Clinical Observation

Severe vital depression as the presenting feature of cyclosporin-A-associated thrombotic microangiopathy

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Introduction

Thrombotic microangiopathy (TMA) is a known complication associated with cyclosporin A (CsA) therapy after renal transplantation, even in patients who do not have haemolytic uraemic syndrome (HUS) as their original renal disease [1]. Manifestations caused by the endothelial swelling and microvascular thrombi include renal failure and neurological symptoms such as headache, confusion, seizures and coma [2,3].

Psychiatric manifestations in the form of severe vital depression have not been reported until now. We describe two patients with CsA-associated TMA several weeks after transplantation in whom the clinical picture was dominated by a severe vital depression without other neurological findings as the sole sign of possible cerebral localization.

Case 1

A 54-year-old woman with renal failure caused by chronic pyelonephritis and treated with CAPD since May 1994 underwent a cadaveric kidney transplantation in December 1996. Immunosuppression consisted of CsA (Neoral®, Novartis), mycophenolate mofetil and low-dose prednisolone. Renal graft function was good initially, but a biopsy-proven interstitial rejection Banff grade I was diagnosed on day 20. After failure to respond to 6 × 1 g i.v. methylprednisolone, treatment with rabbit antithymocyte immunoglobulin with temporary discontinuation of CsA according to our local protocol was instituted. Graft function improved to baseline-level and the patient was discharged in good clinical condition with a creatinine clearance of 50 ml/min.

Two months later she was readmitted with bronchitis and sinusitis with fever up to 39°C. The serum creatinine level had risen from 130 to 265 μmol/l. The maxillary sinuses were drained and therapy with amoxycillin/clavulanic acid was instituted. Sputum and sinus-fluid cultures were positive for Haemophilus influenzae. Renal ultrasound showed no abnormalities. A renal biopsy showed no other abnormalities.

Case 2

A 63-year-old woman received a cadaveric kidney transplant in February 1997. Renal failure from medullary polycystic disease and hypertension had led to the initiation of CAPD treatment in November 1994, which was changed to haemodialysis in May 1996. Immunosuppression consisted of CsA (Neoral®, Novartis) and low-dose prednisolone. Delayed graft function necessitating haemodialysis treatment occurred. While still oliguric a Banff grade I interstitial rejection was diagnosed by renal biopsy on the 10th post-operative day. Since there was no response to
Fig. 1. Case 1. Serum creatinine level (left axis), platelet count (left axis), lactate dehydrogenase serum level (right axis), and haemoglobin level (lower part) in time following renal transplantation. Box at the top of the graph depicts oral cyclosporin treatment, stopped at day 112 post-transplant when thrombotic microangiopathy is suspected.

6 × 1 g of i.v. methylprednisolone, treatment with rabbit antithymocyte immunoglobulin was instituted. According to our local protocol CsA therapy was discontinued during antithymocyte immunoglobulin treatment. Renal function improved, but recovery was unsatisfactory with a serum creatinine of 300 μmol/l. One week after restarting CsA, the patient developed a vital depression with lethargy, anorexia and sleeplessness. Cyclosporin A serum trough levels were in the therapeutic range (80 × 109/l) developed and LDH was slightly elevated at 600 U/l, but renal function improved to a serum creatinine of 200 μmol/l. During treatment with ganciclovir, thrombocytopenia (150–200 × 109/l). No focal neurological abnormalities were found. Laboratory investigation showed progressive anaemia with a drop in haemoglobin level from 7.4 to 5.0 mmol/l, a further decline in platelet count unexplained.

Fig. 2. Case 2. Serum creatinine level (left axis), platelet count (left axis), lactate dehydrogenase serum level (right axis), and haemoglobin level (lower part) in time following renal transplantation. Boxes at the top of the graph depict intravenous ganciclovir and oral cyclosporin treatment. Cyclosporin is stopped at day 59 post-transplant when thrombotic microangiopathy is suspected.
(30 \times 10^9/l), rising LDH level up to 1142 U/l, a low haptoglobin level (<0.1 g/l), and normal coagulation tests. In addition, a second renal biopsy showed signs of microvascular thrombosis and glomerular mesangiosis 
besides a borderline interstitial rejection according to the Banff classification. A diagnosis of TMA was made and CsA therapy was discontinued. Rapid and impressive improvement of the depressive symptoms occurred. Moreover, significant improvement of renal function (serum creatinine 95 µmol/l), accompanied by normalization of other laboratory parameters including the platelet count and haptoglobin level was seen. Immunosuppression was continued with mycophenolate mofetil and prednisolone without recurrence of TMA or depression.

**Discussion**

TMA is a known complication associated with CsA therapy. It was first reported in patients after allogeneic bone marrow transplantation [4] and has been described in renal allograft recipients [1] and patients with use of cyclosporin unrelated to transplantation [5]. Patients with HUS as primary renal disease are especially at risk of developing post-transplant TMA [6]. However, even in renal transplant recipients who do not have HUS as their original disease, de novo TMA occurs [1,7]. Up to 4% of patients receiving a cadaveric renal graft are reported to have laboratory and histological signs of TMA with a substantial risk of death and graft loss [7–10]. The role of CsA in the development of recurrent or de novo TMA post-transplantation is currently unclear. Other factors such as vascular rejection [11], infections such as CMV [7], and the HLA sensitization status of the recipient [10] seem to be associated with an increased risk for TMA. Moreover, TMA may resolve without interrupting cyclosporin treatment [8], or cyclosporin therapy may be resumed after remission of TMA without recurrence [9].

Clinically, CsA-associated TMA often leads to hypertension and renal function impairment. Neurological signs and seizures have been described. However, to our knowledge, severe vital depression without focal neurological signs as the predominant cerebral manifestation of CsA-associated TMA has not been previously described. In both our cases a diagnosis of TMA was made during follow up when graft dysfunction was thought to be caused by rejection, but did not respond to treatment. Although CsA trough levels were in the therapeutic range it was stopped in both cases with impressive improvement of both the mental picture as well as graft function, while microangiopathic changes disappeared. In the first case renal graft biopsy did not show microvascular thrombi or endothelial swelling, not even in retrospect. In the second case a second renal graft biopsy showed histological confirmation of TMA. In both patients other factors than CsA may have contributed to the development of TMA. Rejection episodes had occurred prior to the development of TMA. Furthermore, a period of infection with H. influenzae (first patient) and CMV (second patient) was present shortly before TMA became clinically evident. In line with the idea that post-transplant cyclosporin-A-related TMA is of multifactorial origin is the finding by Noël et al. [12] that as many as 25% of renal transplant patients treated with CsA on close laboratory monitoring show signs of microangiopathic haemolytic anaemia, mostly without clinical signs, especially following a CMV infection or rejection episode.

The most striking finding in our two patients was the occurrence of severe vital depression without focal neurological signs as the main symptom of their TMA. Both patients showed impressive improvement of their mental state coinciding with the remission of the microangiopathic haemolytic changes. Therefore isolated mental changes occurring during CsA therapy should lead to consideration of TMA as a possible cause and to appropriate laboratory investigations to detect or exclude this possibility.

**References**


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