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Thrombotic microangiopathy as a cause of chronic kidney transplant dysfunction: a case report demonstrating successful treatment with Eculizumab

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Abstract

Atypical haemolytic uremic syndrome is a rare disease associated with genetic or acquired defects in complement regulation which frequently leads to renal failure. Disease often re-occurs early after kidney transplantation leading to a rapid irreversible loss of function. Extra-renal features such as haemolysis and thrombocytopenia may not always occur and diagnosis is made by demonstrating the classic features of thrombotic microangiopathy on renal biopsy. Eculizumab, a terminal complement inhibitor, has been used successfully to treat fulminant, early recurrent disease post-transplant. We describe a case of disease recurrence presenting in the second year post transplant with a gradual decline in function and the first report of eculizumab treatment for chronic thrombotic microangiopathy in a transplanted kidney. The resultant diagnostic challenges and successful response to eculizumab in this setting are discussed.

Introduction

Atypical haemolytic uremic syndrome (aHUS) is a rare cause of acute kidney injury which can rapidly progress to end stage renal disease. As opposed to “typical” haemolytic uremic syndrome caused by Shiga-like toxin producing *Escherichia coli*, aHUS is associated with abnormalities in the regulation of the alternative complement pathway leading to its excessive activation and endothelial injury. This results in a thrombotic microangiopathy (TMA) with haemolytic anaemia, thrombocytopenia and end organ damage. As well as the kidneys, the nervous system, gastrointestinal tract and skin can be affected.

Inherited and acquired defects affecting the alternative complement pathway have been described in aHUS with disease being triggered by an infection or pregnancy. These defects can result in either loss of function of complement regulators (factor H, factor I, membrane co-factor protein) or gain of function of complement activators (C3, factor B)^[1]. Autoantibodies to factor H are the most common acquired defect seen in 5-10% of patients. No abnormality is found in 30-40% of cases.

Previously treatment was with plasma exchange but despite this fifty per cent of patients died or developed ESRD within a year of presentation. Transplantation is complicated by a high rate of recurrence of up to 90% in

patients with certain complement mutations^[2, 3]. This is usually early, mostly in the first 3 months, and usually results in graft loss. Therefore, kidney transplantation alone is not a viable option for many patients. Combined liver-kidney transplantation has been used successfully to reverse the complement defect, as most complement proteins are synthesised in the liver, thereby preserving renal function^[4]. However, it is associated with increased surgical risk. Eculizumab, a humanised monoclonal antibody against C5, inhibits the terminal complement pathway and is an effective treatment for aHUS^[5]. Eculizumab has been used both to treat recurrent aHUS in the transplant and prevent recurrence^[6].

We describe here an unusual case of delayed disease recurrence with gradual decline of renal function a year post-transplant in contrast to the fulminant disease more characteristic of aHUS seen early post-transplantation. The diagnostic difficulties and subsequent successful treatment with eculizumab are discussed.

Case report

A 49 year old Caucasian lady presented in 1985 aged 23 after an upper respiratory infection with breathlessness, oedema and hypertension. She was found to be in acute renal failure requiring haemodialysis. Renal biopsy showed thrombotic microangiopathy in keeping with haemolytic uremic syndrome. Despite treatment with steroids and plasma exchange she did not recover renal function and was commenced on peritoneal dialysis. She received her first transplant in 1986 from her brother which was a 1:2:2 human leukocyte antigen (HLA) mismatch. Despite a post-operative episode of steroid-responsive acute T cell mediated rejection, she had a relatively unremarkable initial course. This included an uneventful pregnancy four years post-transplant. The predominant issues later were resistant hypertension and anaemia, for which no causes were found. This was associated with a gradually deteriorating creatinine. In 2000, she restarted peritoneal dialysis. Graft loss was attributed to chronic allograft nephropathy (not biopsy proven). Platelet count was preserved throughout and active haemolysis was never demonstrated.

She received a deceased donor renal transplant in February 2001 which was a 0:1:0 HLA mismatch and CMV mismatch (donor positive, recipient negative). She had multiple problems during the first year including cytomegalovirus colitis and a lymphocele causing graft hydronephrosis with creatinine peaking at 585 μ mol/l. Despite surgical correction, the subsequent year saw further decline in function with biopsy showing severe chronic irreversible tubular damage with Banff 1a acute T cell mediated rejection. There was no evidence of recurrent HUS. She had persistent resistant hypertension throughout this period and eventually started haemodialysis in 2003.

Owing to the two previous transplants she was highly sensitised with multiple anti-class I and II HLA antibodies. Despite this, in December 2010, she received a donor after brain death transplant which was a 0:0:0 HLA mismatch. She received alemtuzumab induction with prednisolone, mycophenolate mofetil and tacrolimus maintenance immunosuppression. Table 1 illustrates the HLA antibodies present pre-transplant and details of the donor's typing.

