ACUTE VASCULAR REJECTION TREATED BY PLASMA EXCHANGE

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Summary

Since 1980 we have treated in 14 patients 19 steroid resistant acute vascular rejection (AVR) episodes by plasmapheresis (PF). Each episode was treated by six PF with 5L plasma being filtered and simultaneously replaced by 3.5 per cent Albumin-Ringer-lactate. After each PF 20g immunoglobulin (Intraglobin®) was given intravenously. In all cases renal function improved following PF. In the long term one graft was lost due to chronic irreversible vascular rejection, all others are still functioning, nine of them six months and eight of them 12 months post PF treatment. They show no signs of rejection. PF with repletion of immunoglobulins after treatment is a simple and safe procedure, which in our hands proved to be quite effective in reversal of AVR.

Introduction

Since acute vascular rejection (AVR) usually does not respond to steroid pulse therapy, it remains a main cause of graft failure after human cadaveric renal transplantation. In AVR, damage in the (small) arterial vessels is the prominent feature histologically. Myoendothelial swelling, proliferation, fibrinoid necrosis and polymuclear infiltrations of the arterial wall are typical [1]. The nature of this type of rejection is not clearly understood. It has been associated with humoral immunity, as immunoglobulins have been demonstrated within the vessel walls in cases of AVR [1,2].

Some authors have reported reversal of acute vascular rejection by plasma-exchange in single case studies [3–5] or in small groups of patients [6–10]. We decided to treat all episodes of AVR by means of plasma exchange starting in 1980 and this study summarises our experience in 14 patients with 19 episodes of AVR.
Patients and methods

Patients

Since September 1980 49 patients have received a first and eight patients a second cadaveric renal transplant in this hospital. Our standard immunosuppressive regimen and blood transfusion policy has been published elsewhere [11].

Diagnosis and therapy of rejection

Rejection was diagnosed, when serum creatinine concentration increased more than 0.5mg/dl in 48 hours and other causes of deterioration of renal function had been excluded. Rejection was initially treated with two or three 1g methylprednisolone bolus doses given i.v. in 24–48h intervals. In steroid resistant rejection episodes a transplant biopsy was obtained. No patient with the confirmed diagnosis of AVR was excluded from plasmapheresis therapy.

Plasma exchange therapy

Plasma filtration (PF) technique was used employing cellulose acetate membrane hollow fibre filters (Asahi Plasmaflo®, Asahi Medical). Six courses of PF, usually three per week, were performed in each case. At each treatment 5L of plasma were filtered and simultaneously replaced with 3.5% albumin-Ringer-lactate solution. Exact volume replacement was achieved using the Sartorius Haemoprocessor® as an automatic balancing unit. No technical problems were encountered.

To prevent complications of severe antibody deficiency 20g IgG (Intraglobin® Biotest) was given i.v. after each PF.

Laboratory investigations

Whole blood leucocytes and platelets were measured using a Coulter counter®. Immunoglobulins (IgG, IgA, IgM) and C₃ values were determined nephelometrically, and albumin and creatinine concentrations in plasma were measured using a Technicon Autoanalyzer.

Results

Fourteen patients developed 19 steroid-resistant rejection episodes, which were subsequently treated with PF. All cases showed a progressive deterioration of transplant function in spite of pulse methyl-prednisolone therapy given in a mean dosage (±SD) of 2.7 ± 1.5g/case. Mean serum creatinine concentration rose from 2.0 ± 0.8mg/dl at the start of AVR to 4.6 ± 2.2mg/dl, when PF was initiated (Figure 1).

After failure of pulse therapy, a transplant biopsy was performed in 13 patients. In one patient a biopsy was not obtained due to concomitant wound infection. All biopsied cases showed typical histological signs of AVR, as defined
Figure 1. Course of serum creatinine concentration (semilogarithmic scale) before and after plasmapheresis. Interrupted lines represent cases with recurrence of AVR and subsequent second or third course of plasmapheresis therapy.
by Zollinger and Mihatsch [1]. Figure 2 shows a typical example with nearly complete occlusion of the lumen of a small artery.

