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Abstract: A 46-year-old female who lost her native kidney function due to biopsy proven collapsing type of FSGS, had a living kidney transplant after which, she developed acute renal allograft dysfunction, thrombocytopenia and microangiopathic hemolytic anemia five days post-transplant. Renal biopsy revealed acute antibody-mediated rejection (AMR). Genetic studies showed that this patient has a homozygous mutation of complement factor B (CFB) gene and heterozygous variant of C3 gene consistent with atypical hemolytic uremic syndrome type 4. Intravenous immunoglobulin (IV IG) and plasma exchange did not resolve these abnormalities. Eculizumab and bortezomib, on other hand, were very effective.

Subjects: Allergology & Clinical Immunology; Immunology; Medicine; Nephrology

Keywords: aHUS; AMR; rejection

1. Introduction

Hemolytic uremic syndrome (HUS) is characterized by thrombi in the microvasculature, hemolytic anemia, consumptive thrombocytopenia, and end-organ dysfunction commonly kidneys (Polito & Kirsztajn, 2010).

Post renal–transplant hemolytic uremic syndrome is a recognized cause of graft failure (Schwimmer, Nadasdy, Spitalnik, Kaplan, & Zand, 2003) and carries significant morbidity and mortality (Bresin...
It may develop de novo or recur in patients with end stage renal disease secondary to hemolytic uremic syndrome. The incidence of hemolytic uremic syndrome in renal allograft varies between 0.8 and 14% in different studies (Noris & Remuzzi, 2010; Ruggenenti, 2002; Schwimmer et al., 2003) and is associated with graft loss in 22% of cases (Schwimmer et al., 2003). Antibody-mediated rejection (AMR), immunosuppressive medications, pregnancy, viral infection and ischemia—reperfusion injury are all recognized triggers of post renal—transplant HUS in susceptible individual (Bresin et al., 2006; Murer et al., 2000; Noris & Remuzzi, 2010; Robson, Cote, Abb, Koffman, & Goldsmith, 2003; Ruggenenti, 2002; Satoskar et al., 2010; Waiser, Budde, Rudolph, Ortner, & Neumayer, 1999). Cyclosporine and tacrolimus are the most common reported triggers of de novo HUS in renal allograft transplant. This is attributed to their endothelial toxicity and vasoconstrictive actions (Pham et al., 2000). The high frequency of the genetic complement regulatory proteins mutations among patients with post renal transplant HUS suggest that genetic abnormalities may represent risk factors for de novo HUS after kidney transplantation and raise the question of the best therapeutic strategies (Le Quintrec et al., 2008; Noris & Remuzzi, 2010; Zuber et al., 2012, 2013). We present a case of what we believe is the first case of post renal transplant de novo HUS in a patient with complement factor B (CFB) and C3 genetic mutation most probably triggered by AMR which was proven by histology and donor specific antibody (DSA) and which did not respond to IV IG and plasma exchange but did respond to eculizumab and bortezomib.

2. Case presentation
This is a case of 46-year-old married smoker lady. She has body mass index of 36. She was diagnosed with chronic kidney disease (CKD) secondary to focal segmental glomerulosclerosis (FSGS) based on a renal biopsy finding which did not respond to steroids, cyclosporine and mycophenolate mofetil and progressed to CKD stage 5 requiring dialysis for eight months dialysis before receiving a living donor transplant. She had a history of hypertension, hypothyroidism and bronchial asthma. She is para 3+0 with no recent blood transfusion.

She was admitted for living unrelated renal transplant from her 24-year-old stepson. Flow cytometry cross matching was negative for B and T cells. There were six mismatches and class I DSA against B65 (4,335 mean fluorescence intensity (MFI)) and B63 (2,735 MFI). Prior to her transplant, she received 2 g of intravenous immunoglobulin (IVIG) and four sessions of plasmapheresis which brought down her B63 DSA to 1,442 MFI and B65 DSA to 2,161 MFI. She was induced with ATG, (cumulative dose of 7 mg/kg), methyl prednisone 500 mg, mycophenolate mofetil 1 g twice a day and tacrolimus 2 mg twice a day at the time of transplantation. The immediate post-transplant course was smooth with the serum creatinine level dropping to 72 μmol/L by the fourth day. Following that, the serum creatinine rose rapidly to reach 500 μmol/L by the ninth day (Table 1).

Repeat cross match, at that time was negative for B cell and positive for T cell. The titer for B63 DSA rose to 12,592 MFI and for t B65 DSA increased to 5,043 MFI (the cutoff value of the assay was 500 MFI).

