Refractory ulcerative colitis complicated by cytomegalovirus infection successfully treated with valganciclovir

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Abstract

Cytomegalovirus (CMV) infection is widespread in the general population. In patients with severe and/or steroid-refractory ulcerative colitis (UC), local reactivation of CMV can be detected in actively inflamed colonic tissue in approximately 30% of cases. However, the role of CMV in patients with UC is not clearly understood. There is evidence to show a possible role in exacerbating a colitis flare, whereas other studies describe CMV as an innocent bystander. We report the case of a patient with severe UC complicated by CMV infection who did not respond to conventional therapy. A complete diagnostic panel for CMV diagnosis, including tissue polymerase chain reaction and immunohistochemistry, was carried out. Three-week therapy with oral valganciclovir resulted in dramatic clinical and endoscopic improvement. Timing of diagnosis and treatment of CMV infection complicating UC is crucial in order to recognize the organ-disease and plan appropriate treatment.

Introduction

Cytomegalovirus (CMV) infection is widespread in the general population with a prevalence of 40-100%.1 In the immunocompetent host, primary infection can result in Epstein-Barr virus-like mononucleosis syndrome. T cells control viral replication and disease but do not obtain complete eradication, leading to viral latency. In immunologically impaired patients, the virus may cause serious multifocal organ involvement and complications due to the CMV-associated disease both in cases of primary infection and, the most frequent event, reactivation.2

In patients with severe and/or steroid-refractory ulcerative colitis (UC), local reactivation of CMV can be detected in actively inflamed colonic tissue in approximately 30% of cases.3 The role of CMV in patients with inflammatory bowel disease (IBD) is not clearly understood. There is evidence to show a role in exacerbating a colitis flare, whereas other studies describe CMV as an innocent bystander.4 Furthermore, patients with IBD are frequently treated with immunosuppressive agents which may increase infection/reactivation risk while inflammation itself is a predisposing factor for infection.

In this study, we report a case of refractory UC complicated by CMV colitis successfully treated with oral valganciclovir.

Case Report

A 64-year-old male with a diagnosis of left UC in the previous eight months came to our observation reporting a 2-month history of repeated hospital admissions for colitis relapse. Disease status until then had been good and the patient had maintained remission with oral and topical mesalamine. Two months before UC diagnosis, he had a heart attack and underwent multiple coronary stenting requiring antiplatelet therapy (clopidogrel 75 mg/day).

During the previous periods of hospitalization, he had received intravenous steroid therapy (methylprednisolone 1 mg/kg/day) continuing with this treatment for more than 40 days (although dose scheduling was not optimal) without clinical improvement. After completing this period of steroid therapy without receiving any benefit, azathioprine was also introduced at 0.85 mg/kg/day but this was suspended at day 4 of treatment due to pancyclopennia. Furthermore, iatrogenic diabetes has developed.

The patient was admitted to our hospital a few days after an adverse reaction to azathioprine and presented with normal vital signs. He reported bloody diarrhea occurring 4-5 times a day, abdominal pain and weakness. On physical examination, his abdomen was slightly distended with normoactive bowel sounds. At ultrasound evaluation, no alterations in liver, spleen, gallbladder or pancreas were found. We started intravenous therapy with methylprednisolone at 1 mg/kg/day and parenteral supplementation with albumin, iron, potassium and folic acid. Since hemoglobin levels decreased up to 8 g/dL, a blood transfusion was provided. It should be noted that the patient required insulin for the persistence of iatrogenic diabetes. No significant clinical improvement was observed over the following five days of hospitalization. Thereafter, a colonoscopy with ileoscopy was performed which displayed multiple deep oval and serpiginous ulcers with undetermined margins and a number of pseudopolyps throughout the colon. No lesions were observed in the terminal ileum explored for 20 cm.

In this context of refractoriness to conventional high-dose therapy and prolonged

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immune-suppressive patient status, before considering alternative medical strategies (i.e. cyclosporine, infliximab, colectomy), the endoscopic pattern moved our clinical suspicions to another cause of persistent severe colitis, such as CMV infection.