In all cases renal function improved following PF (Figure 1). At the end of PF treatment, two weeks later, serum creatinine had dropped to $2.4 \pm 1.0 \text{mg/dl}$. During the next two and a half months, mean serum creatinine concentration remained unchanged or declined further in most patients. Three of these needed a second PF treatment during this period due to histologically confirmed recurrence of AVR, and in one other patient a total of three series of PF were carried out. In one patient renal function gradually deteriorated following the end of PF. In this case graft nephrectomy was performed four months later, histology revealed chronic vascular rejection. Nine patients are still under observation with stable renal function six months after start of PF, and eight patients have been followed up for 12 months or more after PF (Figure 1).

A control transplant biopsy was performed in four patients three to six months after AVR, when a stabilised creatinine concentration and a normal urinalysis suggested tolerance of the graft. In all four cases the biopsy specimen showed largely normal kidney tissue with no signs of ongoing rejection. Focal scarring, however, indicated that some nephrons, presumably in the areas of
formerly completely occluded arteries, had succumbed to irreversible necrosis.

PF treatment was well tolerated in all instances. Due to the relatively high albumin concentration (3.5g/dl) in the substitution fluid plasma albumin concentration did not change significantly during PF (Table I). Immunoglobulins were removed quite effectively by PF. Since 20g IgG was substituted after each treatment, the concentration of IgG before the next treatment was not significantly different from pretreatment values. IgA, IgM and C₃, which were not substituted, fell markedly during the first treatment and were still significantly reduced at the start of the sixth treatment (Table I).

TABLE I. Values of various plasma proteins, leucocytes and platelets before and after first and sixth plasmapheresis (means ± SD, n = 14)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First plasmapheresis</th>
<th>Sixth plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>IgG (mg/dl)</td>
<td>796.6±150.2 **</td>
<td>296.6±91.7</td>
</tr>
<tr>
<td>IgA* (mg/dl)</td>
<td>136.3±55.4 **</td>
<td>63.8±37.6</td>
</tr>
<tr>
<td>IgM* (mg/dl)</td>
<td>104.3±48.1 **</td>
<td>42.4±25.3</td>
</tr>
<tr>
<td>C₃* (mg/dl)</td>
<td>69.6±15.9 **</td>
<td>31.7±12.0</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.81±0.6 †</td>
<td>3.7±0.9</td>
</tr>
<tr>
<td>Fibrinogen* (mg/dl)</td>
<td>264.3±96.7 **</td>
<td>139.6±72.3</td>
</tr>
<tr>
<td>Leucocyte count (x10⁹/L)</td>
<td>7.9±0.3 †</td>
<td>8.6±0.3</td>
</tr>
<tr>
<td>Platelet count (x10⁹/L)</td>
<td>320±196 †</td>
<td>309±178</td>
</tr>
</tbody>
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* p<0.001, when values before first and before sixth plasmapheresis are compared (paired t-test)

** p<0.001, when pre- and post values are compared (paired t-test)

† NS

Fibrinogen also was removed by PF (Table I). When specific staining is performed in AVR, fibrinogen is the prominent protein found in the vascular lesions of the graft. Therefore a lowered plasma fibrinogen concentration may improve the prognosis of AVR. On the other hand no clinical bleeding tendency was observed during or after PF, and in only one patient a potentially dangerous plasma fibrinogen concentration of less than 50mg/dl was seen.

Elimination of cellular elements was not responsible for the observed improvement of kidney function by PF, as whole blood leucocytes and platelets did not change significantly during PF (Table I).

Discussion

PF proved to be a safe and effective mode of treatment in cases of AVR. The mechanism of its action in this clinical situation is not entirely clear. Plasmapheresis has the potential of depressing the humoral as well as the cellular mechanisms of rejection: one by removal of antibodies, the other by depletion of serum factors required for cellular cytotoxicity.
The group we treated consisted of patients who, in our experience rarely recovered significant renal function following rejection. The vast majority of grafts with the established diagnosis of AVR will be rejected irreversibly within three months [12,13] if plasma exchange therapy is not performed. In all our 14 patients treated with PF an initial improvement of transplant function was achieved, and only one graft was finally lost due to irreversible vascular rejection.

