Development of ulcerative colitis under the immunosuppressive effect of cyclosporine

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Summary. In recent studies, cyclosporine has been used for the treatment of both ulcerative colitis and Crohn's disease. The results of these studies were variable. We report on a patient who was treated for 6 years with cyclosporine after kidney transplantation. He developed chronic distal colitis with all the features of ulcerative colitis. An infectious etiology of the colitis was carefully excluded. High-dose treatment with methylprednisolone was required to induce remission. This report shows that immunosuppressive therapy with cyclosporine did not prevent the development of ulcerative colitis in this patient.

Key words: Ulcerative colitis – Cyclosporine – Inflammatory bowel disease – Infectious diarrhea – Immunosuppression

There is increasing evidence that immunoregulatory abnormalities play a central role in the pathogenesis of the inflammatory bowel diseases, ulcerative colitis and Crohn's disease [12]. It has been suggested that a hyperreactivity and increased activation of intestinal T cells are important factors contributing to the ongoing mucosal inflammation in these diseases [12, 13]. A recent case report of a patient with severe Crohn's disease who became infected with human immunodeficiency virus (HIV) later in the course of his disease could indicate a role of CD4⁺ T cells in the disease progression. With the loss of CD4⁺ cells and the development of a manifest immunodeficiency, the patient went into stable remission of the intestinal disease [5]. Thus, patients with inflammatory bowel disease may benefit from immunosuppressive treatment such as cyclosporin A (CsA) which preferentially inhibits T cell function. This drug is widely used in organ transplantation, and initial studies

suggested a beneficial effect when given to patients with certain diseases of autoimmune origin. CsA has also been used in the treatment of severe Crohn's disease, but with variable success [1, 2, 7–9, 11]. Recently, Lichtiger and Present [6] reported favourable results for CsA in the treatment of refractory ulcerative colitis. We report on a patient who developed ulcerative colitis after 6 years of CsA treatment.

Case report

A 60-year-old man with end-stage renal disease of unknown origin had received a cadaver kidney transplant in 1984 after 2 years on chronic hemodialysis. The immunosuppressive therapy consisted of methylprednisolone and CsA. Methylprednisolone was withdrawn 6 months after transplantation, followed by monotherapy with CsA. The CsA dosage was adjusted according to the blood levels (median values around 140 µg/l as measured by the CsA RIA kit, Sandoz, Basel, Switzerland, using CsA-specific antibodies). The kidney transplant function was normal, and there had been no rejection episodes. There were no apparent complications of immunosuppressive therapy with CsA from 1984 to 1990.

In May 1990, the patient complained of intermittent rectal bleeding which he had first noticed in January 1990. When the patient was seen in our hospital, he appeared well, and the head, neck, lungs, heart, and extremities were normal on physical examination. Abdominal and rectal examinations were negative.

The hemoglobin concentration was 12.1 g/dl, and the white blood cell count was $8.1 \times 10^9/l$ with a normal differential count. Serum creatinine and serum urea levels and tests for liver enzymes were normal. Repeated stool and rectal biopsy cultures were negative for *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, pathogenic *Escherichia coli*, *Clostridium difficile*, and others. No parasites were found by repeated microscopical examinations of

Abbreviations: CsA = cyclosporin A; HIV = human immunodeficiency virus; IgM = immunoglobulin M; RIA = radioimmunoassay

Fig. 1. Histological section (H & E stain) from an endoscopic biopsy specimen of the sigma prior to treatment. Inflammatory infiltration and typical mucosal crypt abscesses are seen. Crypts are partially destroyed

fresh stool samples. An anal swab was negative for *Chlamydia trachomatis*. Electron microscopy study of the stool samples was negative for rotavirus, adenovirus, coronavirus, or herpesvirus group. Immunohistology testing of the biopsy specimens from the sigmoid colon showed no evidence for an infection with cytomegalovirus. Serological tests for *Yersinia*, *Campylobacter*, amebiasis, and gastroenteritis viruses, including cytomegalovirus-specific immunoglobulin M, were also negative.

