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Transplantation

Exceptional Case

Posttransplant outcome of atypical haemolytic uraemic syndrome in a patient with thrombomodulin mutation: a case without recurrence

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Abstract

Atypical haemolytic uraemic syndrome (aHUS) is a rare disease characterized by thrombocytopenia, microangiopathic haemolytic anaemia and renal impairment. Mutations in genes encoding inhibitors of the alternative pathway of the complement system are involved in ∼50% of the cases. Thrombomodulin (THBD) gene mutations occur in ∼3–5% of the cases. The risk of aHUS recurrence after kidney transplantation depends on the complement abnormality involved. In all three cases of THBD mutation reported to date, aHUS recurred after kidney transplantation (KT) with early graft loss. No data exist about therapeutic approaches before kidney transplantation to reduce the risk of recurrence in patients carrying this mutation. Favourable data on the use of eculizumab have been reported, in terms of plasmatherapy withdrawal and renal function recovery in aHUS recurrence after KT. To our knowledge, this case report presents the first case of successful kidney transplantation in a patient with aHUS due to THBD mutation who was treated with a single plasma-exchange immediately before surgery without recurrence of the disease 12 months after transplantation.

Keywords: atypical haemolytic uraemic syndrome; kidney transplantation; thrombomodulin mutation

Background

Idiopathic atypical haemolytic uraemic syndrome (aHUS) is a rare disease, with an estimated incidence of two cases per million population in North America. It is characterized by thrombocytopenia, microangiopathic haemolytic anaemia with fragmented erythrocytes (schistocytes) and renal impairment.

In the primary complement-mediated thrombotic microangiopathy (TMA) syndromes [1], the disease is due to a dysregulation of the alternative complement pathway. A mutation in genes encoding regulators or components of the alternative complement cascade is identified in ∼50% of the patients. In many cases the disease is precipitated by infections, use of drugs, pregnancy, organ transplantation and systemic diseases. The most common mutations involve factor H, CFH/CFHR1 hybrid gene, factor I, membrane cofactor protein (MCP), factor B (gain of function) and factor C3; anti-CFH antibodies are detected in 5–10% of the patients.

Growing evidence indicates that the risk of aHUS recurrence after kidney transplantation depends on the kind of gene mutation. Patients with isolated mutations in membrane-bound factors, like MCP, rarely develop posttransplant recurrence [2]. Patients with mutations in genes that encode factor H, I, B or C3 have a higher risk of recurrence.

Thrombomodulin (THBD) is a transmembrane glycoprotein that regulates coagulation, inflammation, fibrinolysis and cellular proliferation. It is expressed in vascular endothelial cell receptor and in many other tissues and cells [3–5]. THBD confers protection against endothelial injury and microvascular thrombosis and it is a negative regulator of the complement system; mutant variants of thrombomodulin may contribute to the development of aHUS in 3–5% of the cases (coagulation-mediated TMA) and have been occasionally reported in patients with venous thrombosis. We report the case of a 49-year-old man with aHUS due to THBD mutation who underwent a cadaveric kidney transplantation after a single plasma-exchange performed before the transplant.

Case report

In 2008 a 49-year-old Chinese man who lived in China until he was 44, developed severe hypertension (180/110 mmHg), nausea and asthenia; laboratory and radiologic tests performed at the emergency unit showed haemolytic microangiopathic anaemia (schistocytes ++), acute kidney

injury and pleural effusion. The patient was treated with blood transfusion, haemodialysis, plasma-exchange and steroids. Subsequently the patient was referred to our unit; the laboratory tests confirmed the diagnosis of haemolytic uraemic syndrome (HUS) without diarrhoea or other suggestive symptoms of infection. Thrombotic thrombocytopenic purpura (TTP) was ruled out by an ADAMTS 13 activity of 50% and by a low title of inhibitors (10.4 U/mL). Secondary forms of aHUS were excluded. The patient was treated with plasma exchange on a daily or alternate day basis, for a total of 23 sessions and haemodialysis was continued due to the lack of renal function recovery. Plasma exchange was stopped after complete and persistent absence of haemolytic microangiopathic anaemia. The patient was discharged on regular haemodialysis therapy. To corroborate the diagnosis of aHUS and to evaluate the risk of recurrence in case of a kidney transplantation, genetic tests were performed to investigate abnormalities in regulators of the alternative complement pathway and components of the C3bBb convertase. The tests showed a missense mutation in the serine-threonine-rich region of THBD gene (D486Y). All coding sequences of the CFH, CFI, MCP, C3, CFB and THBD genes were sequenced showing that the patient was homozygous for the polymorphic variant CFH *tgtgt* haplotype that increases the risk of aHUS [6]. The patient was listed for kidney transplantation at our centre.