During 2012 creatinine increased from a baseline of 100 to 164 μ mol/l. There was associated proteinuria (urine protein creatinine ratio of 110) and haematuria. Platelet count remained stable and no features of active haemolysis were demonstrated. In January 2013, she underwent renal biopsy (figure 1). Out of 14 glomeruli, 8 were globally sclerosed with abnormal appearance of the remaining glomeruli. The main features were basement membrane duplication associated with increased mesangial cellularity. There was moderate chronic tubulointerstitial damage. No glomerulitis or peri-tubular capillaritis typical of antibody mediated rejection (AMR) was seen. In addition C4d staining was weak and not specific to the peri-tubular capillaries which would be expected in AMR. Immunofluorescence showed weak segmental granular deposition of IgM and C4 and moderate capillary loop deposition of C1q only. Electron microscopy again highlighted area of re-duplication of the basement membrane in the glomeruli.

Duplication of the glomerular basement membrane did raise the possibility of transplant glomerulopathy and chronic antibody mediated rejection. However, there was a lack of other typical microscopic feature in the biopsy and C4d staining was not significant (figure 1C). In addition, subsequent testing for donor specific

antibodies (DSA) with single antigen beads showed no HLA antibodies to the only mismatch -DPB1*02:01 (table 1). Non-HLA antibodies have been shown to have a role in late allograft failure, but if there was AMR due to non-HLA we would expect C4d staining to be more prominent.

In addition to AMR, chronic calcineurin toxicity can also cause similar biopsy appearances and therefore, tacrolimus levels were reduced. Blood pressure control was optimised.

From March to May 2013, creatinine continued to rise from 164µmol/L peaking at 396µmol/L (figure 2). This was associated with a rise in lactate dehydrogenase (LDH) to 330 U/L. Platelet count dropped marginally to $130 \times 10^9/L$ and blood film showed fragmented red cells. This suggested an active haemolytic process and raised the possibility that the basement membrane duplication was due to a chronic thrombotic microangiopathy and recurrence of aHUS. The patient was known to be heterozygous for the D1093N mutation in C3 which increases the activity of the pivotal complement activator C3, therefore leading to excessive complement activation ^[7]. These findings, in addition to the lack of more pathognomonic microscopic features of AMR, C4d staining and lack of donor specific antibodies to the only HLA mismatch led us to diagnose recurrent thrombotic microangiopathy as a result of aHUS in her transplanted kidney.

Treatment with eculizumab was started in June 2013. She initially received four weekly doses of 900mg intravenously and continues on fortnightly maintenance infusions of 1200mg. As shown in figure 2, there was an improvement in her creatinine which has been maintained since commencement. Platelet count and LDH also normalised.

Discussion

This case demonstrates an atypical presentation of recurrent aHUS post-transplant. As opposed to the majority of cases when an early, severe TMA causes a rapid deterioration in function, this patient had good initial

function with a slow deterioration in function a year post-transplant. This contributed to the difficulty in diagnosing disease recurrence.

Previous studies have shown the frequent lack of haematological and extra-renal manifestations of HUS when it recurs post-transplant ^[8]. Anaemia if present is often mild with thrombocytopenia seen in less than 50% of cases. Hence, diagnosis of “recurrence” is difficult. In this patient, there were initially no extra-renal manifestations. Diagnosis was aided by the biopsy but the finding of duplication of the glomerular basement membrane is seen in several pathologies. Given the delayed deterioration in graft function, chronic transplant glomerulopathy and chronic calcineurin toxicity were possibilities. The modest rise in LDH and drop in platelet count that occurred in the weeks following the biopsy coupled with lack of DSAs and C4d staining in the biopsy made the recurrence of a TMA most likely.

This patient has a gain of function mutation in C3 predisposing her to develop aHUS ^[9]. In light of the delayed, chronic presentation of the disease following her third transplant, it is possible that recurrent disease was a factor in the loss of the first two grafts. Carriers of heterozygous C3 mutations like this patient have been shown to display a wide range of renal phenotypes ^[9]. At one end of the spectrum is aHUS but carriers have also been shown to display less severe phenotypes such as resistant hypertension and microscopic haematuria. Indeed given this, her resistant hypertension, which contributed to the chronic damage seen with the first and second transplants, could be explained by the underlying mutation.

The success in managing the recurrence of disease with eculizumab is highlighted here. It not only halted the deterioration in function, but an initial improvement in graft function occurred which has been sustained. Without treatment graft failure was the likely outcome. This case also shows the progress that has been made in understanding and managing aHUS over the years. The importance of pre-transplant assessment and full genetic work up to risk stratify patients for disease recurrence and manage accordingly, be it prophylaxis with eculizumab or close surveillance is highlighted.

Figure legends

Figure1. Transplant biopsy demonstrating **A.** Mesangial hypercellularity (arrow, Periodic Acid Schiff stain) and **B.** Double contouring of basement membrane (arrow, silver stain) **C.** Lack of C4d staining

Figure2. Change in eGFR and timing of initiation of eculizumab treatment.

Table 1. Patient and Donor HLA typing, HLA antibody and Crossmatch results

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Figure 1: Transplant biopsy demonstrating **A.** Mesangial hypercellularity (arrow, Periodic Acid Schiff stain) and **B.** Double contouring of basement membrane (arrow, silver stain) and **C.** Lack of C4d staining

A

B

Figure 2 Change in eGFR and timing of initiation of eculizumab treatment.

Table 1 Patient and Donor HLA typing HLA antibody and Crossmatch results

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