Colonoscopy showed an edematous, friable mucosa, with a granular appearance and adhering mucus, some spontaneous bleeding, and multiple submucosal punctate bleedings in the distal colon (rectum to the mid-part of the descending colon). The colonic mucosa proximal to the descending colon was normal. On histological examination, rectal and sigmoidal biopsy specimens showed mucosal hyperplasia with active and chronic infiltrates. Typical mucosal crypt abscesses were found, the crypts were partly destroyed, and there were epithelial regenerates (Fig. 1). These findings confirmed the endoscopically suspected diagnosis of ulcerative colitis. X-radiography studies of the small intestine were normal.

After an observation period of 2 months the patient was treated with sulfasalazine enemas, but the symptoms persisted. Since the patient's abdominal symptoms did not improve and endoscopy showed worsening of the distal colitis, hydrocortisone enemas were given 2 weeks later. However, no clinical improvement was apparent, and the endoscopic appearance still persisted. Therefore, 6-

methylprednisolone was given orally at an initial dose of 48 mg per day and tapered over a 6-week period to a maintenance dose of 8 mg daily in addition to 1 g sulfasalazine 3 times daily. Under this treatment, the patient's symptoms resolved quickly. Repeat sigmoidal and rectal biopsy specimen showed a marked regression of the previous chronic inflammatory infiltrates. Oral medication with 8 mg 6-methylprednisolone and 3 g sulfasalazine was continued, and the patient showed no symptoms for about 1 year. Then he again observed rectal bleeding. Colonoscopy revealed friable mucosa with a granular appearance and punctate mucosal hemorrhage from the rectum up to the descending colon. Hydrocortisone enemas were given, but the symptoms only resolved when mesalazine enemas were introduced. After 3 weeks of topical treatment, 500 mg mesalazine 3 times per day were given instead of sulfasalazine. The remission is stable now for 3 months (March 1992), and oral 6-methylprednisolone has been reduced to 8 mg every other day. CsA treatment has been continued for the whole observation period, adjusted according to blood levels, and the kidney transplant function is still normal.

Discussion

To our knowledge this is the first report of a patient who developed ulcerative colitis during continuous therapy with the immunosuppressive agent CsA. In immunocompromised patients, chronic intestinal infections are found which are macroscopically and histologically indistinguishable from in-

inflammatory bowel disease [10]. Therefore, special efforts were made including multiple stool and biopsy examinations, electron microscopy, immunohistology, and serology to rule out an infectious cause for the chronic colitis in our patient.

Our observation may be important since CsA has been applied as a therapeutic agent in severe inflammatory bowel disease [1, 2, 4, 6–9, 11]. Most treatment studies were done so far in Crohn's disease. In one randomized, placebo-controlled study, a significant improvement was described in comparison with placebo [1]. However, this study has been criticised with respect to the grade of improvement [3]. From the available data, it seems that it is possible to reduce the disease activity for a relatively short period, but an early flare-up was observed in a considerable percentage of patients. In the one study on the treatment of ulcerative colitis with CsA [6], there was a favorable outcome in 11 of 15 patients, but the period of observation was relatively short, and the study was not placebo-controlled.

Data on the effect of CsA on the highly specialized intestinal immune system are lacking except for one study: In an animal model of intestinal inflammation, *Chlamydia trachomatis* proctitis of nonhuman primates, it was shown that CsA can inhibit the primary antibody response to *C. trachomatis* and the *C. trachomatis*-specific proliferation of peripheral blood lymphocytes after rectal infection with this agent. However, the *C. trachomatis*-specific proliferation of spleen and mesenteric lymph node lymphocytes was not inhibited [15]. These results indicate that during CsA administration, antigen-reactive lymphocyte populations stimulated in the mucosal environment may expand in tissue sites, even when the antibody and peripheral cellular immune responses are inhibited [14]. This may be of importance for the treatment of inflammatory bowel diseases with CsA: While the systemic immune responses are suppressed by CsA, the imbalanced immune reaction at the level of the mucosa may still persist. The clinical finding of an early flare-up soon after or still under the influence of CsA is consistent with this hypothesis.

Our observation of the onset of ulcerative colitis in a CsA-treated patient shows that this disease can develop under the immunosuppressive effect of CsA. It is an indication that CsA cannot prevent the initial event leading to the chronic intestinal inflammation seen in ulcerative colitis. Interestingly, only high-dose treatment with methylprednisolone was able to induce remission in our patient. Final conclusions on the role of CsA in the treatment of ulcerative colitis cannot be drawn from our observation. It may, however, serve as a note

of caution for the introduction of this agent in the treatment of ulcerative colitis.

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