HIPPOKRATIA 2005, 9, 3: 138-140

CASE REPORT

Mycophenolate mofetil late gastrointestinal toxicity causing chronic diarrhea after renal transplantation

Vergoulas G[1], Avdelidou A[1] , Ioannou K[1] , Eleftheriadis Th[1] , Miserlis Gr[1] , Solonaki F, Nikolaidis N[2] , Giouleme O[2] , Leontsini M[3] , Papagiannis A[1] , Takoudas D[1]

[1] OrganTransplant Unit, Hippokratio General Hospital, Aristotelian University of Thessaloniki, Thessaloniki, Greece
[2] 2nd Propedeutic Clinic of Internal Medicine, Hippokratio General Hospital, Aristotelian University of Thessaloniki, Thessaloniki, Geece
[3] Pathology Department, Hippokratio General Hospital, Thessaloniki, Greece

The gastrointestinal (GI) complications in renal transplant recipients can be categorized into four general types: ulcers, esophagitis/gastritis/pancreatitis, diarrhea and intestinal perforation. Diarrhea is one of the most common gastrointestinal system complications after transplantation. Although diarrhea is considered minor complication compared to others, like colonic necrosis or perforation, might lead to discontinuation of immunosuppression. After the great improvement that has been accomplished in short and long - term patient and renal graft survival, the attention has been focused on other parameters one of which is quality of life. Chronic intractable diarrhea is a side - effect that can result in weight loss, activity deterioration, patient non – compliance and seriously compromised quality of life. Diarrhea may be due to infection, toxic effect of immunosuppressive agents or a combination[1]. We describe two patients with chronic intractable diarrhea due to late mycophenolate mofetil toxicity. *Hippokratia 2005; 9 (3): 138-140*

Key words: *kidney transplantation, mychophenolate mofetil, toxicity, diarrhea*

Corresponding author: Vergoulas G, 53 Alkminis str, 542 49 Thessaloniki, Greece, Tel: +30 2310 302 311, E-mail: geover@otenet.gr

First case

A forty – year old man with a history of chronic glomerulonephritis (no biopsy), who was on chronic hemodialysis since 30.6.94, received a LRD transplant on 8.10.97. He received triple drug immunosuppression (methylprednisolone – Mdr, cyclosporine – CsA and Mycophenolate Mofetil – MMF) and he had a relatively uneventful posttransplant course without side-effects due to immunosuppression or major complications, except an acute rejection episode (grade I, Banff classification) during the immediate posttransplant period (14.10.97) which was treated with methylprednisolone pulses successfully. His serum creatinine on discharge was 2.0 mg/dl and he was taking MMF, CsA and Medrol in a dose 2.0 gr/d, 600 mg/d and 12 mg/d respectively. On 3.2.98 he was admitted to the Hospital because of a rising serum creatinine (3.1 mg/dl). The biopsy disclosed CsA toxicity and the CsA dose was reduced from 400 mg/d to 225 mg/d.

Four years and three months after transplantation, he was admitted to the Hospital because of diarrhea, nausea, vomiting, anorexia, weakness and loss of 3 kg body weight in a period of one month. At that time he was taking MMF 1.5 g/d, CsA 150 mg/d and Medrol 8 mg/d, serum creatinine levels were between 1.8 and 2.0 mg dl and WBC was 9100 (22.4% lymphocytes). Anti – diarrheic agents were not administered at that time. As the symptoms continued he underwent stool examination by light microscopy for inflammatory cells, repeated stool specimen cultures for salmonella, shigella and campylobacter species and parasitologic stool examination. All these examinations were negative. Stool examination for occult blood was negative as well. The ultrasonographic examination of the upper abdomen and the radiological examination (barium enema) of the large intestine did not show any pathology.

After a short period of remittance (six months) during which the patient gained body weight, the diarrheic syndrome relapsed. Although anti – diarrheic agents were administered (loperamide, nifuroxazid) the loose or liquid bowel movements (more than three episodes per day) continued. Endoscopic examinations of the stomach, the duodenum and the large intestine were performed. Upper gastrointestinal endoscopy did not show lesions causing diarrhea. The duodenum biopsy revealed malabsorption syndrome (grade III-IV, Figure 1) and the biopsy of the sigmoid had slight distortions of non specific enterocolitis (Figure 2). The stool microscopy for clostridium difficile and assay for clostridium difficile toxin were negative.

