CASE REPORT

The importance of genetic mutation screening to determine retransplantation following failed kidney allograft from recurrent atypical haemolytic ureamic syndrome

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SUMMARY

We report the case of a patient with familial atypical haemolytic uraemic syndrome (aHUS) who underwent successful retransplantation 30 months following his failed first kidney allograft from recurrent aHUS. He achieved excellent graft function (creatinine 90 µmol/L), with no evidence of disease recurrence on standard maintenance immunosuppression 9 months after his second deceased donor kidney transplantation. Genetic mutation testing was not available prior to first transplant but screening prior to retransplant identified the patient as having a newly discovered mutation, c.T3566A, within exon 23 of the complement factor H (CFH) gene. Currently, public financing and subsidisation for eculizumab, a costly but effect complement (C5) inhibitor for the treatment of aHUS is not available in Australia. The decision for retransplantation must balance between the risk of disease recurrence and greater risk of death on dialysis. The absence of a more severe CFH genotype assisted in the decision for retransplantation and suggests the importance of genetic mutation screening in order to stratify the risk of disease recurrence and graft loss versus the benefit of transplantation.

BACKGROUND

Haemolytic uraemic syndrome (HUS) is a systemic disorder characterised by widespread thrombotic microangiopathy, manifesting as non-immune haemolytic anaemia, thrombocytopoenia and multiple end-organ damage including the kidneys, central nervous system, heart and gastrointestinal tract. The typical pathophysiology of HUS is due to complement pathway activation by Shiga toxin producing (Stx) *Escherichia coli* or *Streptococci* infection. Atypical (aHUS) is a genetic disorder resulting in chronic unregulated activation of the alternative complement pathway.

Unlike the typical infection-related HUS disease, patients with aHUS generally have much poorer clinical outcomes, with over 50% of patients progressing to end-stage kidney disease and 25% mortality.[1 2] Certain genetic mutations of the complement system are associated with high rates of recurrence. Complement factor H (CFH) gene mutations have the highest rates of postkidney transplantation recurrence at 80–90%, followed by complement factor I (CFI) mutations (70–80%), complement component 3 (C3) and complement factor B (CFB) mutations (40–50%), the presence of circulating antifactor H antibodies (20%) and membrane cofactor protein (MCP) mutations (15–20%).[2]

It is recommended that genetic screening in patients with aHUS-related end-stage renal disease (ESRD) be undertaken prior to listing for transplantation.[3] However, cost and limited availability precludes routine screening in these patients. Furthermore, up to 30–40% of patients with aHUS do not have identifiable genetic mutations and the risk of recurrence in these patients remains unknown.[4] There have been several CFH mutations associated with aHUS. Mutations within the C-terminal of the CFH gene involving short consensus repeat (SCR) domains 19 and 20 are associated with the poorest prognosis.[4] It is well known that previous allograft failure from recurrent aHUS is a strong risk factor for disease recurrence in subsequent grafts, suggesting that retransplantation may not be a viable option for many of these patients.[5] Although our patient had a CFH gene mutation within the SCR20 domain and has had a previous failed kidney allograft from aHUS recurrence (recurrent disease occurred within 1-year post-transplant but allograft life was 11 years), we felt that the benefit of retransplantation outweighed the risk of recurrent disease and graft loss, particularly with a less common CFH genetic mutation.

CASE PRESENTATION

The patient is a 23-year-old man who was diagnosed with aHUS at the age of 6 years. The investigations and management following this diagnosis were unclear but he did receive at least 2 weeks of plasmapheresis with fresh frozen plasma. Despite treatment, he rapidly progressed to ESRD requiring the start of continuous ambulatory peritoneal dialysis. He also had bilateral nephrectomy for refractory hypertension. His half-sister, aged 6, was also affected by aHUS but she died from neurological complications associated with this disease following two failed kidney transplants (both failed from disease recurrence). Furthermore, his paternal aunt was diagnosed with aHUS at age 14 years, and subsequently had three failed kidney transplants from recurrent aHUS, all within the first 3 months post-transplant.

