CLINICAL CASE

Severe systemic cytomegalovirus infections in patients with steroid-refractory ulcerative colitis treated by an oral microemulsion form of cyclosporine: Report of two cases

Infections systémiques sévères à cytomegalovirus chez des patients atteints d’une rectocolite hémorragique corticorésistante et traités par une forme orale de ciclosporine en microémulsion : à propos de deux cas

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Summary  CMV reactivation is frequently observed in acute flares of ulcerative colitis (UC), particularly those which do not respond to intravenous steroids. Several recent series have suggested that, in most cases, CMV reactivation does not lead to severe complications and resolves spontaneously with the UC flare and discontinuation of immunosuppression. In the present paper, we describe two patients with active UC who developed a severe systemic CMV infection during a treatment with an oral microemulsion form of cyclosporine. This is of concern, particularly in a context of increasing use of immunosuppressive drugs in UC. We propose a prophylactic and curative approach to decrease morbidity related to CMV infection in active UC.

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Severe systemic cytomegalovirus infections in patients with steroid-refractory ulcerative colitis

Résumé  La réactivation d’une infection à cytomegalovirus (CMV) est fréquente au cours des poussées aiguës de rectocolite hémorragique (RCH), surtout chez les patients qui ne répondent pas aux corticotéroides intraveineux. Habituellement, la réactivation du CMV n’entraîne pas de complications et se résout spontanément avec l’amélioration de l’épisode aigu de la RCH et l’arrêt de l’immunosuppession. Nous décrivons deux infections systémiques sévères à CMV chez deux patients traités par une microémulsion orale de ciclosporine dans le traitement de poussées aiguïes corticorésistantes de RCH. Cette complication est importante à connaître, surtout dans le contexte actuel d’augmentation de l’utilisation des immunosuppresseurs en traitement de la RCH. Nous proposons une approche prophylactique et curative afin de réduire la morbidité de l’infection à CMV chez les sujets atteints de RCH.

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Introduction

Severe acute colitis can kill. Emergency colectomy is necessary in patients who do not respond to intravenous corticosteroids. Cyclosporine has been shown to induce response and prevent colectomy in 60–80% of steroid-refractory ulcerative colitis (UC) patients [3,4]. However, opportunistic infections, sometimes lethal, have also been reported using cyclosporine, and this is of concern [5]. More recently, infliximab [6] has been shown to be active in UC. The anti CD3 antibody visilizumab has shown promising results in a phase 1 study of refractory UC [7]. Both drugs are immunosuppressants and may induce opportunistic infections. Among these, CMV infection deserves a special mention. Several recent series [8—20] and a comprehensive literature review [21] suggest that CMV reactivation is common during UC attacks and in most cases, resolves spontaneously. The present paper describes two patients who had a severe systemic CMV infection while being treated with an oral cyclosporine microemulsion (Neoral®) for an active UC. It shows that, in this context, CMV reactivation can lead to severe complications.

Case report 1

Miss G was born in 1983. At age 18, in 2001, she had a seizure. In June 2002, bloody diarrhea appeared and the diagnosis of UC localized in the rectum and sigmoid was made. Remission was obtained with oral 5-ASA. In February, 2003, a relapse was treated successfully by oral 5-ASA and steroid enemas. In February 2004, she presented with lower abdominal pain, bloody diarrhea, and a 39°C fever. She did not respond to oral 5-ASA and steroid enemas nor to oral prednisone at a dose of 1 mg/kg per day for 15 days. A colonoscopy was performed and revealed a pancolitis with numerous superficial ulcerations; the terminal ileum was normal. Biopsies did not show any CMV inclusions. The patient was admitted to our department. The search for CMV antibody and systemic markers of CMV infection was not performed initially. She did not respond to three days of intravenous methylprednisolone at a dose of 0.8 mg/kg per day. Oral microemulsion cyclosporine was started at a dose of 6 mg/kg per 24 h, with a monitoring of blood pressure, cyclosporine blood level, creatininemia, and serum transaminase. A clear response was observed after two days of treatment. Renal function was normal. On the third day of Neoral®, the patient complained of dysphagia and epigastric pain, without relapse of bloody diarrhea. The upper GI endoscopy showed an esophageal candidiasis. Oral fluconazole was started. On the seventh day of Neoral®, a 39.8°C fever appeared. The chest X rays showed interstitial pneumonia. A mild increase in serum transaminase levels and a mononuclear syndrome were observed. Serum searches for IgM and IgG anti CMV were positive as well as pp65 antigenemia and PCR for CMV. The load of CMV DNA was of 150,000 copies/mL. Broncho-alveolar lavage showed typical CMV inclusions. Since systemic CMV infection was evident and there was no sign of colitis, we did not perform a colonoscopy. Intravenous ganciclovir was prescribed for 28 days and led to complete clinical remission and disappearance of CMV DNA as well as pp65 antigen from the serum. Steroids were tapered; Neoral® was reduced to 3 mg/kg per 24 h for one month and then stopped. Azathioprine was prescribed. Two months after ganciclovir had been stopped, a clinical relapse occurred. A colectomy was performed for UC relapse after corticosteroids had failed. The pathological study of the colectomy specimen showed numerous CMV inclusions, and immunohistochemical staining was positive against CMV antigen. In the postoperative course, the patient had a 40°C fever and neutropenia. PCR was positive for CMV. A new course of intravenous ganciclovir was prescribed, resulting in complete clinical remission and the disappearance of CMV DNA as well as pp65 antigenemia from the serum. Subsequently, the patient underwent a proctectomy with ileal pouch anal anastomosis in August 2004, with an uneventful postoperative course and good functional results.