During the same period, the platelet started to fall and LDH started to rise (Table 1) with the presence of schistocytes in the blood film, a hematological picture consistent with HUS. The patient was given IVIG, tacrolimus was switched to cyclosporine and plasmapheresis commenced with no response. Eculizimab was, therefore, given with good and marked response in platelet count, LDH level, and plateauing and subsequent decrease of serum creatinine. Histological examination showed morphological features of acute AMR. The glomeruli showed mild increase in mesangial matrix with no significant increase in mesangial cellularity. Segmental glomerular scarring in the form of obliteration of the glomerular capillaries and adhesion of the glomerular tufts to the Bowman's capsule was identified in three glomeruli. The glomerular basement membranes (GBM) showed segmental mild increase in thickness on periodic acid Schiff (PAS) and methenamine silver special stains. No spike reaction or definite double contouring of the GBM was seen. Mild transplant
glomerulitis was noted. Segmental glomerular fibrinoid necrosis with karyorrhexis was evident in one glomerulus (Figure 1a), and arteriolar intimal fibrinoid necrosis was seen at the hilum of one glomerulus. There was no endocapillary hypercellularity, crescent formation or glomerular microthrombi. Moderate interstitial inflammation that involved approximately 30% of renal cortical parenchyma was present, and consisted mainly of lymphocytes and neutrophils (Figure 1b). This was associated with focal mild lymphocytic tubulitis. Dilatation of the peritubular capillaries and severe peritubular capillaritis (PTC3) were evident; the inflammatory cells in the peritubular capillaries were mixed of mononuclear and polymorph nuclear cells. There was mild interstitial fibrosis and tubular atrophy. Focal mild endarteritis was identified, along with focal interstitial arteriolar fibrinoid necrosis. Immunohistochemical staining for C4d (dilution 1:40, polyclonal Abcam, Cambridge, UK) showed diffuse and strong linear staining in the peritubular capillaries (C4d 3+) in the renal cortex and medulla (Figure 1c).

Table 1. Biochemical hematological and immunological changes from day of transplant onwards

| Day of transplant | Serum creatinine (μmol/L) | LDH (u/L) | Hemoglobin (g/L) | Platelets count (×1000/μl) | B 63 Antibody titer (MFI) | B 65 Antibody titer (MFI) | Treatment given |
|-------------------|--------------------------|----------|------------------|---------------------------|--------------------------|--------------------------|----------------|
| Day 0             | 370                      | 132      | 161              | 1,442                     | 2,161                    |                          |                 |
| Day 1             | 207                      | 170      | 119              | 155                       |                          |                          |                 |
| Day 4             | 70                       | 110      | 177              |                          |                          |                          |                 |
| Day 5             | 93                       | 113      | 243              | 12,592                    | 5,043                    | IVIG and plasmapheresis commenced |
| Day 6             | 171                      | 109      | 231              |                          |                          |                          |                 |
| Day 7             | 259                      | 109      | 154              |                          |                          | Eculizumab commenced     |                 |
| Day 8             | 357                      | 717      | 101              | 102                       |                          |                          |                 |
| Day 11            | 509                      | 1,087    | 67               | 31                        |                          |                          | Eculizumab commenced     |
| Day 30            |                          |          | 67               | 53                        |                          |                          | Bortezomib commenced     |
| Day 90            | 148                      | 251      | 11.3             | 193                       |                          |                          |                 |

Notes: IVIG: intravenous immunoglobulin, MFI: mean fluorescence intensity.
Accordingly, four doses of bortezomib (2.5 mg subcut) were given as rescue therapy for severe AMR. Genetic screening for mutations for atypical HUS revealed type 4 mutational abnormality (homozygous mutation CFB and heterozygous mutation C3). The patient was maintained on eculizumab, tacrolimus and mycophenolate mofetil. Her latest laboratory investigations, three months after transplant showed serum creatinine of 148 μmol/L, FK level of 5.6 ng/ml, LDH level of 251 u/L and a platelet count of 193 × 1,000/μl. No protein was detected in the urine.