PF as treatment of AVR has substantially improved the overall results of renal transplantation in our hospital. In the 49 patients who received their first cadaveric transplant after the introduction of PF, cumulative one year graft survival has increased to 88.5 per cent.

In the literature, however, not only positive results are reported. Two controlled trials studying plasmapheresis in the treatment of renal allograft rejection failed to improve the prognosis [14,15]. From a theoretical point of view, plasmapheresis has not only potentially positive effects on the graft. Antibodies with a beneficial effect on graft survival, such as cold reacting cytotoxins [16] could be eliminated and antibody-dependent, cell mediated cytotoxicity, as described in melanoma patients, could be induced by plasmapheresis [17]. The abrupt decrease of immunoglobulins achieved by plasma exchange might induce, as a rebound phenomenon, the increased production of antibodies, among them those capable of attacking the graft.

Due to the fact that we substituted 20g immunoglobulins (Intraglobin®) i.v. immediately after PF, increased production of potentially harmful antibodies might have been suppressed. At least in cancer patients an increased production of immunoglobulins after plasmapheresis has been prevented by administration of large doses of immunoglobulins after plasma exchange [18].

The combination of plasma exchange therapy with effective elimination of humoral factors involved in AVR and subsequent substitution of large amounts of immunoglobulins, thereby possibly blocking the new production of graft-threatening antibodies, may be of importance in the explanation of the excellent results achieved in our series. We did not encounter any problems with infection in our patients after PF, which again suggests the importance of immunoglobulin substitution.

References

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Open Discussion

SIEBERTH (Chairman) Other authors have shown that approximately 50 per cent respond to plasmapheresis. They have not performed biopsy and have not made a selection like you. Many groups obtain a fine needle biopsy or cytological examination from the urine. I think we need a biopsy to make the correct decision. Can you comment on this point?

FASSBINDER You certainly need a conventional biopsy to be sure of the diagnosis. You have to have an intact small vessel within the histological specimen. In some instances we have even taken a second biopsy if no vessel had been seen in the first.

GABRIEL (London) Might I ask you please for the precise timing and duration of the administration of the intravenous methylprednisolone and the duration between that and when you commenced plasma separation? Not all kidneys reverse acute rejection in the 36 to 48 hours over which intravenous prednisolone is given, and this is critical to the reversal of graft rejection.

FASSBINDER Methylprednisolone was given for three to four days in the average case. Never longer than five days and never shorter than two days. We started plasma separation on the day after biopsy. There is a 24 to 36 hour interval between the histological diagnosis and the start of treatment. Treatment has to be rapid — I think that is an important point.

GABRIEL So plasma separation was started two days after the end of methylprednisolone treatment?

FASSBINDER Yes.

McGEOWN (Belfast) Since the Spring of 1980 we have been treating patients who have had acute vascular rejection by the same method of membrane plasma exchange. All rejections have been proven by biopsy and all have received at least one course of oral prednisolone and failed, and most have had two courses. We have treated 17 patients by this protocol of which nine still have surviving
grafts. Our criteria for using it are somewhat tougher than yours and so we in fact have lost more grafts. I suspect there is something in it when you say that it is essential to treat early, because we have noted that when extensive damage, such as micro-infarcts, is already present in the biopsy then the chance of getting a good functioning graft is considerably reduced. We feel that plasma exchange is valuable for patients whose grafts might otherwise well be lost from vascular rejection. Now there have been other studies in the literature, though not so large and not so well controlled by percutaneous biopsy. Most of those have used the other method of plasma exchange, the haemonectics method, and it may well be that plasma exchange by membrane does something different and therefore has more effect on the rejection process.

FASSBINDER That may be one of the reasons. In your cases with a creatinine less than six the success rate was nearly as high as in our series. Only in those patients who had a higher creatinine, indicating loss of kidney function, possibly by infarction, was therapy too late.

McGEOWN I think that is true, but even a patient whose serum creatinine was as high as 800μmol/L has surviving graft function since January 1981 with a current serum creatinine of about 500μmol/L.