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Research Article

A retrospective study on clinician's practice on testing and treating for cytomegalovirus infection in patients with acute ulcerative colitis in a tertiary care center in India

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ABSTRACT

Background: Reactivation of cytomegalovirus (CMV) may occur in patients with ulcerative colitis (UC) while on immunosuppressive treatment. Whereas some workers suggested that treatment of CMV is needed in them, others contradicted this. We aimed to retrospectively evaluate, a) how frequently clinicians evaluate for CMV in patients admitted with acute severe colitis, b) prevalence of its occurrence, and c) how frequently clinicians treated CMV infection in a tertiary care center.
Methods: Data on consecutive patients with UC admitted to the department of Gastroenterology during a seven-year period at a tertiary care center were retrospectively reviewed. Frequency of evaluation for CMV (IgM antibody, polymerase chain reaction or inclusion body in H and E-stained sections by the treating clinicians was evaluated. Any one test positive out of all the three tests was considered as evidence of CMV infection. Frequency of treatment directed against CMV by treating clinicians was evaluated.
Results: Among 181 admitted patients with UC, 41 (22.6%) were tested for CMV infection, of whom 28 (59.6%) were male. Fourteen of 41 (34.1%) were CMV positive (one of three above mentioned tests positive). Twelve had detectable CMV DNA by PCR and 3 had IgM antibody positive (one of whom also had inclusion body on histopathology). Three of 14 patients with CMV infection received anti-viral treatment (ganciclovir in two, ganciclovir followed by valganciclovir in one).
Conclusions: These data suggest that investigating and treating CMV as a cause for acute ulcerative colitis is becoming obsolete About one-fourth of patients admitted with severe UC in a tertiary centre are screened for CMV infection, about one-third of whom tested positive to at least one test. Only one-fifth of patients with positive result to the test were treated against the infection.

Keywords: Inflammatory bowel disease, Ulcerative colitis, Colectomy, Ganciclovir, Ayurvedic

INTRODUCTION

Cytomegalovirus (CMV) is a host species-specific pathogen that causes lifelong persistent infections and CMV is a β-herpesvirus has a 235 kbp genome. It is a DNA virus and a member of the Herpesviridae family, along with herpes simplex viruses 1 and 2, Epstein-Barr virus, and varicella-zoster virus.[1] Between 40% and 70% of the world's population is seropositive for CMV.[2,3] Initial CMV infection in the immune competent host

typically is mild and goes undetected clinically. This is followed by a chronic latent state, during which the virus remains present within host cells, but viral proliferation is prevented by host cell-mediated immunity. Latent CMV evades the host immune system, remaining dormant in myeloid progenitor cells and endothelial cells, without active viral replication or manifestation of clinical symptoms.[4] Failure of immune containment may lead to reactivation with viral proliferation and severe systemic illness. CMV reactivation, seen clinically in acquired defects of cellular immunity, such as with immunosuppressant therapy, chemotherapy, bone marrow or solid organ transplantation, and HIV/AIDS, can lead to high disease activity and mortality.[2] Inflammatory bowel disease (IBD) patients are frequently treated with immunosuppressive agents, including corticosteroids, azathioprine, cyclosporine, and methotrexate etc., either alone or in combination.[5,6] Therefore, severe or refractory IBD patients are thought to be at an increased risk of infection with CMV. About 15.8%-34% of IBD patients have CMV disease.[7] Gastrointestinal CMV infections can resolve without the use of antiviral therapy.[8]

Ulcerative colitis (UC) is common all over the world; including India and presentation of acute attack of UC and of CMV colitis have been reported to be similar.[9-11] Some workers suggested that treatment of CMV is needed in them, others contradicted this. In a previous study from our center, we prospectively analyzed frequency, risk factors and outcome of CMV infection in UC patients.[12] In the present study we aimed to retrospectively evaluate, a) how frequently clinicians evaluated for CMV in patients admitted with acute severe colitis, b) prevalence of its occurrence, and c) how frequently clinicians treated CMV infection in a tertiary care center.

METHODS

Data retrieval

Data on patients admitted during a seven-year period with acute UC to the Department of Gastroenterology at our tertiary care centre were retrieved from electronic medical records, paper-based records including the discharge summary. UC was diagnosed by clinical picture, typical endoscopic findings, histology and exclusion of an infective etiology. Severity of the disease was determined using Truelove and Witt's classification.

Evaluation for CMV infection

Data on frequency of evaluation for CMV infection by the clinicians at a tertiary care center were retrieved by records on request for tests such as IgM antibody and DNA by polymerase chain reaction (PCR) through electronic medical records or reports of these.

Criteria for CMV infection

If any of the three tests i.e. IgM antibody, (PCR) or inclusion body in H and E-stained sections was positive, diagnosis of CMV infection was made.

Retrieval of data on treatment

Treatment data were retrieved from prescriptions, nursing records and discharge summaries regarding previous use of immunosuppressant (steroid, azathioprine, methotrexate etc.), 5-ASA compounds (sulfasalazine, mesalamine, balsalazide etc.) or any other supportive treatment including complementary medicine (e.g. Ayurvedic treatment), treatment for current active disease and use of antivirals to treat CMV infection.

