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CASE REPORT

Renal transplantation in patients with atypical haemolytic uraemic syndrome: a tailor made approach is necessary

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ABSTRACT

A 33-year-old woman with a history of chronic transplant dysfunction because of repeated bouts of haemolytic uraemic syndrome (HUS) was considered for a second transplant. Extensive genetic investigation of the complement system was executed to rule out known mutations prone to development of HUS. This case illustrates the importance of genetic screening in patients with recurrent HUS.

KEYWORDS

Atypical haemolytic uremic syndrome, transplantation, factor H

INTRODUCTION

HUS is a disorder characterised by thrombotic microangiopathy (TMA) with thrombocytopenia, haemolytic anaemia and renal failure. Two different forms can be described. The typical form is usually associated with food-borne infections with Shiga-like toxin producing *Escherichia coli* O157:H7 (*E. coli* O157:H7) causing diarrhoea and in approximately 6% end-stage renal failure (ESRD); however, the long-term prognosis is good. Atypical HUS (aHUS), is most frequently seen in adults and is not caused by infection with the toxin-producing *E. coli*. The prognosis is less favourable, up to 50% progress to ESRD.[1] Dysregulation of the complement system due to mutations in its inhibitors can be found in the majority of cases of aHUS. In the presence of certain triggers this causes unrestrained complement activation.[2]

Mutations can be divided into two groups: mutations in inhibitor proteins circulating in plasma and mutations of inhibitors that are membrane bound. Atypical HUS caused by mutations of the membrane bound protein (MCP) has a good prognosis but mutations in plasma factors factor H (CFH) or factor I (CFI) are known to have a poor prognosis as well as a high recurrence rate of HUS in the transplant.[3-5] We present a case where a patient with a factor H polymorphism was successfully transplanted with pre- and postoperative plasmapheresis and infusion of fresh frozen plasma (FFP).

CASE REPORT

A 33-year-old woman was referred to our hospital because of a considered second renal transplantation due to failure of the first transplant, which she received when she was 13 years old. The initial diagnosis was ESRD due to IgA nephropathy (also in retrospect without signs of TMA).
Because of two proven episodes of HUS we suspected a possible dysfunctioning complement system which consequently was thoroughly investigated. Levels of her complementary proteins C3 and C4 were both within normal range. Factor B was low: 72 mg/l (90 to 320 mg/l) and factor I was measured at 71% (expressed as percentage of normal: 70-130%). The levels of her factor H were normal, being 120% (65 to 140%). Also, no antifactor H antibodies were detectable. However, six heterozygote DNA polymorphisms were found on the gene encoding for factor H.[6] Of these, the polymorphism c.2016A>G in exon 14 and c.2881G>T in exon 19 have been proven to be associated with the development of HUS.[7]

Initially her HLA-matching sister was willing to donate her kidney; however, because family members of patients with abnormal factor H have higher risks of having complement abnormalities themselves, she was not considered eligible as a possible donor. Most fortunately, a living unrelated donor was available.

At the time of admission, serum creatinine was as high as 634 µmol/l, serum urea 30.9 mmol/l her haptoglobin was as low as <0.2 g/l and complement C3 0.56 g/l.

To prevent postoperative recurrence of aHUS we started preoperative plasma exchange therapy with infusion of FFP. Plasma exchange of 1.5 times the plasma volume was continued postoperatively once a day for the first week, every other day the next week and twice in the third week. It was stopped after a total of 13 procedures at day 23. Immunosuppression after transplantation consisted of tacrolimus 3 mg twice daily, mycophenolate mofetil 2 g twice daily and low-dose prednisolone (20 mg once daily, rapidly tapered to 10 mg). She was discharged from the hospital on day 28 after transplantation in a good condition, with no signs of recurrence of HUS and a serum creatinine of 90 µmol/l. Now, three years later, her renal function is still excellent with a serum creatinine of 84 µmol/l.

DISCUSSION

A feature underlined by this case but already proven in several other cases is that no patient suffering from aHUS should be transplanted without additional measures. There has been some experimenting with several modalities of treatment in aHUS. When caused by autoantibodies against factor H plasmapheresis alone has been proven efficient because the antibodies are then removed from the circulation.[8] However, when aHUS is caused by a mutation in factor H or factor I this is not sufficient and infusion of FFP containing large amounts of factor H and I will be necessary. When there is a total deficiency of factor H a combined kidney and liver transplantation has been recommended. In that case, it is also indispensable to take preoperative as well as postoperative measures given the massive complement activation during ischaemia reperfusion, which cannot be counteracted since initially the freshly transplanted liver is not capable of synthesising sufficient amounts of factor H, resulting in primary non-functioning of the liver.[9,10]

It is essential in all of these cases to realise that only approximately 50% of all mutations causing HUS have been discovered. Two cases of HUS in the donor have been described very short after donation in which no (as yet established) mutations in the regulatory complement inhibitors could be identified.[10] For that reason it is strongly advised not to perform a living donor transplantation with a family member as donor, even if genetic screening reveals no mutations in their complement inhibitors.[11]

The need for a trial of complement inhibitors, such as eculizumab, now already used in trials for acute aHUS and plasma-resistant HUS, is definitely warranted in the future.[12] The options of using recombinant factor H are also being investigated and promising results have already been published (*in vitro* studies).[13]

In conclusion, this case report describes the importance of investigating the complement profile including genetic screening in patients with aHUS and gives a schedule for plasma exchange therapy with infusion of FFP. Family members cannot be used as donor, even when the recipient has a sporadic form of HUS as original disease.

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