3. Discussion
Post renal transplant thrombotic microangiopathy may be localized within the kidney transplant or be associated with a full-blown hemolytic uremic syndrome (Noris & Remuzzi, 2010; Schwimmer et al., 2003). It may be recurrent or be de novo (Noris & Remuzzi, 2010; Ruggenenti, 2002; Satoskar et al., 2010; Zuber et al., 2011). All known causes of HUS that are seen in general population may also affect the renal transplant recipient. However, HUS in renal transplant recipient may be specially associated with calcineurin inhibitors (CNI), mTOR inhibitors, infections (including parvovirus, CMV) and AMR (Bresin et al., 2006; Murer et al., 2000; Noris & Remuzzi, 2010; Robson et al., 2003; Satoskar et al., 2010; Waizer et al., 1999). Both AMR and HUS can trigger the development and propagation of each other, affect the renal microvasculature and cause endothelial damage (Artz, Steenbergen,
Hoitsma, Monnens, & Wetzels, 2003; Bresin et al., 2006; Noris & Remuzzi, 2010; Satoskar et al., 2010; Vergoulas, 2006; Zuber et al., 2011). This may explain why patients who have acute vascular rejection with underlying HUS as the primary disease present with more severe rejection episodes compared to the patients without HUS (Artz et al., 2003; Vergoulas, 2006). De novo HUS can affect 3–14% of kidney transplant recipients (Ruggenenti, 2002). Thirty percent of renal transplant recipients who develop de novo HUS post renal transplantation have genetic abnormalities in complement regulators (Zuber et al., 2011). Usually post-renal transplant de novo HUS occurs in the early post-transplant period but it may also occur at latter stage (Karthikeyan, Parasuraman, Shah, Vera, & Venkat, 2003; Noris & Remuzzi, 2010; Satoskar et al., 2010; Zarifian, Meleg-Smith, O’Donovan, Tesi, & Batuman, 1999). In our case, the finding of positive C4d staining along the cortical peritubular capillaries and presence of circulating donor–specific antibodies (DSA) are in keeping with diagnosis of AMR. In addition, the presence of schistocytes in blood smear, hemolytic anemia, high LDH level, negative direct coomb’s test and thrombocytopenia with complement factors mutations are typical of aHUS. These clinicopathological findings are compatible concurrent with complement mediated de novo HUD and AMR.

The clinical and laboratory manifestations in our patient which poorly responded to treatment with daily plasma exchange and intravenous immunoglobulin, responded effectively to eculizumab and boretzomib. Eculizumab, a monoclonal C5 inhibitor antibody prevents induction of the terminal complement cascade (TCC) and has recently emerged as a therapeutic option for AMR (Locke et al., 2009; Lucas, Co, Nwaogwugwu, Dosani, & Sureshkumar, 2011). Very few cases of AMR induced by, or manifested as de novo HUS have been reported and some were associated with mutation in complement factor H-related protein (Broeders, Stordeur, Rorive, & Dahan, 2014; Noone et al., 2012). Noone et al. (2012) reported a case of a highly sensitized 13-year-old female with end-stage kidney disease secondary to spina bifida-associated reflux nephropathy, who developed severe steroid, ATG and plasmapheresis-resistant AMR with HUS one week after her second kidney transplant, but responded well to eculizumab therapy. Their patient was proven to have genetic abnormality of complement factor H-related protein 3/1 (CFHR3/1). Chandran, Baxter-Lowe, Olson, Tomlanovich, and Webber (2011) reported a case of a 34-year-old female who underwent simultaneous pancreas—kidney transplantation and who developed AMR and de novo HUS seven days post-transplant. She also responded well to eculizumab. Genetic screen for complement abnormality was not performed in this patient. The third case was reported by Broeders et al. (2014). This was a 41-year-old female with CFH abnormality. Noticeably, all reported cases of AMR and HUS were females and the disease presentation was at the early post renal transplant period and all responded effectively to eculizumab. While our case showed CFB and C3 abnormality, the other two cases in which genetic studies were done, showed complement factor H abnormality. Bortezomib, a proteasome inhibitor, was used in our case as rescue therapy for severe AMR and to reduce the high DSA titer (Everly et al., 2008; Lucas et al., 2011; Noris & Remuzzi, 2010). It was not used in the other reported cases. The primary renal disease of the native kidneys in our case was FSGS, which can result in nephrotic range proteinuria induced endothelial injury of the glomerular capillaries and subsequent development of TMA (Manenti et al., 2013). On the other hand, acute ischemia induced by TMA may aggravate proteinuria by causing podocyte fusion and dysfunction (Barisoni, Schnaper, & Kopp, 2007). The clinical significance of such association between FSGS and HUS remains to be defined further.

Screening for complement mutations should be considered in patients with AMR associated HUS since this has implications on the management, prognosis, immunosuppressant choice, future renal transplant and living related kidney donation.

Eculizumab seems very effective in management of such patients who respond poorly to IV IG and plasmapheresis (Broeders et al., 2014; Noone et al., 2012; Noris & Remuzzi, 2010; Zuber et al., 2012). It is not clear, at this stage, whether adding bortezomib has additional prognostic value although it has been recently shown to be of some benefit in AMR (Everly et al., 2008; Lucas et al., 2011).

To the best of our knowledge, this is the first case report of a patient carries CFB and C3 genetic mutations, who developed de novo HUS induced by AMR after renal transplantation.
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Competing Interests
Authors declare no conflict of interest.

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