REVERSAL OF REJECTION AND SUBSIDENCE OF IMMUNOGLOBULINURIA BY INTENSIVE PLASMAPHERESIS

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Most transplant centres monitor acute rejection by standard clinical and laboratory parameters. To date, there has not been a consistently helpful laboratory test to confirm the diagnosis of rejection and to determine graft prognosis. We have previously shown [1] a high correlation between the degree and persistence of immunoglobulinuria and the reversibility of acute rejection in renal allograft recipients. Previous investigators have suggested some correlation with the excretion of fibrin split products [2], histuria [3] and increased levels of alpha-2 microglobulin [4]. Immunoglobulinuria has been previously identified during rejection crisis [5], but its quantitation has not been used to monitor the fate of the rejecting graft. Our previous studies were hampered by a delay of 72 hours in quantitating immunoglobulin levels by immunodiffusion techniques, but the use of a new, rapid one hour method using a Hyland PDQ Nephelometer confirmed our previous findings in a clinically acceptable time period.

The most widely practiced therapeutic anti-rejection regimen involves the use of corticosteroids. Various treatment protocols, oral and parenteral, have been described [6–8]. An infrequently used modality that may be useful as part of anti-rejection therapy is plasmapheresis or intermittent plasma exchange (IPE). Recent work [9, 10] suggests that this modality may alter the humoral antibody load attacking the allograft. To test this hypothesis, we treated two patients with clinically inexorable rejection with IPE, after all other modalities had failed. In both instances, there was a response to IPE with stabilisation of function. Additional evidence of stabilisation was the prompt fall in urinary immunoglobulin levels with the institution of IPE.

Case histories

Two cadaveric recipients were studied and treated. The first recipient of a cadaveric graft was a juvenile diabetic, 28 years old. A severe crisis evolved at approximately three weeks post-transplant with apparent reversal of the rejection with large doses of Prednisone. However, this therapy resulted in the development of
a serious catabolic state, including lean muscle loss, weakness, diabetic instability, and a serious threat to the life and well-being of the recipient. Four weeks later, a second severe rejection episode occurred. We thought it was clinically unwise to institute a second course of Prednisone, and IPE was started following the reinstitution of dialysis. With the introduction of IPE, renal function improved, urinary immunoglobulins plummeted, and the patient remained off dialysis for three and a half months, at which time another rejection episode resulted in graft loss (Figure 1).

Figure 1. Reversible rejection in plasmapheresis-treated patient. The fall in immunoglobulins as illustrated by IgG occurred with the institution of plasmapheresis, and with the start of clinical improvement
Figure 2. Irreversible rejection (Group III) with increasing spillage of immunoglobulins
The second patient was a 24 year old cadaveric graft recipient. The graft functioned well for approximately five weeks when he was re-admitted to the hospital with a severe rejection episode, accompanied by massive immunoglobulinuria, graft tenderness, fever, and oliguria. A renal biopsy confirmed the presence of acute rejection. A randomisation study placed him in the non-ATG treated control group, and oral Prednisone anti-rejection dosages were begun. There was no clinical improvement, and dialysis had to be reinstated. IPE was added, followed by an improvement in his condition with an increase in urine output, stabilisation of his blood urea nitrogen and serum creatinine, and a rapid fall in urine immunoglobulins. Dialysis was stopped. This stabilisation lasted approximately three months when another rejection episode resulted in the loss of the graft.

Discussion

The finding of immunoglobulinuria helps to confirm the diagnosis of acute rejection. It is a fairly constant phenomenon, and is noted in over 90% of our cases undergoing an acute crisis. Its level and persistence following the institution of anti-rejection therapy suggests a poor prognosis (Figure 2). Conversely, a lower or absent level following grafting, suggests continued graft viability, and is seen in the best of cadaveric grafts, and in the majority of living related grafts.

IPE is an infrequently described method of altering a rejection response. While we utilised it in desperation to restore graft function, others [9] have suggested its use as part of routine anti-rejection therapy. Its mechanism of action is not understood. Our studies suggest that an absolute lowering of humoral antibody levels may play a part as reflected in the fall in urine immunoglobulins, but the role of leucopheresis [11] as a concomitant phenomenon should not be discounted. Our present concept suggests that with rejection more immunoglobulins flood the graft along with an increase in glomerular membrane permeability to those proteins. With the reversal of rejection, healing occurs, and less immunoglobulin leakage is noted.

Though the grafted kidneys were eventually lost to rejection, the results were interesting enough to warrant further therapeutic testing which may include IPE as a prophylactic form of anti-rejection therapy.

Conclusion

IPE has been shown occasionally to salvage a kidney graft which would otherwise be rejected. In our experience, this treatment can be effective in temporarily reversing an inexorable rejection. There is also chemical evidence of improvement with special reference to the spillage of immunoglobulins in the urine.

References

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