Case Report

Uneventful re-treatment with cyclosporin in two cases of cyclosporin-induced haemolytic uraemic syndrome

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Introduction

Cyclosporin A (CyA)-induced haemolytic uraemic syndrome (HUS) has been clearly documented in many post-renal transplantation cases [1–3]. It remains a serious complication of CyA therapy. The exact mechanism of induction of HUS by CyA, although still unexplained, involves endothelial cell toxicity by CyA, which seems to be dose dependent [4]. In accordance with this hypothesis, clinical management of CyA-induced HUS generally starts with discontinuation of CyA or reduction of its dose [1,5]. However, in all cases where CyA was discontinued, restarting CyA therapy is mentioned only exceptionally.

We report herein two cases of CyA-induced HUS, successfully managed by withdrawal of CyA, intravenous immunoglobulin in one case and plasmapheresis in the second case. Reintroduction of CyA after recovery from HUS was uneventful.

Cases

Case no. 1

A 48-year-old woman who suffered from chronic pyelonephritis underwent a 1-haplotype living renal transplantation from her son on October 10, 1992, before starting any form of renal replacement therapy. Intraoperatively, the patient received 4 mg/kg intravenous (i.v.) CyA and 250 mg i.v. methylprednisolone. The graft functioned immediately and her serum creatinine dropped from 656 μmol/l to 73 μmol/l on post-operative day 2 (D2). Post-operatively (PO), the immunosuppressive regimen included anti-thymocyte globulin and prednisolone. Oral CyA introduced on day 2 was discontinued the same day, as laboratory studies revealed a Coombs-negative microangiopathic haemolytic anaemia (MAHA) with thrombopenia: haemoglobin decreased to 6.8 from 8.5 g/dl (D1), lactate dehydrogenase (LDH) increased to 987 from 140 IU/l (D1), very low haptoglobin (0.02), presence of schizocytes, total bilirubin increased to 83 μmol/l, platelet count decreased to 50 000 from 168 000/l (D1).

There was no clinical or serological evidence of infection, and blood and urine cultures were negative. There was no evidence of disseminated intravascular coagulopathy (DIC). Antibody titres for cytomegalovirus (CMV), herpes simplex and herpes zoster did not show any increase.

From D3 to D8, the patient received i.v. immunoglobulin infusion at a rate of 0.4 g/kg/day along with 5 units of fresh frozen plasma per day. On day 5, the platelet count decreased further to 11 000 and creatinine increased to 202 μmol/l. On day 10, the patient recovered almost completely from HUS (platelet count 115 000, haemoglobin 9.2, creatinine 112 μmol/l). CyA was reintroduced on day 20 with no similar event.

Case no. 2

A 47-year-old man who suffered from chronic pyelonephritis underwent a 1-haplotype living related renal transplantation from his brother, on March 24, 1994. Intraoperatively, the patient received 4 mg/kg intravenous (i.v.) CyA and 250 mg i.v. methylprednisolone.

The graft functioned immediately and serum creatinine decreased from 1321 μmol/l to 697 μmol/l on post-operative D2. Post-operatively (PO), the immunosuppressive regimen included anti-thymocyte globulin and prednisolone. Oral CyA, introduced on D2, was discontinued the same day, as laboratory studies revealed a Coombs-negative MAHA with thrombopenia: haemoglobin decreased to 6.2 from 7.4 (D1), LDH increased to 709 from 201 (D1), haptoglobin was almost undetectable (0.02), presence of schizocytes, platelet count decreased to 93 000 from 218 000 (D1).

There was no clinical or serological evidence of infection, and blood and urine cultures were negative. There was no evidence of DIC. Antibody titres for
CMV, herpes simplex and herpes zoster did not show any increase.

On day 3, the situation worsened, with a platelet count of 51000, LDH 1010. At this time, the patient was started on i.v. immunoglobulin for five consecutive days at a rate of 0.4 g/kg/day.

On day 8, as no improvement occurred (platelet count 47000, haptoglobin 0.02, persistent presence of schizocytes, decreased urine output and increase of creatinine to 431 from 325 on day 3), six plasma exchange sessions on six consecutive days were undertaken along with three haemodialysis sessions. The response was excellent, with disappearance of HUS and normalization of renal function. CyA was reintroduced on day 20 with no similar event.

Discussion

Our two patients fulfilled the criteria for HUS as first described by Gasser et al., including Coombs-negative microangiopathic anaemia, thrombocytopenia and renal failure [6]. CyA could be incriminated in inducing HUS on the basis of early onset of HUS in the post-transplantation period [3,7] and absence of other known triggering factors of the disease [8]. The patients did not have a history of diarrhoea. Studies to exclude infection with enterohaemorrhagic Escherichia coli were not performed.

Early diagnosis and treatment are essential for graft survival. For many nephrologists, CyA-induced HUS is more prevalent than previously recognized [3,9,10]. Its incidence is, in fact, underestimated by diagnostic criteria, requiring in some centres histological and biological findings [9,10], and by difficulties in differentiating HUS from acute vascular rejection [11].

In our cases, the usefulness of monitoring haptoglobin in early detection of haemolysis is confirmed [9]. It would be of great help as well in conditions where biological findings are absent or delayed (thrombocytopenia, MAHA, elevated LDH) [9,10].

Management of the condition has also focused on reduction of CyA dose or its discontinuation [5]. Although Hochstetler et al. could manage some patients with continued CyA therapy at the same dose [3], other reports show that only withdrawal of CyA could allow reversal of the microangiopathic process [1,10,12]. In the absence of a consensus on the position to adopt toward CyA in this context, we believe that discontinuation of CyA remains the safest way, along with active intervention on HUS with plasmapheresis or i.v. immunoglobulin.

Reintroduction of CyA in our two patients was eventful. It was done after recovery from HUS and normalization of renal function. This aspect of rechallenge with CyA is rarely reported. In the few papers available, rechallenge with CyA has been successful in one patient in remission from HUS with serum creatinine 2 mg/dl [10] but not in another patient whose haemolysis process was not over [1]. A recent work confirmed the high success rate of rechallenge with CyA once thrombotic microangiography was in remission [13]. It is therefore not mandatory to convert to another immunosuppressive therapy, particularly when the condition could be managed in some patients elsewhere with CyA maintained at the same or lower dose [3,9].

In conclusion, early diagnosis seems very useful in the management of CyA-induced HUS along with discontinuation of CyA. Rechallenge with CyA once the haemolytic process is over and renal function back to normal appears to be feasible and safe.

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References