Retrieval of outcome data

Final outcome of CMV positive patients was recorded regarding control of the active disease by medical treatment alone, need for colectomy or death occurring during the course of the illness.

RESULTS

During 7 years period, 181 patients were admitted with severe UC. Among these, 41 (22.6%) were tested for presence of CMV infection, of whom 28 (59.6%) were male.

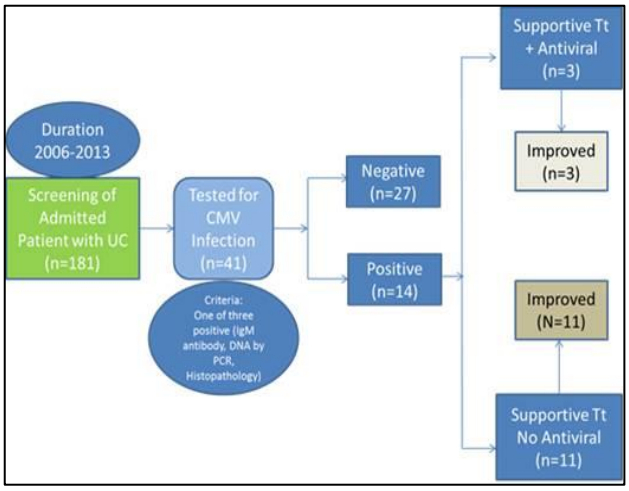

Figure 1: Study plan and outcome data (UC= ulcerative colitis, CMV= cytomegalovirus, TT=Treatment).

CMV infection

Fourteen of 41 (34.1%) were CMV positive (one of three tests positive). Twelve had CMV DNA by PCR and 3 had IgM antibody (one of whom also had inclusion body on histopathology).

Treatment

Previously, steroid followed by azathioprine was given in 5 patients, steroid followed by 5-ASA in 5 patients and 5-ASA alone in 4 patients to control the disease. One patient used ayurvedic treatment for disease control but without any response. Three of 14 (21.4%) patients with CMV infection received anti-viral treatment. Two patients received intra-venous ganciclovir 300 mg twice daily for three weeks and in one, ganciclovir was given for five days followed by 16 days of oral valganciclovir 450 mg twice daily.

Outcome

Active disease was controlled by medical treatment alone in all 14 patients. None of the patient needed colectomy. No death occurred.

DISCUSSION

The present study suggests that about one-fourth of patients admitted with severe UC in a tertiary centre are screened for CMV infection, about one-third of whom tested positive to at least one test. Only one-fifth of patients with positive result to a test were treated against the infection.

In patients with severe ulcerative colitis, local reactivation of CMV can be detected in actively inflamed colonic tissue in approximately 30% of cases.[13] In present study 34.1% of the total tested patients had CMV infection while in the previous study from our center 15.8% of patients had CMV infection.

Although there is ample data on the presence of CMV infection in immunosuppressant use, an association between acute severe UC and CMV disease of the colon in patients with no prior use of immune suppressants has been described only in few case reports.[14-21] In our study CMV was detected in 5 patients who had used only 5-ASA and no immunosuppressant in the past for disease control.

There are conflicting results on the association of CMV reactivation with azathioprine. Some studies found association of CMV reactivation with azathioprine.[12,22] other studies, however, did not show an association between CMV reactivation and azathioprine.[3,23] In our study azathioprine was given in 5 patients.

Studies have shown increased risk of colectomy and mortality up to 67% and 33% respectively and treatment with IV antiviral improves outcome.[2,12,28] In our study 3 patients got antiviral treatment and all improved. There was no mortality or nor colectomy was needed.

A few studies have suggested that CMV is an 'innocent by stander' i.e. the presence of CMV represents tropism towards areas of dysplasia and inflammation rather than a true disease and there is no difference in remission and colectomy rates between UC patients with CMV reactivation and non CMV UC patients.[8,26] However in the first study only serological markers were used for evidence of CMV reactivation and in the second study 3 of 3 patients with CMV infection proceeded to urgent colectomy, and the one patient who was treated for CMV received intra-venous acyclovir rather than ganciclovir or forscarnet.

In our study antiviral was given in one-fifth only however all patients improved. The present study showed that in admitted patients with acute severe UC in a tertiary care center, investigations for CMV is somewhat uncommonly undertaken by the treating clinicians and even when detected, these patients are uncommonly treated against CMV infection. This data suggests that most clinicians might believe that CMV may not be important in management of acute severe colitis.

This contention is also supported by the fact that the most patients in this series improved without treatment directed against CMV infection and none needed colectomy. However, the present study has limitation as it is retrospective in nature, a large number of patients admitted with acute severe colitis were not tested for CMV infection as decision to test or not was based on clinician's judgment rather than any pre-decided protocol.

Hence, it is possible that those who required work-up for CMV infection most might not have undergone any test. This is supported by the fact that female patients were not tested for CMV more often than male patients. The earlier study suggested that female patients are more often CMV positive. [12]

In conclusion, this study highlights that about one-fourth of patients admitted with severe UC in a tertiary centre is screened for CMV infection, about one-third of whom tested positive to at least one test. Only one-fifth of patients with positive result to a test were treated against the infection. These data suggest that the trend among clinicians for searching and treating CMV as a cause for acute severe ulcerative colitis is becoming obsolete.

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