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Eculizumab Prevented Recurrence of Atypical Hemolytic Uremic Syndrome in a Kidney Donor after a Third Kidney Transplantation

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Abstract

A man developed atypical Hemolytic Uremic Syndrome (aHUS) 14 months after donating a kidney to his daughter, who also had aHUS.

He received kidney transplants 4 and 6 years after his disease debut but aHUS soon recurred in both grafts. Genetic analysis revealed a complement factor H mutation.

A third kidney transplantation was performed in 2012. In addition to immunosuppressant, eculizumab (C5 inhibitor), has been given every second week ever since. There has, as yet (Sep 2014) been no rejection or recurrence. However he developed BK nephropathy, which lowered the kidney function permanently.

aHUS recurrences in transplantation grafts are major obstacles in patients with factor H mutation, but can be prevented by eculizumab. The optimal dosage needs further studies and evaluation.

Keywords: Kidney donor; Kidney transplantation; aHUS; TMA; BK nephropathy; Eculizumab

Introduction

Atypical Hemolytic Uremic Syndrome (aHUS) is a rare but severe disease, first described by Kaplan in 1975 [1,2,3]. The annual incidence is about 2/million inhabitants. aHUS is usually associated with complement dysfunction secondary to mutations within the alternative complement system. The disease causes complement activation leading to endothelial cell damage and lesions in platelets and erythrocytes. The severe form of aHUS is characterized by hemolytic anemia with fragmented erythrocytes, thrombocytopenia and renal impairment. Both severity and the likelihood of recurrence vary depending on disease etiology and the type of mutation involved. Factor H and factor I mutation generally lead to renal insufficiency that requires dialysis. Recurrence after kidney transplantation is also more common in patients with these abnormalities.

The new complement factor C5-inhibitor - eculizumab, is now established as a treatment for this disease [4].

Patient Case

Pre-donation investigation and donation procedure

A healthy 30-year-old man was investigated as a kidney donor for his 2-year-old daughter with aHUS. All tests in the donor work-up were completely normal. The kidney donation, performed in February 1995, was uneventful. Unfortunately, the daughter had a relapse of severe aHUS and died.

Diagnosis of aHUS and Initial Therapy

Fourteen months later the donor suffered tiredness and severe headache. At hospitalization his blood pressure was 210/100, hemoglobin 72 g/L, platelet count 44 x 10 (9)/L, creatinine 722 µmol/L and lactate dehydrogenase 66.7 microkat/L. Plasma exchange was started immediately, along with blood transfusions. Hemodialysis was started a few days later. Plasma exchange was given daily but at the twelfth treatment he developed pulmonary edema due to transfusion-related acute lung injury and plasma exchange was stopped. Kidney function did not recover and regular hemodialysis became a permanent necessity. His headache continued and computed tomography showed local changes in the white substance of the temporal-occipital region, left side. Six weeks later the blood samples concerning hemolysis became better and blood pressure normalized to 120/80. Genetic investigation showed the H-factor mutation S1191L identified by the Goodship group [5].

Two years later, in 1998, the patient had breathing difficulties and epileptic seizures. A cerebral computer tomography was normal. The symptoms were relieved after fluid removal and his dry weight was reduced by 6 kg. This dramatic episode shows how difficult it may be to set a correct dry weight in dialysis patients without heart failure. In 1999 he had a painful calcium deposition detected by X-ray. At that point, the patient became interested in kidney transplantation. By now 157 units of plasma and 7 units of packed red cells had been given.

The first kidney transplantation

The first kidney transplantation took place in February 2000. The donor was the patient's stepfather. The immunosuppressant was comprised of prednisolone, azathioprine and tacrolimus. Symptoms of Thrombotic Microangiopathy (TMA) occurred within the first month with signs of hemolysis, anemia and renal insufficiency.

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Plasma exchanges were given but had no effect. The patient's own remaining kidney was removed and tacrolimus was switched to cyclosporine, still without any effect. After 3.5 months he was back in regular dialysis and the graft was removed.

The second kidney transplantation

The patient received a kidney from a deceased donor in November 2002. The immunosuppressive regimen was now sirolimus, Mycophenolate Mofetil (MMF), prednisolone and daculiziumab. Already within the first month there were signs of TMA; plasma exchanges were performed 1-3 times weekly for 5 months without renal recovery but slowly increasing creatinine. The patient perceived this period as the worst time in his life. After 11 months, regular hemodialysis resumed.

The third kidney transplantation

In 2012, after another nine years of dialysis, a third kidney transplantation was attempted. The patient felt that he had no meaningful life when in hemodialysis 5 times per week, near-constant severe musculoskeletal pain, lethargy, and weakness. Despite intense hemodialysis he often had hyperkalemia with K > 7.0 mmol/L, which comprised a significant health risk.