The patient received his first deceased donor kidney transplant at the age of 9 years. He was

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maintained on tacrolimus, azathioprine and prednisolone. Kidney allograft biopsy for deteriorating graft function at 10 months demonstrated histological changes suggestive of recurrent aHUS (thrombotic microangiopathy), resulting in the cessation of tacrolimus (an agent known to be associated with thrombotic microangiopathy). He remained on dual immunosuppression with azathioprine and prednisolone with stable creatinine of 130 µmol/L. He had no systemic complications of aHUS and his serum complement levels were always within normal range. He had progressive deterioration in his kidney allograft function with associated proteinuria over the ensuing 4 years with multiple kidney biopsies demonstrating features consistent with chronic HUS. He restarted haemodialysis in June 2010. He had difficult-to-control hypertension requiring four antihypertensive agents.

The decision to relist him for deceased donor kidney transplantation was made following extensive discussion with the patient and his family about the genetic mutation result and the risk of disease recurrence in the second graft. Unfortunately, eculizumab, the C5 inhibitor an effective complement binding inhibitor for the prevention and treatment of recurrent aHUS after kidney transplantation was unavailable on the pharmaceutical drug listing in Australia.

He received his second deceased donor kidney transplant in January 2013, 18 months following restarting dialysis. He had received induction therapy consisted of polyclonal T-cell depleting antibody (thymoglobulin) and was maintained on tacrolimus (delayed introduction), mycophenolic acid and prednisolone. He had also received intravenous immunoglobulin over a 2-week period (total of 120 g in divided dosages) in light of the presence of a moderate donor-specific antihuman leucocyte antigen (HLA) antibody directed against a shared antigen with his first kidney allograft (HLA DQ7 Luminex mean fluorescent intensity of 2471, OneLambda). His post-transplant course was uncomplicated achieving serum creatinines between 100 and 115 µmol/L. A 3-month protocol kidney biopsy was unremarkable and he continues to have stable allograft function 9 months after transplantation.

INVESTIGATIONS

When aHUS is suspected, investigations to exclude infection-associated HUS, thrombotic thrombocytopoenic purpura (TTP) and autoimmune disease such as systemic lupus erythematosus (SLE) are essential. These investigations include stool culture (to exclude Shiga-toxin-producing *Escherichia coli*), a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) 13 activity (to exclude TTP) and antinuclear antibody (to exclude autoimmune diseases). Levels of complement products are usually unhelpful as the majority of the patients with aHUS have normal protein levels or expressions of C3, C4, CFH, CFI, CFB and MCP. Anti-CFH antibodies and MCP expression on leucocytes are other useful adjunctive tests to complement mutation genotyping if aHUS is suspected.

DIFFERENTIAL DIAGNOSIS

Diagnoses of shiga-toxin-associated HUS, TTP and SLE should be excluded. Less common differential diagnoses include idiopathic thrombocytopoenic purpura, paroxysmal nocturnal haemoglobinuria (PNH), antiphospholipid syndrome (APS) with recurrent thromboses, or heparin-induced thrombocytopoenia syndrome (HITS).

OUTCOME AND FOLLOW-UP

At 9 months postkidney transplantation, the patient continues to have stable allograft function with a creatinine of 100 µmol/L. There is no protenuria or microscopic haematuria. Serum complement levels are within normal range. Blood pressure consistently normal (range 110–130/60–70 mm Hg) without antihypertensive agents.

DISCUSSION

It is generally accepted that ESRD attributed to aHUS is associated with a high risk of recurrence postkidney transplant, often resulting in graft loss particularly in those with CFH and CFI genetic mutations. Although genetic mutation screening pretransplantation has helped clinicians to stratify the risk of disease recurrence, up to 40% of patients with aHUS do not have identifiable genetic mutations.

CFH gene mutation is considered an absolute contraindication to kidney-alone transplantation. Simultaneous liver–kidney transplantation is considered the preferred option, with the rationale that the transplanted liver will provide a source of functioning circulating complement components.[6] Early cases of simultaneous liver–kidney transplantation in patients with aHUS with CFH gene mutation were unsuccessful, with both patients losing the liver grafts to fulminant liver failure.[6–8] The introduction of peritransplant anticoagulation and plasmapheresis has led to several successful cases of combined liver–kidney transplantation for patients with CFH gene mutation.[6 9–11] Nevertheless, four successful cases of kidney-alone transplantation with peritransplant plasmapheresis have been reported.[12–14] Although two of the four patients developed recurrent aHUS, they maintained excellent graft function with the reintroduction of plasmapheresis.

