Case Report

Renal transplantation for end-stage renal disease due to paroxysmal nocturnal haemoglobinuria

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Introduction

Paroxysmal nocturnal haemoglobinuria (PNH) is characterized by nocturnal haemoglobinuria, haemolytic anaemia, and thrombosis [1]. Most patients have anatomical and functional renal abnormalities, although renal function deterioration often remains unrecognized. The pathogenesis could be related to iron deposition or to repeated vascular thrombosis. The present case illustrates that renal transplantation is a possible treatment option for end-stage renal disease in PNH.

Case

A 60-year-old patient received a cadaveric kidney graft for end-stage renal disease in the course of PNH. Thirty years earlier the diagnosis of PNH had been made based on a positive Ham’s test after an episode of frank haemolysis with lower back pain and gastrointestinal bleeding. The haemoglobin at that time was 4.5 g/dl. In the following 20 years he experienced about five haemolytic crises per year, complicated with progressive renal failure. Levels of lactate dehydrogenase were constantly above 2000 IU/l. Despite treatment with high doses of recombinant human erythropoietin, repeated transfusions were necessary. End-stage renal disease ensued at the age of 58, when peritoneal dialysis using bicarbonate-based solutions was started. Afterwards transfusions continued to be administered at an average rate of two units of washed red blood cells per month.

Two years later the patient received a cadaveric kidney graft. In the immediate postoperative period there was a pronounced drop in haemolytic activity, with a concomitant rise in blood platelets and white blood cell count despite immunosuppressive treatment with cyclosporin, steroids, and mycophenolate mofetil (MMF) (Table 1). Furthermore, the patient became independent of transfusions. In the following 9 months three major haemolytic crises occurred. A striking finding was that the first two crises seemed to be elicited by renal function deterioration (Figure 1). The first episode was preceded by urinary obstruction due to ureteral stenosis, for which a pyelo-pyelostomy was performed. A new stenosis developed at the anastomosis a few months later, requiring surgical re-intervention. The third haemolytic crisis accompanied a bronchial infection 6 months after renal transplantation. At the latest outpatient clinic, 9 months after renal transplantation, renal function remained stable with a serum creatinine of 117 µmol/l. A MRI scan at that time showed evidence of iron deposition in the renal graft.

Discussion

PNH is a rare, acquired genetic disorder of the pluripotent stem cell characterized by complement-mediated haemolysis and thrombosis. The molecular defect is a deficient synthesis of glycosyl-phosphatidylinositol molecules by the haematopoietic cells. These molecules anchor decay-accelerating factor (CD 55) and other

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>-12</th>
<th>-6</th>
<th>0</th>
<th>+1</th>
<th>+3</th>
<th>+6</th>
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<td>Hb (g/dl)</td>
<td>8.9</td>
<td>8.7</td>
<td>9.1</td>
<td>10.1</td>
<td>8.9</td>
<td>8.1</td>
</tr>
<tr>
<td>BP (10⁹/mm³)</td>
<td>86</td>
<td>79</td>
<td>86</td>
<td>115</td>
<td>77</td>
<td>104</td>
</tr>
<tr>
<td>Creat(µmol/l)</td>
<td>766</td>
<td>907</td>
<td>800</td>
<td>128</td>
<td>133</td>
<td>142</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>4536</td>
<td>4850</td>
<td>1922</td>
<td>722</td>
<td>1012</td>
<td>1197</td>
</tr>
</tbody>
</table>

Month 0, time of renal transplantation.
Hb, haemoglobin; BP, blood platelets; creat, creatinine, LDH: lactate dehydrogenase.
Transplantation for ESRD from paroxysmal nocturnal haemoglobinuria

Fig. 1. (A) Evolution of haemoglobin, creatinine and transfusions (arrow) before and after renal transplantation. (B) Evolution of lactate dehydrogenase before and after renal transplantation.

inhibitory proteins to the cell membrane [1]. The defect in PNH results in a pronounced sensitivity of all three cell lines to the lytic action of complement. Gross haemoglobinuria is usually only intermittently present, while some patients also have mild granulocytopenia and thrombocytopenia. Activation of platelets may result in venous thromboses which are a major cause of death. The clinical course can be quite variable, however. Acute renal failure during acute haemolytic exacerbations is well documented, whereas chronic renal failure is not always recognized. The patient described is to our knowledge the first with PNH to receive a cadaveric kidney graft.

The pathophysiological mechanisms of renal failure caused by PNH have not been fully elucidated, but may be related to intrarenal deposition of haemosiderin or to a direct toxic effect of iron [2]. Since deposition of iron in the kidneys can be very extensive, it is remarkable that only a few patients develop progressive renal failure. It seems more probable, therefore, that renal failure is not related to iron deposition, but to repeated episodes of microvascular thrombosis [3]. In the series of Clark et al. [3], nine patients of 17 in whom IVP was performed had radiological evidence of cortical infarction.

Very little is known about renal replacement therapy in these patients. Once end-stage renal disease had developed in our patient, peritoneal dialysis with bicarbonate-based solutions was started because it was hypothesized that this would cause less haemolysis than lactate-based solutions. The bicarbonate solutions are clearly the most biocompatible, but they did not completely obviate the need of repeated transfusions. Haemodialysis was not considered in the fear of exacerbating haemolysis over the extracorporeal circuit, as heparin is also known to cause increased haemolysis in patients with PNH.

An abrupt decrease in haemolytic activity was observed after renal transplantation. This can be explained by several factors. First, uraemia per se...
causes some degree of haemolysis, but it is unlikely that the resolution of uraemia is responsible for the observed effect. Nevertheless, two consecutive haemolytic episodes clearly seemed to be related to renal function deterioration.

Renal function deterioration could be a non-specific trigger for haemolysis in these patients, as surgery or an intercurrent infection often is. A direct effect of the immunosuppressive therapy on the PNH cell line could be another explanation. Since the patient was receiving treatment with steroids, cyclosporin, and mycophenolate mofetil, each one of these medications may be responsible for the observed effect. However, there was no increased expression of the phosphatidylinositol-bound antigen CD59 after renal transplantation. Steroids have some efficacy in the treatment of PNH, although their mode of action is not clear. The doses of prednisone required are high; therefore, some authors advocate alternate-day dosing regimens [4,5].

Our patient was treated with a daily dose of 20 mg methylprednisolone during the first month. The tapering of this dose afterwards may have caused the rebound of haemolysis. Mycophenolate mofetil (MMF) has found broad approval in renal transplantation, and is getting newer applications now in several autoimmune disorders. Zimmer-Molsberger et al. [6] applied MMF effectively as a second-line medication in two patients with severe autoimmune haemolytic anaemia. As PNH is not considered to be an autoimmune haemolytic anaemia, the efficacy of MMF in PNH remains uncertain.

Bone marrow transplantation is capable of replacing the abnormal stem cells and has been advocated in cases of PNH with pronounced marrow hypoplasia, but the morbidity and mortality of this treatment precludes widespread application. Renal transplantation has offered our patient a considerably better quality of life. We therefore conclude that renal transplantation is a viable option in patients with end-stage renal disease caused by PNH. However, the follow-up period is still limited and the risk of immunosuppressive therapy on the development of malignancies has to be envisaged, especially in the knowledge of the association of PNH with leukaemia.

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References


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