

Acute antibody mediated rejection associated with acute herpetic gingiva-stomatitis in kidney transplant patient: A case report

Usama A Sharaf El Din^{1*}, Dina O Abdulazim², Ahmed Abdo³, Mohammed Hassan³, Essam Rashad³

¹Professor of Nephrology, International Kidney Center.

²Lecturer of Rheumatology and Rehabilitation, School of Medicine, Cairo University, Egypt.

³Fellow of Nephrology, International Kidney Center.

***Correspondence Author:** Professor Usama AA Sharaf El Din, International Kidney Center, 58th Abbas El Akkad St, Nasr City, Cairo, Egypt. Post Code: 11759

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Abstract

Introduction: Antibody-mediated rejection (AMR) is the most serious cause of renal allograft loss. Most of the acute AMR attacks occur within the first week post-transplant.

Subject: In this case report, we present a case of AMR that occurred five months post-transplant in association with acute oral viral infection. This patient had history of bone marrow hypoplasia two months following onset of hemodialysis and was maintained on cyclosporine and prednisolone beside switch to hirudin as anticoagulant. During that period, she also received 6 units of whole blood till she underwent kidney transplant after 2 years on dialysis. The post-transplant course was uneventful till the patient developed severe acute herpetic gingivostomatitis 5 months post-transplant that was associated with abrupt rise of renal chemistry. Biopsy proven AMR showed resistance to treatment with plasma exchange [PE] and Intravenous immunoglobulins. The patient was readmitted to regular hemodialysis unit for 2 months together with minimization of immunosuppressive treatment.

Outcome: During routine follow-up investigations, kidney function tests became near to the pre-rejection levels. We discontinued dialysis and re-administered the initial immunosuppressive regimen.

Conclusion: This is the first reported case of AMR in association with acute Herpes simplex infection that shows delayed spontaneous recovery.

Key words: case report; acute antibody mediated rejection; amr; kidney transplantation; herpes simplex

Introduction

AMR is a serious challenge in the field of kidney transplantation being an important cause of allograft dysfunction and graft loss. 1–10% of kidney transplant recipients develop AMR [1]. Alloantibodies against the transplanted renal graft are responsible for the destructive immune reaction observed in AMR. These antibodies might be directed against human leucocyte antigens (HLA antigens) on the surface of the transplanted graft cells (these antibodies are called donor specific antibodies; DSA), or non-HLA antigens like endothelial antigens, angiotensin II type 1 receptor, major histocompatibility complex class-I-related chain A (MICA), C-terminal laminin G (LG3), fibronectin and collagen type 4 [2,3]. Interaction between antibodies directed to their specific antigens usually activates the classic complement pathway with consequent linear peritubular capillary wall deposition of C4d. complement activation leads to cell lysis, inflammatory cells recruitment, platelet activation and endothelial cell damage [2,3]. An alternative mechanism of allograft damage can occur through the adherence of the natural killer cells to the Fc region of the offending antibodies with subsequent release of cytotoxic cytokines. This mechanism would be

responsible for C4d negative AMR [3].

The Banff 2015 kidney meeting report has suggested the following criteria for the diagnosis of acute AMR: first, histologic evidence of acute tissue damage that includes microvascular inflammation, intimal or transmural arteritis, acute thrombotic microangiopathy (TMA) and acute tubular injury in the absence of other causes that would explain such changes. Second, linear C4d staining in peritubular capillaries with at least moderate microvascular inflammation. Third, the presence of donor specific antibodies (DSA) against HLA or other antigens [4]. Acute AMR may be early or late in onset. Early acute AMR occurs in the first few days to weeks after transplantation. Late acute AMR occurs months to years after transplantation. This late onset rejection is usually mixed cellular and AMR and is commonly due to non-compliance or non-adherence to immunosuppressive treatment [5]. PE and IVIG are the standard of care for the treatment of acute AMR [6].

The setting of immune suppression after solid organ transplantation offers a suitable chance of herpes virus infection or reactivation. Herpes simplex virus (HSV-1) infection usually manifests with oral, while HSV-2

manifests with genital mucocutaneous disease. Varicella Zoster virus (VZV) reactivation usually manifests with unilateral painful vesicular eruption involving a single dermatome as herpes zoster [7]. Controversy about the association between viral infection and AMR still exists. While some reports deny the association between viremia and/or viral infection and alloimmune events [9, 10], others confirm its existence [11, 12]. Viruses accused in this association include cytomegalovirus (CMV), Epstein Barr virus (EBV) and VZV. However HSV was not accused before.