Several new genetic mutations have been identified and although these mutations are located within the CFH and CFI regions, it remains unclear whether certain less common genotypes are associated with less aggressive disease. A patient with a new CFI mutation involving exon II, whereby arginine is substituted for proline at amino acid 50, has undergone a successful kidney transplant without the need for peritransplant plasmapheresis.[15] Certain CFH mutations, particularly those involving the hybrid genes CFH/CFHR1 and CFB/C3, are associated with a 4-fold greater risk of post-transplant recurrence compared to those without these mutations.[5]

The new heterozygous mutation c.T3566A is located within exon 23, in the SCR 20 domain which determines the amino-acidic substitution Leu1189His. It is believed that the C-terminal domains (SCR 19 and 20) of the CFH gene may be associated with more severe disease because they are critical in binding endothelium, thereby protecting against endothelial injury associated with complement activation in patients with aHUS.[2 16] Although c.T3566A mutation is located within SCR 20, the disease process in our patient appears less severe (ie, lack of systemic complications other than rapid progression to ESRD, first kidney allograft lasting 11 years, and no disease recurrence in the second graft) suggesting that perhaps not all mutations within the SCR 19 and 20 domains are associated with the same severe phenotype. In addition, the Instituto di Ricerche Farmacologiche Mario Negri in Italy has screened 125 healthy controls and have not identified this mutation. In our patient, there were no mutations demonstrated in the CFI, MCP, CFB or thrombomodulin (THBD) genes.

Eculizumab is a humanised anti-C5 monoclonal antibody that binds to complement component 5 (C5), blocking its cleavage to proinflammatory C5a and C5b. This agent therefore prevents the formation of the membrane attack complex (MAC) C5b-9, which is the terminal component of complement activation and tissue injury.[17 18] The effectiveness of this agent has been shown in multiple complement-mediated disease process including the treatment of PNH, aHUS, antibody-mediated rejection in kidney transplantation, C3 glomerulopathies and thrombotic microangiopathy-related

APS.[19] Eculizumab appears to be well tolerated without significant side effects,[19–21] although vaccination against *Neisseria meningitides* is recommended.[22] However, the high drug cost and uncertainties over the duration of treatment have resulted in the limited use of this agent only in patients with PNH in Australia.

The association between various genotypes and severity of clinical disease in patients with aHUS remains unclear and ongoing research and case reports will be invaluable in further understanding of this disease. In this case report, a newly discovered c.T3566A CFH mutation appears to be associated with a less aggressive phenotype of aHUS but this must be interpreted not just in the context of this patient's disease, but also the more severe clinical disease of his sister and aunt assuming they have the same mutation. Longer-term follow-up of our patient is essential to better understand the natural history of this disease associated with this novel mutation. This case highlights the importance of genetic testing in patients with aHUS, with the critical aim of helping clinicians and patients for risk stratification and instigation of the various treatment options such as kidney transplantation. Unrestricted availability of eculuzimab would allow an increase in transplant potential of patients with aHUS, regardless of their genetic mutation.

Patient's perspective

If my first transplant had lasted for 11 years despite disease recurrence, then surely my second transplant would last for a similar time irrespective of what genetic mutation I have. I rather have a transplant and take my chance then remain on dialysis, where my lifespan is much shorter and I will have a poor quality of life.

Learning points

- Genetic mutation screening is an essential component of pretransplant testing in patients with end-stage renal disease secondary to atypical haemolytic uraemic syndrome (aHUS).
- The newly discovered complement factor H gene mutation, c.T3566A mutation in exon 23 may be associated with a less aggressive phenotype of aHUS and kidney transplantation with this mutation should be considered.
- Previous failed kidney allograft from recurrence of aHUS does not preclude retransplantation, but the decision should take into account the genetic mutation (if present) and careful informed consent of the patient outlining the benefits and risk of transplantation.

Competing interests None.

Patient consent Obtained.

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