After a period of time of about 25 months with exacerbations and remittances of the diarrheic syndrome the patient had a total loss of body weight of about 12 kg. He also developed depression and he needed psychiatric help and medical treatment.

As all the laboratory and endoscopic examinations

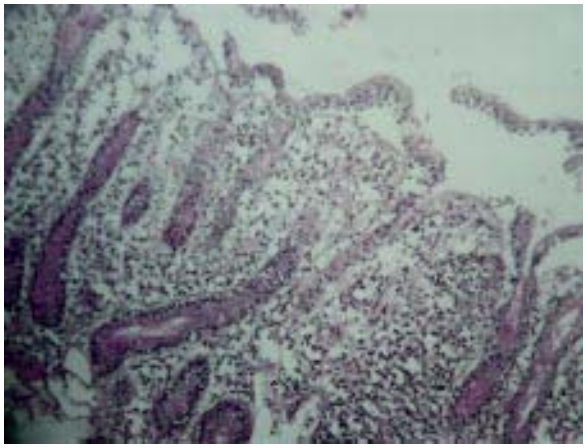

Figure 1. *Severe villus abnormality with the mucosal flattening, increase of intra epithelial lymphocytes and marked increase in cellularity in the lamina propria. A+E X 100*

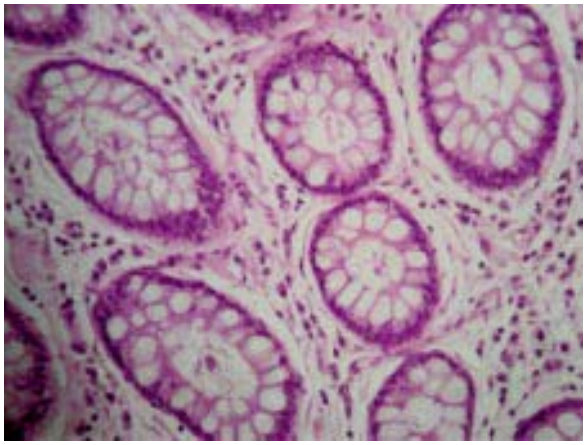

Figure 2. *Mild colitis with oedema and sparse inflammatory cells in the lamina propria without mucin depletion of the glands. A+E X 200*

did not reveal any obvious cause, we decided that, for some not identified reason and in spite the MMF low dose, there was late MMF toxicity and azathioprine in a dose of 100 mg/d was substituted for MMF. The change of immunosuppression was followed by immediate remission of diarrhea and the patient started gaining body weight. In a three month period he gained 9 kg body weight, his serum creatinine level remained stable (2.0 mg/dl), the WBC was 11.200 and his quality of life improved dramatically.

Second case

A thirty year old female with primary renal disease chronic glomerulonephritis (no biopsy), who was on continuous ambulatory peritoneal dialysis (CAPD) since 15.5.96 received a cadaveric kidney transplantation on 30.5.99. She received triple drug immunosuppression (Mdr, CsA and MMF) and she was discharged having serum creatinine 0.9 mg/dl and taking MMF 1.5 g/d, CsA 250 mg/d and medrol 12 mg/d.

During the first three posttransplant years, the patient had repeated episodes of urinary tract infection related to her sexual life and mild complications due to immunosuppression (gain of body weigh, hirsutism and gum hypertrophy).

On her first admission for a diarrheic syndrome (about 38 months after transplantation) there was fever, nausea, vomitus and abdominal pain. At that time she was taking MMF 1.5 g/dl, CsA 125 mg/d, Medrol 6 mg/d and her serum creatinine was 1.3 mg/dl. As the diarrhea relapsed many times, routine stool examinations for infectious agents and parasites were performed and the MMF dose was reduced to 1.0 g/d. Stool specimens examined for salmonella, shigella, campylobacter species parasites and ova were negative. Blood cultures taken to check for systemic infection were negative.

