Brief report

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Reversal of acute glomerular renal allograft rejection: a possible effect of OKT3

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Abstract. A major cause of renal allograft loss is glomerulovascular rejection. This case report is about an episode of histologically proven acute glomerular rejection that was successfully reversed. Monoclonal antibody OKT3 may have been the effective agent.

Key words: Rejection, reversal, kidney, OKT3 – OKT3, reversal of rejection – Acute glomerular rejection, OKT3

Glomerulopathy in acute renal allograft rejection is frequently associated with graft loss [1, 7]. It is also frequently accompanied by features of vascular rejection. Recently, claims have been made that monoclonal antibody OKT3 is effective in treating acute vascular rejection in renal transplantation [2]. In this report we describe a renal allograft recipient in whom OKT3 may have reversed an episode of glomerular rejection.

Materials and methods

After ultrasonic definition of the transplant, biopsies were done by a closed technique using a trucut needle (Travenol, Deerfield, Ill., USA). One μ sections were cut from paraffin blocks and stained with haematoxylin and eosin, French-Masson, periodic acid-Schiff, chromotrope aniline blue, silver methanamine and acid fuchsin orange green. Peripheral blood T cells were counted on a Spectrum III Flow Cytometer (Ortho Diagnostic Systems, Raritan, N.J., USA) by detecting the CD3 antigen with monoclonal antibody OKT3 (Ortho Pharmaceutical, Raritan, N.J., USA).

Case report

The case record is summarised in Fig. 1. In brief, a 43-year-old, non-sensitised, white male with biopsy-proven focal glomerular sclerosis received his first cadaveric renal transplant from a non-heart-beating donor (warm ischaemia time 25 min). The operative transplant biopsy showed 0–4 polymorphs in each glomerulus (20 examined), degenerate and vacuolated tubular epithelial cells and protein casts in tubules. The immunosuppressive treatment consisted of cyclosporin A (CyA; 4 mg/kg IV) and methylprednisolone (MP; 500 mg IV) preoperatively and CyA (12.5 mg/kg) and prednisolone (P; 0.3 mg/kg per day) postoperatively. For the first 13 days post-transplantation, the patient had oliguric acute renal failure due to acute tubular necrosis. On the 8th and 19th postoperative days, he developed histologically proven acute cellular rejection. Both episodes responded to treatment with MP (500 mg IV daily for 3 days).

Then, on the 32nd postoperative day, he developed a third episode of acute rejection that was cellular in type (14 glomeruli examined). His immunosuppressive treatment was then CyA (7.5 mg/kg per day), azathioprine (Aza; 1.5 mg/kg per day) and P (0.3 mg/kg per day). Because the rejection was not controlled by MP (500 mg IV daily for 3 days), antithymocyte globulin (ATG; Fresenius, Munich, FRG) was then given for 6 days (postoperative days 34–39) at doses of 100–400 mg/day. Each daily peripheral blood T-cell count (flow cytometric measurement of CD3 positive cells) was less than 200 cells/mm^3. CyA was stopped on the 34th postoperative day. The patient's serum creatinine (SC) fell from 0.38 mmol/l (34th postoperative day) to 0.29 mmol/l (38th postoperative day). But on the 40th postoperative day he became acutely ill: he was febrile (38.6 °C), oliguric (270 ml/day) and his SCr rose to 0.43 mmol/l (Fig. 1). The biopsy that day showed glomerular and cellular rejection (9 glomeruli examined; Fig. 2). The glomeruli showed mesangial prominence with mild focal mesangial cell proliferation. Glomerular capillary loop hyaline thrombi were present in one glomerulus and one medium-sized artery had endothelial cell proliferation with narrowing of the arterial lumen. In the interstitium there were oedema, haemorrhage and an infiltrate of mononuclear cells. Unfortunately, tissue for immunofluorescence was not available. Three cytomegalovirus (CMV) IgM titres between postoperative days 34 and 40 were negative. Cultures of saliva, blood and urine for CMV on the 34th postoperative day were also negative. The CMV IgG titres done preoperatively and on the 40th postoperative day remained constant (1/8). Hence, the patient was considered to have acute combined glomerular and cellular rejection. He was treated with OKT3 (5 mg IV) with covering MP (80 mg IV) daily for 10 days. In addition, he received Aza (0.7 mg/kg per day) and P (0.3 mg/kg per day). His SCr rose to 0.90 mmol/l (45th postoperative day) and then dropped to 0.27 mmol/l (60th postoperative day). On the 49th postoperative day, CyA was restarted (8.5 mg/kg per day). The patient developed two further episodes of histologically proven acute cellular rejection on the 65th and 113th postoperative days. These responded to OKT3 and ATG, respectively. A final biopsy (Fig. 3) done on the 115th postoperative day showed interstitial fibrosis that warranted conversion from CyA to Aza (2.5 mg/kg) while maintaining P (0.3 mg/kg). For 4 years after transplantation he was clinically