After 5 years without any new episodes of thrombotic microangiopathy (TMA), the patient underwent a cadaveric kidney transplantation. Immediately before surgery a single plasma exchange session was performed. The immunosuppressive regimen included basiliximab, microemulsioned cyclosporin, enteric-coated mycophenolate sodium and methylprednisolone. Laboratory tests for the assessment of aHUS recurrence were performed daily. No signs of aHUS recurrence were detected and the patient was discharged 13 days after transplantation without any further plasmatherapy sessions. Six months after transplantation a kidney biopsy was performed due to a rising serum creatinine without signs of TMA. Histologic evaluation showed low-grade interstitial fibrosis and tubular atrophy in the absence of classical TMA-related endothelial damage. Luminex test and C4d were both negative. Renal function returned to the pre–admission values after cyclosporin dose adjustment. One year after kidney transplantation, renal function was stable (sCr 1.4 mg/dL, creatinine clearance 7 mL/min) and no signs of aHUS recurrence were detected (Table 1). During our observation, the patient did not develop infections or other possible aHUS triggers.

Table 1. Laboratory data at the aHUS onset and in the post-transplant period

		Time from KT		
	aHUS onset	1 month	6 months	12 months
Creatinine (mg/dL)	22.3	2.1	1.6	1.4
Urea (mg/dL)	282	70	68	40
Haptoglobin (g/L)	<0.05	1.10	1.18	1.27
Haemoglobin (g/dL)	9.3	8.9	12.7	16.2
Platelets (cell*10^9/L)	82	192	158	160
LDH (UI/L)	960	188	269	209
C3(g/L) (n.v.: 0.9–1.8)	0.45	0.65	0.80	0.77
C4 (g/L) (n.v.: 0.1–0.4)	0.21	0.21	0.23	0.23
Schistocytes	++	–	–	–

KT, kidney transplantation; aHUS, atypical haemolytic uraemic syndrome.

Discussion

aHUS is a rare disease with a high rate of recurrence after kidney transplantation; it is now well recognized that the kind of mutation of the genes encoding regulatory proteins of the alternative complement pathway is crucial for assessing the risk of recurrence. THBD is a transmembrane protein involved in thrombin-mediated cleavage of protein C, but it also exists as a soluble form in plasma, generated by the cleavage of the intact protein; plasma THBD levels seem to be inversely correlated with the development of vascular diseases [3] and negatively regulate complement by accelerating the inactivation of C3b.

Little published data exist about kidney transplantation in patients with THBD mutations making it impossible to estimate the risk of aHUS recurrence. In one case, aHUS recurred 3 days after transplantation with graft loss [7]. Another patient with aHUS due to THBD mutation (D486Y) who underwent two kidney transplantations, relapsed after each transplantation; at the time of the second transplant, the patient received plasmapheresis for 3 weeks after surgery, nevertheless aHUS recurred 3 months after transplantation and eculizumab therapy was started, with poor results in terms of renal function recovery [8]. In a recently published series of 12 aHUS patients [9] only one had THBD mutation and he developed early recurrence after kidney transplantation without recovery of renal function. No data exist about therapeutic approaches before kidney transplantation to reduce the risk of recurrence in patients with THBD mutations (Table 2), and the available data are too limited for therapeutic recommendation [5]. Plasmatherapy remained the first line treatment for aHUS until 2010; this treatment was based on expert opinion rather than clinical trials and the benefit of this procedure is scarcely documented in THBD mutations. We have identified in our patient a heterozygous THBD mutation in the serine-threonine-rich region of the protein (D486Y) associated with CFH *tgtgt* haplotype. This kind of mutation is associated with a defective suppression of the alternative complement pathway activation and it is clearly involved in the pathogenesis of aHUS. In fact the D486Y variant and the other aHUS-associated mutant forms of THBD are

Table 2. Transplant options and frequency of the complement abnormalities among patients with aHUS