In this case report we present a kidney transplant lady that was compliant with her adequate immunosuppressive regimen that developed late onset acute AMR instantaneous with the acute herpetic gingiva-stomatitis. Patient lost graft function in spite of 5 sessions of PE and total dose of IVIG of 2 gm/kg body weight.

Case presentation

DHS is a 30 years old single pharmacist accidentally discovered to have chronic kidney disease. She started regular hemodialysis treatment on May 2017. Two months after dialysis onset, the patient developed pancytopenia and consulted a Hematologist and underwent bone marrow aspiration. She was prescribed prednisolone plus cyclosporine A as a therapy for idiopathic hypoplastic bone marrow. Gradual improvement of peripheral blood film occurred starting three months after treatment onset. During this period, she received 6 units of whole blood and one year later the hemogram became normal. On February 2019, the patient underwent successful living unrelated kidney transplant and the patient was maintained on quadruple immunosuppressive treatment in the form of neoral 100 mg, enteric coated mycophenolic acid 720 mg, and evelolimus 0.75 mg twice daily beside 5 mg of prednisolone daily. The post-transplant course was uneventful for 5 months, serum creatinine was between 0.7 and 0.9 mg/dL. The patient developed acute herpetic gingivostomatitis that involved the buccal cavity, the fauces and the skin around the mouth opening in 27th of July 2019. Serum creatinine on that day of presentation was 2.6 mg/dL. Sonography guided allograft biopsy revealed acute thrombotic microangiopathy (TMA) together with linear staining of peritubular capillaries by anti C4d. Glomeruli showed prominent basement membrane together with moderate focal mononuclear cell infiltrate. Endothelial swelling, mesangiolytic and intracapillary fibrin thrombi were observed within three out of sixteen glomeruli. Tubules showed focal mild tubulitis and moderate tubular injury. Interstitium showed mild focal lymphocyte infiltration. Peritubular capillaries showed mild focal capillaritis by mononuclear cells. Interlobular arteries showed endothelial swelling and arterioles showed focal fibrin thrombi (Fig.1). She was prescribed Valacyclovir 500 mg every 12 hours, PE every other day and 0.4 gm/Kg of IVIG following each PE session. Herpetic lesions showed excellent response to treatment while serum creatinine continued progressive increase and became 8.9 mg/dL following the 5th PE session. Follow up renal biopsy showed persistence of TMA with persistent tubular damage but C4d became negative (Fig. 2)

. She was admitted to regular hemodialysis and immunosuppressive treatment was switched to Neoral 25 mg twice daily together with 50 mg azathioprine and 5 mg prednisolone each morning. Two months after starting regular dialysis, predialysis serum creatinine became 2.3 mg/dL she was asked to collect urine to estimate residual kidney function (Kru) following this session. Kru was 19 ml/min. We decided to stop dialysis and to go back to the immunosuppression protocol before AMR mentioned before. One week later, serum creatinine became 1.2 mg/dL.

Discussion

This is the 1st case report for the association between acute AMR and acute HSV-1 infection. The association between virus infection and AMR is controversial. The studies that support this association are in favor of

HLA antibody formation upon viral infection through activation of pre-existing memory B cells [12]. Activation of bystander memory B cells by viral infections can take place by different mechanisms. B cells display various Toll like receptors (TLRs), which can be responsible for memory B cells activation with consequent activation of B cells, regardless of their antigen specificity [13]. In addition, different cytokines liberated on viral infection can lead to B cell activation [14]. Cytokines can work in concert with TLR signaling. Our patient did not conceive before, however, the history of repeated blood transfusion during the episode of bone marrow hypoplasia could have triggered the formation of memory B cells that have been activated by acute HSV1 infection. The patient is a pharmacist and is very compliant with her medications negating the possibility of noncompliance as the cause of late acute AMR. Moreover, contrary to most of the reported late acute AMR episodes, which are usually mixed with acute cell mediated rejection, this patient had only acute AMR.

The decision to discontinue PE in this patient was based on many reasons, first the high expense, the second was the persistence of pathology in the second biopsy, and the third was the fear of the impact of excess immunosuppression on the general health of the patient. In addition, there is no consensus on the management of acute AMR based on follow up biopsy. The spontaneous recovery 2 months after discontinuation of PE highly suggests that follow up pathology is not helpful. This patient probably was suffering acute tubular necrosis that can explain the continuous rise of renal chemistry during PE. This possibility can also explain the delayed recovery of kidney functions after 2 months of regular hemodialysis

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