment with IVIG and plasmapharesis
Result*	Type IIA ACR; C4d+ AMR	Type 1A ACR; C4d-; no AMR	Rare tubulitis; no ACR; C4d-; no AMR;
Tubulitis	Significant	Numerous foci	Few foci
Glomeruli	Epithelial cell foot process effacement	Areas of segmental hypercellularity	Patchy foot process effacement
Endothelitis	Yes	No	No
IF/TA**	No IF/TA	No IF/TA	No IF/rare TA
Figure	1A	Not shown	1B

* Result classified by modified Banff 2007 criteria

** IF: interstitial fibrosis; TA: tubular atrophy