On 24.1.03 she was admitted to the hospital because of elevated levels of serum creatinine (2.8 mg/dl) and the renal biopsy revealed acute rejection which was treated with methylprednisolone pulses successfully. At that time tacrolimus at a dose of 2 mg/d was substituted for cyclosporine. The diarrheic syndrome continued and plain abdominal radiograph and ultrasound of the abdomen did not reveal pathological findings. Upper gastrointestinal endoscopy showed esophagitis (grade I). Staining for helicobacter pylori was negative. Colonoscopy was performed with mucosal biopsies. There were no ulcerations but there were findings of non-specific enterocolitis.

The patient mentioned frequent relapses of the diarrheic syndrome and a total loss of body weight of about 8 kg in a period of 18 months was recorded. During this time she was receiving anti – diarrheic agents (loperamide and nifuroxazid) without any result. Stool examination and biopsy findings for clostridium difficilae were +/- and she received metronidazol for fifteen days without result.

As no infectious or other cause was found it was thought that there was late MMF toxicity and azathioprine in a dose of 100 mg/d was substituted for MMF. Diarrhea stopped immediately. Serum creatinine level remained stable (1.7 mg/dl) and the patient gained 5 kg weight in a two month period (wbc: 6000 mm^3).

Discussion

Diarrhea is defined as three or more loose or liquid bowel movements per day and according to the World Health Organization diarrhea lasting >1 month is considered chronic. The two case reports meet these criteria. It is known that steroids, MMF, CsA, tacrolimus and serolimus can cause diarrhea which is usually manifested during the first posttransplant month, is dose dependent and appears with different frequency for each drug[2,5]. Late diarrheas are of infectious etiology and run longer in immnosuppressed patients. These two cases are characterized by a late onset diarrhea when the drug dose was low and a negative history of diarrhea during the first posttransplant period when the drug doses were much higher.

In transplant patients it is of great importance to distinguish between infectious and drug associated diarrheas. Four characteristics can help in making this distinction in favor of a diarrhea of drug toxicity: a) fever should not be present, b) absence of inflammatory cells in the stool specimen, c) absence of abnormalities in endoscopy or computed tomography, d) absence of peripheral leukocytosis. Although these characteristics are helpful in making a differential diagnosis not one of them is specific and there is considerable overlap[3,4].

The patients we describe had inconclusive symptoms and findings and were diagnosed as having drug associated diarrhea by the method of exclusion. All other causes of diarrhea were excluded with the help of serology, endoscopy, histology, ultra sound and radiology. Although diarrheas of such origin are not usually life-threatening, they affect seriously patients' quality of life. The recurrent admissions and the many laboratory examinations which have to be undertaken is the one parameter of this problem. On the other hand, the loss of body weight is an objective problem. The close follow up of these patients is mandatory to recognize and treat early acute rejection episodes as it was in the second case report.

The late MMF toxicity happened while the patients were taking low daily dose of this drug, 51 and 38 months after kidney transplantation respectively. We were not able to identify other late toxicity reports in the literature and the question remains to be answered, why these patients presented MMF toxicity in such a remote time point after transplantation. Possibly there are other unrecognized or elusive factors or metabolic abnormalities that can trigger MMF toxicity.

References

1. Altiparmak MR, Trablus S, Pamuk ON, et al. Diarrhea following renal transplantation. Clin Transplant 2002; 16:212-216
2. Pescovitz MD and Navarro MT. Immunosuppressive therapy and post - transplantation diarrhea. Clin Transplant 2001; 15(Suppl 4):23-28
3. Rubin RH. Gastrointestinal infectious disease complications following transplantation and their differentiation from immunosuppressant - induced gastrointestinal toxicities. Clin Transplant 2001; 15(Suppl 4):11-22
4. Maes BD, Dalle I, Geboes K, et al. Erosive enterocolitis in Mycophenolate Mofetil treated renal-transplant recipients with persistent afebrile diarrhea. Transplantation 2003; 75:665-672
5. Maes BD, Lemahieu W, Kuypers D, et al. Differential effect of diarrhea on FK506 versus cyclosporine A trough levels and resultant prevention of allograft rejection in renal transplant recipients. Am J Transplant 2002; 2:989-992