Gene or subgroup	Risk of recurrence after KT	Frequency in aHUS	Transplant options
CFH	75–90%	20–30%	CLKD or prophylactic eculizumab/PE
Anti-CFH antibodies	30%	6%	KT combined with PE and corticosteroids and/or rituximab
CFI	45–80%	4–10%	CLKD or prophylactic eculizumab/PE
MCP	<20%	5–15%	Single KT, no prophylaxis
C3	40–70%	2–10%	KT with prophylactic eculizumab/PE
CFB	03/03	1–4%	KT with prophylactic eculizumab/PE
THBD	03/04[a]	3–5%	No therapeutic recommendations

[a]Including the case of the present report.
aHUS, atypical haemolytic uraemic syndrome; CFH/I/B, complement factor H/I/B; MCP, membrane cofactor protein; THBD, thrombomodulin; KT, kidney transplantation; CLKD, combined liver-kidney transplantation; PE, plasma-exchange.

less effective than wild-type THBD in facilitating CFI-mediated inactivation of C3b in the presence of CFH [5]. The decision to treat the patient with a single PE session before surgery was made taking into consideration that undiscovered gene mutations are responsible for 50% of the cases of aHUS. Moreover a combined mutation involving a membrane-bound protein and unknown soluble factors may be present. This pathogenetic mechanism could explain the aHUS recurrence after kidney transplantation in carriers of THBD mutations. We had to consider also that patients homozygous for the CFH tgtgt haplotype, as in this case, have a greater risk of developing aHUS [6] even if there are no clinical data about the risk of post-transplant recurrence. Furthermore THBD, as already mentioned, also exists as a soluble factor and the mutant soluble THBD may be inadequate to provide sufficient protection, causing the recurrence of the disease [7, 8] in particular after the trigger of ischaemia-reperfusion injury. A case against intensive plasmatherapy is the recurrence of aHUS reported at discontinuation. The prompt availability of eculizumab and also the favourable results reported with eculizumab in the treatment of aHUS recurrence, regardless of preventive plasmatherapy [10, 11], supported our choice for this treatment option. There is growing evidence that early treatment with eculizumab in aHUS recurrence is able to obtain a complete reversal of the disease activity and a delay in initiating eculizumab inversely correlates with the degree of renal function recovery [12].

In conclusion, this case report illustrates a successful kidney transplantation performed in a patient with THBD mutation and homozygous for the polymorphic variant CFH *tgtgt* haplotype without intensive plasmatherapy or eculizumab preventive treatment. In patients with aHUS, tailored strategies on the genetic complement abnormalities remain a crucial element to prevent recurrence after transplantation. More studies are required to understand the role of environmental, epigenetic or other genetic factors in the pathogenesis of aHUS due to THBD mutation.

Conflict of interest statement. None declared.

References

1. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014; 371: 654–666
2. Zuber J, Le Quintrec M, Morris H *et al.* Targeted strategies in the prevention and management of atypical HUS recurrence after kidney transplantation. *Transplant Rev* 2013; 27: 117–125
3. Van de Wouwer M, Collen D, Conway EM. Thrombomodulin-protein C-EPCR system: integrated to regulate coagulation and inflammation. *Arterioscler Thromb Vasc Biol* 2004; 24: 1374–1383
4. Boehme MW, Deng J, Raeth U *et al*. Release of thrombomodulin from endothelial cells by concerted action of TNF-alfa and neutrophils: in vivo and in vitro studies. *Immunology* 1996; 87: 134–140
5. Delvaeye M, Noris M, De Vriese A *et al*. Thrombomodulin mutations in atypical hemolytic-uremic syndrome. *N Engl J Med* 2009; 361: 345–357
6. Fremaux-Bacchi V, Fakhouri F, Garnier A *et al*. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. *Clin J Am Soc Nephrol* 2013; 8: 554–562
7. Noris M., Remuzzi G. Thrombotic microangiopathy after kidney transplantation. *Am J Transplant* 2010; 10: 1517–1523
8. Sinibaldi S, Guzzo I, Piras R *et al*. Post-transplant recurrence of atypical hemolytic uremic syndrome in a patient with thrombomodulin mutation. *Pediatr Transplant* 2013; 17: 177–181
9. Matar D, Naqvi F, Racusen LC *et al*. Atypical hemolytic uremic syndrome recurrence after kidney transplantation. *Transplantation* 2014; 98: 1205–1212
10. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis* 2011; 6: 60
11. Zuber J, Le Quintrec M, Sberro-Soussan R *et al*. New insights into postrenal transplant hemolytic uremic syndrome. *Nat Rev Nephrol* 2011; 7: 23–35
12. Zuber J, Le Quintrec M, Krid S *et al*. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. *Am J Transplant* 2012; 12: 3337–3354

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