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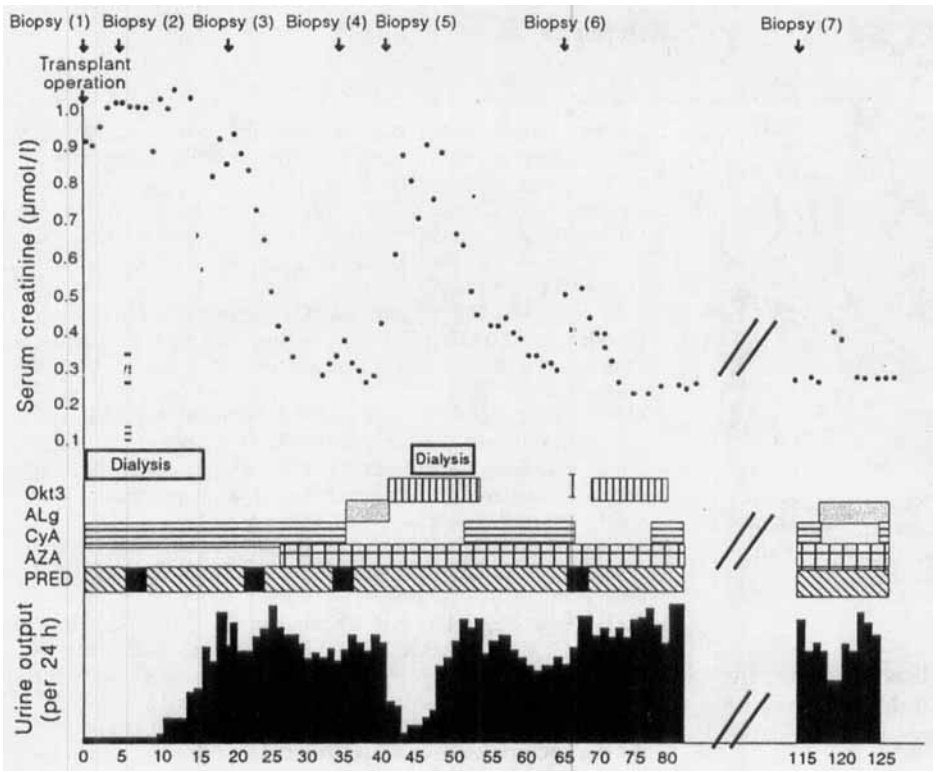

Fig. 1. Renal allograft function in relation to treatment for the first 125 days of engraftment. ■ A course of high-dose methylprednisolone (500 mg IV daily for 3 days)

stable with normal blood pressure, negative urinalysis and SCr ranging from 0.16 to 0.20 mmol/l.

Discussion

This case report illustrates that during engraftment glomerular rejection developed that seemed refractory to ATG but sensitive to OKT3. It is possible, however, that the glomerulopathy was related to CyA [4, 5]. Yet, this seems unlikely because CyA had been ceased for 6 days before the glomerulopathy appeared and, second, no other changes of CyA toxicity were present, particularly the arteriopathy. Although it is possible that the glomerulopathy was due to CMV [6], this seems unlikely because repeated IgG, IgM assays and viral cultures failed to confirm CMV infection. It is impossible to be sure that OKT3 reversed the glomerular component of this rejection episode because many other immunosuppressive drugs were used during engraftment. It is plausible, however, that it did because glomerular rejection is mediated by T cells, at least in part [3].

