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Accelerated rejection, thrombosis, and graft failure with angiotensin II type 1 receptor antibodies

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Abstract

Background—Angiotensin II type 1 receptor antibodies (AT_1R-Abs) have been implicated in renal transplant rejection and failure; however, the mechanism of allograft damage, patterns of clinical presentation, and response to desensitization of AT_1R-Abs have not been clearly established.

Case diagnosis/treatment—We present the case of a 7-year-old boy with preformed AT_1R-Abs who developed accelerated vascular and cellular rejection and renal allograft thrombosis despite desensitization and treatment with angiotensin receptor blockade. Although an association between AT_1R-Abs and microvascular occlusion has been previously described, we are the first to describe an association between AT_1R-Abs and renal artery thrombosis, leading to devastating early allograft failure.

Conclusions—This case highlights the risk of allograft thrombosis associated with AT_1R-Abs and illustrates that previous treatments utilized for AT_1R-Abs may not always be effective. Further studies are needed to better characterize the mechanisms of AT_1R-Ab pathogenesis and to establish safe levels of AT_1R-Abs both pre- and post-transplantation. Given the outcome of this patient and the evidence of pro-coagulatory effects of AT_1R-Abs, we suggest that the presence of AT_1R-Ab may be a risk factor for thrombosis. The role of treatment with anti-coagulation and novel immunomodulatory agents such as tocilizumab and bortezomib require further investigation.

Introduction

Human leukocyte antigen (HLA) donor-specific antibodies (DSA) have a well-known role in the pathogenesis of antibody-mediated rejection (AMR) and eventual allograft failure [1–3]. By contrast, non-HLA antibodies such as MHC class I related chain A antibodies (MICA-Abs), anti-endothelial cell antibodies (AECAs), and angiotensin II type 1 receptor antibodies (AT_1R-Abs) have all been implicated in transplant rejection and failure [2, 4–7], but preliminary studies have not been adequate to implement routine testing for these

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antibodies in clinical practice [2]. Furthermore, the mechanism of allograft damage, patterns of clinical presentation, and response to desensitization of non-HLA antibodies have not been clearly established.

Angiotensin II type 1 receptor (AT_1R) is a G-protein-coupled receptor that under normal physiologic circumstances mediates the actions of angiotensin II including blood pressure regulation and salt and water balance. AT_1R-Abs, which behave agonistically, may be formed as a result of inflammation, injury, sensitization, or medication non-compliance [5]. We present an instructive case of an HLA-sensitized 7-year-old boy with preformed AT_1R-Abs who developed accelerated rejection, allograft thrombosis, and failure despite desensitization.

Case report

The patient was a 7-year-old Caucasian male with end-stage renal disease from posterior urethral valves who received his first living-related renal transplant from his father at 9 months old. His post-transplant course was complicated by BK nephropathy, chronic severe hypertension, development of anti-HLA DSA, and chronic AMR, leading to graft failure after 6.5 years. Prior to his second transplant, he had a negative hypercoagulability work up with the exception of a mildly elevated homocysteine to 15 μmol/l (normal 4–14 μmol/l) for which he was on folic acid supplementation. He was negative for factor V Leiden mutation, prothrombin G20210A variant, anti-phospholipid antibodies, and had normal anti-thrombin III, factor 8, lipoprotein A, protein C functional activity, and protein S functional activity. Additionally, his infectious disease work-up was negative for BK virus, cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, syphilis, coccidioidomycosis, and hepatitis B and C.

Although the patient was sensitized to HLA with a calculated panel reactive antibody (cPRA) of 71 %, he received a 3/6 HLA-A, B, DRB1 matched living-unrelated kidney through the National Kidney Registry (NKR) paired exchange program with negative pre-transplant flow crossmatches. Luminex single antigen bead (SAB) assay confirmed the absence of DSA. Because of the severe hypertension that he suffered during the course of his first transplant, we had a clinical suspicion of AT_1R-Abs. As part of our protocol for re-transplant patients, Luminex SAB MICA-Ab test [8], enzyme-linked immunosorbent-based AT_1R-Ab test [5], and flow cytometry-based anti-endothelial cell crossmatch (ECXM) [8] were performed to detect non-HLA antibodies in addition to routine pre-transplant HLA antibody testing. The patient had negative pre-transplant ECXM and MICA-Ab testing. However, he had a high AT_1R-Ab of 109.55 U/ml (normal <10 U/ml) (Fig. 1). Pre-transplant desensitization including 3 days of plasmapheresis, 3 days of intravenous immunoglobulin (IVIG) (1 g/kg), and one dose of rituximab (375 mg/m^2) reduced his AT_1R-Ab level to 33.76 U/ml. He was induced with thymoglobulin (ATG) (1.5 mg/kg), and maintained on steroid-based immunosuppression with tacrolimus and mycophenolate mofetil. He was not anti-coagulated post-transplant because he had no clinical history of thrombosis, and his pre-transplant hypercoagulability work-up was negative.