Computed tomography showed no signs of calcification in his iliac arteries. Coagulation investigations showed him to be resistant to activated protein C (heterozygote). He had antibodies against human leukocyte antigen Class I (A29 and B45) and Class II (DR 4, 7, 9 and DQ 7, 8, 9). A female friend was investigated as a donor. There was a repeated mis-match for HLA-A3. Both the cytotoxic and the FACS cross-match tests were negative.

The patient was vaccinated against meningococcal infection in October 2011 (Menveo®). The complement assay tests showed normal function (CH 50) with 87% activity in the alternative pathway and 84% activity in the classical pathway.

The kidney transplantation was performed in August 2012. Immunosuppressant consisted of basiliximab, tacrolimus, MMF and prednisolone. Surgery was uneventful and the kidney functioned immediately.

Eculizumab (900 mg) was given intravenously weekly for 3 weeks pre-transplantation, this preemptive treatment was given to assess the efficacy and tolerance. An extra dose was given at the time of surgery, and then weekly for 3 weeks. After that the dosage was increased to 1200 mg given every second week. No side effects were observed.

The patient developed no signs of TMA. Due to increasing s-creatinine after 3 months a transplant biopsy was performed, showing low-grade rejection class Banff Ia. He received methylprednisolone 0.5 g for 3 days but renal function did not improve. He developed cytomegaloviral infection which was treated successfully with valganciclovir. BK virus was found in blood with 44,000 genomes/mL(PCR technique) and BK nephropathy was confirmed by a new biopsy showing toxic, tubular changes without any signs of rejection. The dosages of tacrolimus and MMF were now reduced and after 6 months the BK virus had subsided. Kidney function stabilized with s-creatinine around 175 μmol/L and eGFR around 30 mL/min. He currently has no microalbuminuria and his blood pressure is normal with a low dosage of AII inhibitor. Functional testing of the complement shows 1-2% activity before he receives his dose of eculizumab. He is feeling great and is living a new life.

Discussion

Issues often discussed in relation to patients with aHUS are use of living donors, risks of recurrence after transplantation and costs of the complement inhibitor eculizumab.

This male kidney donor had the complement factor H mutation, which is associated with 80% risk of recurrence [6,7]. With eculizumab treatment, his third kidney transplantation 17 years after the donation succeeded without any signs of TMA. A series of kidney transplant recipients with aHUS has been described by Zuber et al [8].

Our patient had no severe rejection despite being a highly immunized patient but developed BK nephropathy, which lowered his kidney function to 30 ml/min. Our second patient with aHUS having a kidney transplant recently also developed BK nephropathy (personal experience). This raises the question if eculizumab is adding to over-immunosuppression?

In Sweden we always try to find a living donor, searching not only among the recipient's family, but also among unrelated persons. Long-term follow-up indicates that living donation is safe [9]. The occurrence of aHUS in a kidney donor was first described in 1974, and this was a sibling donor who developed TMA within 3 weeks after the donation [10]. This supports the use of unrelated donors, and here the donor was a friend.

We know that the cost of eculizumab is very high. However in this case we have special obligations since it was a former living donor. An important issue is to find the adequate dosage of immunosuppressant for kidney transplant recipients with aHUS.

Acknowledgement

The patient described here has consented to publication of details about his disease and outcome.

References

1. Kaplan BS, Chesney RW, Drummond KN. Hemolytic uremic syndrome in families. N Engl J Med. 1975; 292: 1090-1093.
2. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011; 6: 60.
3. Besbas N, Karpman D, Landau D, Loirat C, Proesmans W, Remuzzi G, et al. A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. Kidney Int. 2006; 70: 423-431.
4. Köse O, Zimmerhackl LB, Jungraithmayr T, Mache C, Nürnberger J. New treatment options for atypical hemolytic uremic syndrome with the complement inhibitor eculizumab. Semin Thromb Hemost. 2010; 36: 669-672.
5. Donne RL, Abbs I, Barany P, Elinder CG, Little M, Conlon P, et al. Recurrence of hemolytic uremic syndrome after live related renal transplantation associated with subsequent de novo disease in the donor. Am J Kidney Dis 2002; 40: 22.
6. Le Quintrec M, Zuber J, Moulin B, Kamar N, Jablonski M, Lionet A, et al. Complement genes strongly predict recurrence and graft outcome in adult renal transplant recipients with atypical uremic syndrome. Am J Transplant. 2013; 13: 663-675.
7. Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, Macher MA, Niaudet P, Guest G, et al. Different impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2007; 18: 2392-2400.

8. Zuber J, Le Quintrec M, Krid S, Bertoye C, Gueutin V, Lahoche A, et al. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. Am J Transplant. 2012; 12: 3337-3354.

9. Fehrman-Ekholm I, Kvarnström N, Söfteland JM, Lennerling A, Rizell M, Odén A, et al. Post-nephrectomy development of renal function in living kidney donors: a cross-sectional retrospective study. Nephrol Dial Transplant. 2011; 26: 2377-2381.

10. Bergstein J, Michael A, Kjellstrand C, Simmons R, Najarian J. Hemolytic-uremic syndrome in adult sisters. Transplantation 1974;17;487-490.

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