Two groups have reported that OKT3 is effective in reversing an allied lesion – the vascular component of acute rejection [2, 8]. In the first study, Delaney et al. found that steroid-resistant, predominately vascular rejection responded to OKT3 monoclonal antibody therapy histologically in 2/3 and functionally in 3/3 patients. In the second study, Zlabinger et al. [8] found that 24/40 episodes of severe interstitial rejection or acute vascular rejection were reversed by OKT3 monoclonal antibody therapy. Thus, a controlled study to examine the ability of OKT3 to reverse predominate glomerulovascular rejection is now needed in clinical renal transplantation.

Glomerulovascular rejection is probably mediated by both T cells and antibodies directed against class I antigens of the major histocompatibility complex (MHC). This antibody production is dependent upon T–B interaction after T cells have recognised class I MHC antigens on the transplant. The reversal of glomerulovascular rejection by OKT3 may be due to its ability to produce a rapid and almost complete T-cell depletion. Thus, the rejecting transplant is almost completely depleted of T cells and al-

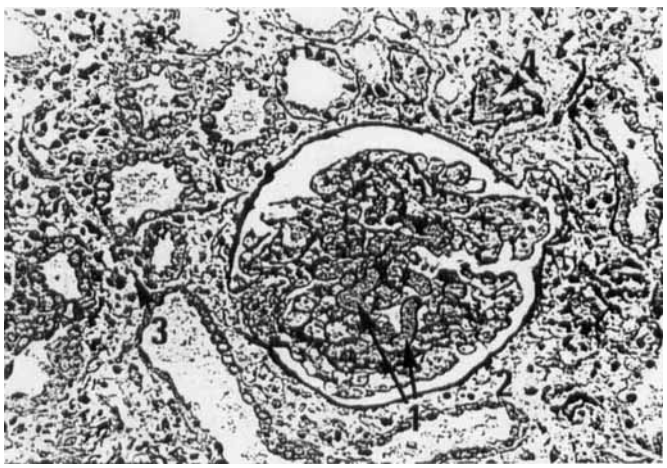

Fig. 2. Glomerulus with capillary loop hyaline thrombi *(1)* and polymorphonuclear cells (biopsy 5, 40th postoperative day). The surrounding interstitium is oedematous *(2)* and contains a mononuclear infiltrate *(3)* with foci of haemorrhage. Patchy tubular atrophy is also present *(4)*. These changes are consistent with mixed interstitial and glomerular rejection. (Nine glomeruli examined; silver methanamine and French-Masson's stain, x 250)

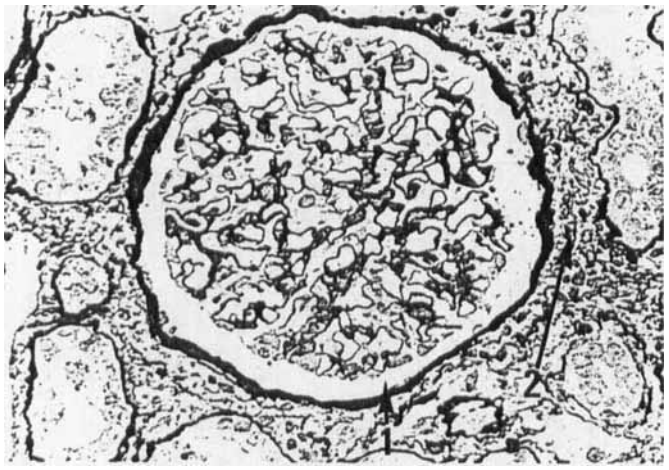

Fig. 3. Normal glomerulus *(1)* (biopsy 7, 115th postoperative day). The surrounding interstitium shows mild fibrosis *(2)* with minor, persisting mononuclear infiltrate *(3)*. (12 glomeruli examined; silver methanamine and French-Masson's stain, x 400)

loantibody production is stopped, at least temporarily. Other anti-T-cell reagents, e.g. ATG and CyA, may be less effective in this regard because they produce partial T depletion or paralysis.

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