He initially did well post-transplantation, reaching a nadir serum creatinine (Cr) of 0.4 mg/dl on day 2 post-transplant (Fig. 1). Hypertension to 130 s/90s (>99 % for his age and height) improved with losartan (1 mg/kg), and he was normotensive throughout the remainder of his post-transplant course. Due to an increase in his Cr and persistent AT_1R-Ab of 27.96 U/ml, plasmapheresis was performed on days 6–9 with decrease in both Cr and AT_1R-Ab (12.87 U/ml). HLA class I and II DSA, AECA, and MICA-Ab remained negative. He was discharged on day 10 post-transplant with a Cr of 0.5 mg/dl and AT_IR-Ab level of 13 U/ml. He was readmitted 5 days later with hematuria, graft tenderness, fever, and rising Cr. HisAT_1R-Ab level was 17 U/ml and his HLA class I and II DSAs were negative. A renal ultrasound with Doppler was normal with normal flow in the main renal artery and vein. He was treated with methylprednisolone pulse (5 mg/kg), plasmapheresis, ATG (1.5 mg/kg), and eculizumab (600 mg), while biopsy results were pending. Biopsy revealed acute cellular rejection (ACR) IB with endarteritis and C4d-negative AMR characterized by glomerulitis, and peritubular capillaritis. Given the C4d negativity, eculizumab was discontinued. Initially, his Cr and oliguria improved with treatment; however, he developed acute pain and anuria. Ultrasound and magnetic resonance angiogram revealed renal artery thrombosis with resultant allograft loss on post-transplant day 21.

Discussion

Non-HLA antibodies, such as AT_1R-Abs, have been implicated in allograft rejection and poor long-term graft outcomes, especially in highly sensitized patients [2, 4–7]. We report the first case of renal artery thrombosis and accelerated rejection associated with AT_1R-Ab that was refractory to desensitization and resulted in early allograft failure. Our patient illustrates unique points that could help optimize treatment and improve allograft outcomes associated with AT_1R-Ab. First, our patient developed large vessel occlusion, which has not been previously described and highlights the potential need for anti-coagulation in patients with AT_1R-Abs. Additionally, he had accelerated vascular rejection, which was unresponsive to AT_1R blockade, plasmapheresis, IVIG, corticosteroids, and eculizumab. This underscores the need for further investigation into the pathogenic mechanisms of AT_1R-Abs and the importance of utilizing novel therapies.

Although AT_1R-Abs have been associated with microvascular renal infarcts [4], our case highlights the potential severity of AT_1R-Ab-mediated allograft injury and its association with thrombosis. AT_1R-Abs have pro-coagulant properties and can disrupt the coagulation cascade by inducing tissue factor expression and inhibiting fibrinolysis [4, 9]. Patients with AT_1R-Ab-mediated AMR develop small artery thrombosis and positive tissue factor staining on renal biopsies along with renal cortical infarcts on magnetic resonance imaging [4]. Tissue factor has also been associated with thrombosis in anti-phospholipid syndrome and with clotting abnormalities in cardiac allografts [10, 11]. Additionally, in animal models, AT_1R-Abs cause renal artery constriction in the setting of renal transplantation [12], which along with an increase in tissue factor expression, may have contributed to renal artery thrombosis in our patient's allograft.

We recognize that our patient's ongoing rejection and age were risk factors for allograft thrombosis independent of the direct pro-coagulant effects of AT_1R-Ab. Although his AT_1R-

Ab level was notably reduced at the time of allograft thrombosis, the pro-coagulant effects of AT_1R-Abs may have already been established prior to the thrombotic event. Alternatively, the AT_1R-Abs may have localized to the kidney, leading to a deceptively low serum level at the time of the event. Unfortunately, frozen sections from his biopsy were inadequate to elute antibody from allograft tissue and his allograft was completely necrotic at the time of nephrectomy.

Our patient did not respond to angiotensin receptor blockade. Thus, he differs markedly from those recipients in the study of Dragun et al. who responded to losartan, with reduction of tissue factor expression and improvement in microvascular occlusions [4]. This raises the question of the need for anti-coagulation in patients such as ours. Currently, most centers decide on anti-coagulation by evaluating individual patient risk, the personal history of thrombosis, and a hypercoagulability work-up. Given the outcome of this patient and the association of pro-coagulation effects with AT_1R-Ab, we suggest that the presence of AT_1R-Ab may be a risk factor for thrombosis. In addition to starting angiotensin receptor blockade in these patients, anti-coagulation may reduce the risk of both small, and more importantly, large, vessel occlusions. While heparin and warfarin target downstream effectors of the tissue factor pathway, direct factor Xa and thrombin inhibitors may provide enhanced downstream inhibition by blocking the actions of both circulating and clot-bound factor Xa and thrombin [13, 14]. Additionally, tissue factor/factor VIIa inhibitors are in development, which may provide more directed therapy against the pro-coagulant effects of AT_1R-Ab [15, 16]. Caution must be taken, however, in using these novel anticoagulant agents in patients with renal insufficiency given the lack of experience in their pharmacokinetics and risk of irreversible overdose.