Case report 2

Mr. P was born in 1982. In April 2001, he had an episode of bloody diarrhea and the diagnosis of UC was made. Remission was obtained with oral and topical 5-ASA. From 2001 to 2004, every summer, the patient had a relapse which was treated with oral and topical 5-ASA. In May 2005, he experienced another relapse. Oral and topical 5-ASA were prescribed but failed to improve the patient’s condition. In August 2005, he was seen in our hospital and oral prednisolone was prescribed at a dose of 1 mg/kg per day. After 10 days, no response was observed and the patient was admitted to our unit. Serum searches for antibody to CMV, pp65 Ag and PCR for CMV were negative. Intravenous methyl-
prednisolone was prescribed at a dose of 0.8 mg/kg per day. After five days, no response was observed. The patient was given Neoral® at a dose of 4 mg/kg/d, with a monitoring of blood pressure, cyclosporine blood level (between 100–400 ng/mL), creatininemia, and serum transaminase. A response was obtained at Day 4. Renal function remained normal. Three days after discharge, he complained of profuse watery diarrhea, pain in his legs, mild dyspnea and a 40°C fever. He was readmitted to the hospital. A mild increase in serum transaminase levels and a mononuclear clear syndrome were observed. The pp65 Ag and PCR for CMV were found to be strongly positive at the second admission. CMV DNA load was 347,660 copies/mL and pp65 Ag was 200 positive cells. Since systemic CMV infection was evident, we did not perform a colonoscopy. Intravenous ganciclovir was instituted, Neoral® was stopped and prednisolone was gradually tapered. The patient’s fever persisted for 14 days but complete clinical remission was finally obtained after two weeks of IV ganciclovir and one week of oral valganciclovir. PCR for CMV and pp65 antigen disappeared 30 days after the start of IV ganciclovir. After five months of follow-up, the patient became steroid dependent. A colectomy was performed. The pathological examination of colectomy specimen did not find immunohistochemical or histological sign of CMV reactivation.

**Discussion**

The present case reports describe severe systemic CMV infections in two patients with active UC treated with Neoral®. In both cases, outcome was favorable with IV ganciclovir and reduction in cyclosporine as well as steroid dosage. We used Neoral® instead of IV cyclosporine since we [22] and others [23–26] have suggested that both forms have a similar efficacy. Initial Neoral® dosage varied between 5 mg/kg per 24 h [23], and 7.5 mg/kg/24 h [26]. Response rates were similar between these studies and none of them except ours mentioned the occurrence of systemic CMV infections. Patient 1 was started with 6 mg/kg of body weight of Neoral®; at the time of response, she had a C0 of 203 ng/mL and a C2 of 992 ng/mL. Patient 2 was started at a dose of 4 mg/kg and had a C0 of 62 ng/mL and a C2 of 1,193 ng/mL at the time of response. In our series of 20 patients with severe UC treated with Neoral®, the mean dose of Neoral® was 4.6 (3.3–6.0) mg/kg per 24 h, the mean C0 level was 103 (32–294) ng/mL and the mean C2 level was 761 (183–1390) ng/mL. In the series by De Saussure et al., the mean C0 for all measurements was 149 ng/mL and the mean C2 level (measured in a subgroup of five patients) was 826 ng/mL. No systemic CMV infection was observed in their series [25]. From these data, no obvious correlation appears between cyclosporine dosage or serum level and systemic CMV infection.

**Four-phase model of CMV activation in IBD**

After primary infection, CMV persists latently within the peripheral blood mononuclear cells and can be reactivated by a severe inflammation or immunodepression. Recently, Hommes et al. proposed a three-phase model of CMV activation and replication during active IBD [21]. In the first “initiation phase”, serum search for CMV Ig is positive but intestinal biopsies are negative, as well as PCR for CMV in blood and feces. In a second “reactivation phase”, anti CMV Ig is positive, intestinal biopsies show CMV inclusions and immunoperoxidase stain positively for CMV antigens, but PCR for CMV in blood and feces are negative. During a third “consolidation phase”, viral particles are shed in blood and inflamed intestine and can be detected by a positive PCR for CMV in blood and feces. This model fits well with clinical observations, particularly, the observed correlation between UC attacks and viral reactivation, evidenced by serological, histological, and viral markers. It has been hypothesized that inflammatory response may aggravate during the consolidation phase. CMV reactivation may not only aggravate inflammatory response, it may also lead to a systemic infection, as in the two cases reported in the present paper. Thus, a fourth “opportunistic infection phase” should be added to the model.