Specific serum IgG but not IgM to CMV were detected. Nevertheless, leukocyte polymerase chain reaction (PCR) showed CMV viremia. Blood sample copy number of CMV DNA was 284 copies/mL. Furthermore, biopsy specimens obtained from the margin and base of the ulcers showed typical CMV nuclear inclusion bodies (Hematoxylin and Eosin staining) and DNA amplification by PCR on colonic tissue was positive for CMV replication, with a copy number of CMV DNA of 10 copies/mg.

These findings indicated that CMV reactivation was associated with UC exacerbation. Methylprednisolone was, therefore, gradually tapered, and valganciclovir (450 mg twice daily) was administered orally for three weeks. Following the initiation of antiviral therapy, abdominal symptoms gradually resolved and laboratory tests slowly returned to normal range. After three weeks of valganciclovir, a sigmoidoscopy was performed which showed a dramatic improvement in the endoscopic lesions. At the same time, serum CMV-DNA was no longer detected and PCR on colonic tissue resulted negative for CMV replication. Hematoxylin and eosin staining performed on biopsy samples showed no typical inclusions suggestive of CMV organ-disease. The patient stopped antiviral therapy and was discharged with oral mesalamine 3.2 gr/day.

Discussion and Conclusions

In the present case, we describe a superinfection with cytomegalovirus occurring in an immune-compromised host with UC. Treatment failure after five days of intravenous steroid therapy and endoscopic findings suggested CMV infection in addition to UC. This was confirmed by leukocyte and colonic tissue PCR positivity along with the presence of cytomegalic cells at Hematoxylin and Eosin staining (Figure 1).

Patients with IBD are at higher risk of CMV infections due to the frequent use of immune-suppressive therapies, the particular tropism of CMV for sites of inflammation and the altered immunological state which is consistent with the molecular pathogenesis of intestinal disease.\(^5\) Given the association of CMV colitis with refractory UC, CMV infection should be ruled out with rectal biopsy and serology whenever a patient presenting with UC exacerbation does not respond to conventional therapies. In particular, we must consider a possible CMV colitis when patients in remission or with mild-stable symptoms unexpectedly develop a severe or atypical exacerbation, complicated by steroid-refractoriness.\(^6\)

As shown in Table 1, there are several methods for detecting CMV disease. Histological examination is a relatively easy approach, but sensitivity is not high (10-87%). In this study, antigenemia pp65 was not performed given that it has been demonstrated that it is not predictive of underlying CMV detection in colonic tissue of patients with IBD. In fact, it is largely being replaced by the introduction of leukocyte PCR which provides better quantification of viral presence.\(^7\) A combination of the above listed methods may increase the CMV detection rate.\(^8\)

The most recent European Crohn's and Colitis Organization guidelines (ECCO) recommend tissue PCR or immunohistochemistry to investigate CMV in immunomodulator-refractory cases of IBD.\(^9\) Furthermore, the role of endoscopy in patients with UC complicated by CMV infection has been recently addressed.\(^10\) So, specific endoscopic findings, such as those reported in this study, may facilitate the early recognition of CMV colitis. As regards antiviral therapy, CMV colitis is usually treated

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<th>Methods</th>
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<td>Serum IgG</td>
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<td>Serum IgM</td>
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<td>Leukocyte PCR</td>
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<td>Antigenemia pp65</td>
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Ig, Immunoglobulin; H&E, Hematoxylin and Eosin; IHC, immunohistochemistry (both on colonic tissue); PCR, polymerase chain reaction.
with ganciclovir, although foscarnet, valganciclovir, and cidofovir have also been suggested. Any benefits of antiviral therapy must outweigh the risks associated with the medication used. According to ECCO guidelines, treatment with antivirals is recommended when CMV is detected in colonic tissue. However, intravenous administration of ganciclovir requires hospitalization; therefore, we preferred to use valganciclovir for outpatient management of the disease.

CMV infection in UC patients, especially in those who are immune-compromised by steroid therapy, can produce severe systemic disease and often leads to colectomy. Particularly severe and unrecognized cases may display an even poorer clinical outcome. Clinicians should evaluate what are the best methods and timing needed to control the infection, in order to recognize the so-called organ-disease and plan appropriate treatment. It is becoming clear that early diagnosis would help to prevent the worst consequences. Clinicians should be aware of the importance of considering CMV infection in a setting of UC when clinical and laboratory data are suggestive of refractory colitis.

### References