The experience with our patient also emphasizes the importance of understanding the pro-inflammatory and immunogenic responses of AT_1R-Ab to optimize current therapeutic regimens. Our patient had ACR with endarteritis and C4d-negative AMR, which is consistent with previous studies of AT_1R-Ab-mediated allograft rejection [4–7]. Unfortunately, he was resistant to robust anti-rejection therapy, suggesting that multiple inflammatory and/or immunological factors are likely mediating severe AT_1R-Ab-mediated rejection that extend beyond complement-fixation or antibody-dependent cellular cytotoxicity. IL-6 has been implicated in the pathogenesis of preeclampsia due to AT_1R-Ab [17] in addition to increasing immunogenic responses of HLA antibodies in allograft rejection [18]. Therefore, inhibiting IL-6 using tocilizumab might alter the effects of AT_1R-Ab by not only reducing production of antibodies by modulating B cells and plasma cells but also tempering inflammatory responses. Additionally, the role of proteasome inhibition with bortezomib to modulate plasma cells [19] and therefore decrease production of AT_1R-Abs merits consideration, given that our patient's AT_1R-Ab level never normalized.

In summary, our case highlights the risk of allograft thrombosis in addition to vascular rejection associated with AT_1R-Ab. Further studies are needed to better characterize the mechanisms of AT_1R-Ab pathogenesis and to establish safe levels of AT_1R-Ab both pre- and post-transplantation. Additionally, the role of anti-coagulation, more extensive plasmapheresis to levels below 10 U/ml, and immunomodulatory therapy with such agents as tocilizumab and bortezomib, warrant further investigation in controlled trials.

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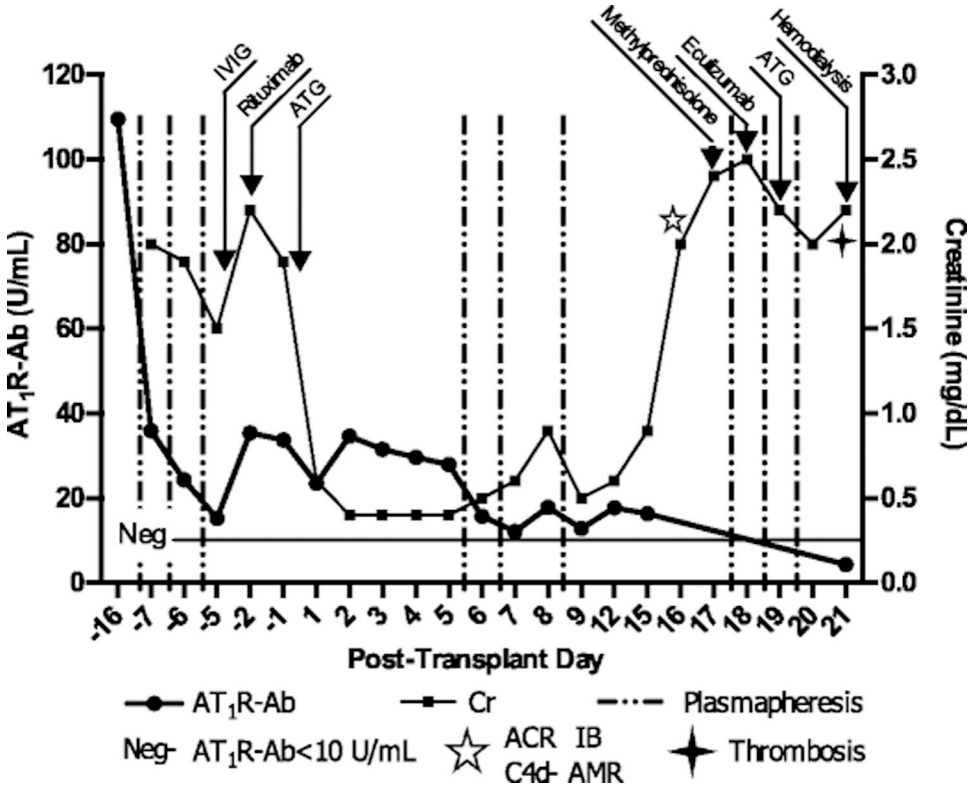

Fig. 1.

Clinical course and response to therapy of patient with AT_1R-Abs. The time course of serum creatinine and AT_1R-Ab level are shown. The days of medication administration, plasmapheresis, hemodialysis initiation, biopsy, and allograft thrombosis are indicated