**Frequency of CMV activation in Crohn’s disease and UC**

Several recent studies have assessed the frequency of CMV reactivation in patients with inflammatory bowel disease [8–20]. Markers of CMV activation were sought either within colonic biopsies or colectomy specimens (typical CMV inclusions or immunohistochemistry) or in the serum (pp65 antigen, PCR). These markers appeared to be rare in active Crohn’s disease; in two recent series, no marker of CMV activation were found in 41 and 49 patients respectively [11,18]. By contrast, in the same series, markers of CMV infection were found in 20 and 17% respectively of UC patients, either in colonic mucosa or in the serum. These markers are more frequently found in corticosteroid-refractory patients than in those with non-refractory UC [9,14,16]. Additionally, Hommes et al. have found that PCR of CMV was positive in blood and feces in respectively 50 and 88% of severe acute flares of UC, exclusively in CMV-seropositive patients [12]. In most cases, these markers of CMV replication disappeared with the resolution of the flare and without antiviral treatment [12]. These series showing that CMV reactivation resolves spontaneously may be underpowered to detect patients who develop severe infections. Several case reports have described severe and sometimes lethal CMV infection either systemic or confined to the colon [27–33]. Most, but not all of the patients with severe systemic CMV infection were treated with steroids or immunosuppressive agents. It has been recently shown that cyclosporine increases CMV antigenemia and PCR level in CMV seropositive patients with active UC [8].

**Management of CMV activation in UC**

Management of CMV activation in UC patients is poorly defined. We propose a therapeutic scheme based upon the available literature and our personal experience. However, further prospective studies are needed to validate this therapeutic scheme.
Overt systemic infection

Overt systemic CMV infection is defined by the association of clinical and biological signs (fever with or without specific organ injury such as lung and retina, mild hepatisis, mononucleus syndrome) and a high level of CMV PCR (> 10^6 copies/mL) and/or pp65 Ag (10 or more positive cells [34]). It is an unequivocal indication of IV ganciclovir. Whether corticosteroids and immunosuppressive agents should be continued or stopped in patients with overt CMV systemic infection is another issue. Continuing corticosteroids and immunomodulators might aggravate CMV infection. Stopping these drugs may induce a severe UC relapse, leading to colectomy while CMV infection is not controlled. In the present paper, we decreased Neoral® and corticosteroid dosage in patient 1 and stopped Neoral® in patient 2. CMV infection was controlled and urgent colectomy was avoided.

CMV replication without clinical or biological signs of systemic CMV infection

When there are markers of CMV replication (CMV PCR, and/or pp65 Ag, colonic CMV inclusions) but no clinical or biological signs of overt CMV infection, indication of IV ganciclovir is debatable. Some case reports have shown an improvement with IV ganciclovir in the setting of acute steroid resistant UC. However, a recent study has shown that the values of CMV PCR are low (1.0 x 10^3 to 4.6 x 10^4 copies/mL in UC patients and 3.0 x 10^4 to 7.0 x 10^6 copies/mL in hematopoietic stem cell transplantation recipients with gastrointestinal CMV disease) and become undetectable with the decrease in immunosuppression [34]. Additionally, the response rate to cyclosporine is not different in patients with active UC, with or without CMV reactivation [8,34]. Taken together, these data may suggest that IV ganciclovir is not indicated in UC patients with CMV reactivation without overt systemic infection. However, some patients may have high levels of CMV DNA (> 10^6 copies/mL) and/or pp65 Ag (10 or more positive cells) without clinical symptoms of systemic CMV infection and could be at risk for overt systemic CMV infection. We suggest to reduce cyclosporine and steroid dosage in these patients in order to avoid overt systemic CMV infections. Whether prophylactic IV ganciclovir should be prescribed in these patients remains an unresolved issue.

Conclusion

CMV reactivation in active UC may evolve to a severe infection. This is of concern in a benign condition which affects young adult patients. Risk factors of CMV infection in UC are the following: acute flare, failure to respond to corticosteroids, use of immunosuppressive agents, particularly cyclosporine. We propose to monitor CMV PCR in these patients. Those with no clinical or biological signs and low levels of CMV PCR probably do not need any additional treatment. Those with overt systemic CMV infection need IV ganciclovir and a reduction in steroid and cyclosporine dosage. In patients with high values of CMV PCR without overt systemic infection, we suggest to reduce steroid and cyclosporine dosage.

References


