

Quarterly Review

Cytomegalovirus infection in patients with Inflammatory Bowel Disease: A major player or an innocent bystander?

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ABSTRACT

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Cytomegalovirus (CMV) infection was described in patients with Inflammatory Bowel Disease (IBD) about 50 years ago. CMV infection may mimic a relapse of IBD. The role of CMV in IBD remains controversial. Of 23 studies during 1999 to 2015, 16 of 23 studies during 1999 to 2015, 16 studies found that CMV had an unfavorable impact on the disease status where as there was no impact on disease status in 7 studies. Recent literature suggests a way to recognize patients who need treatment for CMV. Patients older than 30 years, those with steroids and immunosuppressant resistance and those needing increase in dose of immunosuppressant drugs need to be investigated for CMV colitis. Histological examination of colonic mucosa (Hematoxylin and eosin, and immunohistochemistry), colonic mucosal biopsy PCR DNA amplification assay and blood PCR for viremia are the diagnostic tests advised for the diagnosis of CMV colitis and CMV infection.

KEYWORDS: Cytomegalovirus; inflammatory bowel disease.

Introduction

With the advent of immunosuppressants, there is increasing risk of superimposed infection in patients with Inflammatory Bowel Disease (IBD). Superimposed infective episodes not only worsen the symptoms, they may also mimic a relapse of IBD and are often difficult to differentiate.

Powell and Levine independently reported Cytomegalovirus (CMV) infection in IBD patients in the 1960's.^{1,2} However, later studies did not find an association between CMV and IBD. This review will

attempt to delineate the role of CMV in the pathogenesis of IBD, as either an innocent bystander or a major player.

CMV Factsheet

1. Although almost 70 % of human beings are likely to be infected with CMV, the majority, being immunocompetent, are unlikely to manifest.³ CMV can cause infection in immunocompromised individuals.⁴

2. The inflamed mucosa in IBD patients is more susceptible to infection by CMV. CMV is unlikely to invade endoscopically normal mucosa.^{5,6}
3. CMV infection occurs more often in patients with ulcerative colitis than in patients with Crohn's disease. This may be explained by the pathogenesis of CD, which is a Th1 type of inflammatory process, with high expression of Interferon - γ . IFN - γ suppresses CMV reactivation.⁷
4. CMV infection may rarely involve ileo-anal pouch.⁸
5. Histological prevalence of CMV in new onset ulcerative colitis is 4.5%, in exacerbation of IBD 8 to 10.4% (histology and colonic tissue PCR), acute colitis admissions 16.6% and in severe ulcerative colitis 13.8%.⁹⁻¹⁴
6. We need to differentiate between diagnostic tests for CMV infection and diagnostic test for CMV colitis.

The diagnostic tests for *CMV infection* include.¹⁵

Serological tests

IgG and IgM. Multiple reports suggest that IgM antibody to CMV does not appear in patients with CMV colitis.^{5,16}

Antigenemia assay

pp65 antigen in peripheral neutrophils- This is semi-quantitative test. Although it has good sensitivity and specificity, it does not differentiate between latent infection and active disease.

PCR DNA amplification in blood

This test also does not differentiate between latent and active infection in IBD. There is correlation between PCR and detection of colonic CMV.¹⁷ Some investigators have stratified patients according to copies per mg of tissue.

PCR assay in stool

Although this assay is performed on stool sample, it is not commonly used.

Histology

Histological diagnosis with hematoxylin and eosin (H & E) staining shows presence of enlarged cell and intranuclear inclusions. It has a specificity of 92-100% but sensitivity of only 10-87%. Immunohistochemistry (IHC) is the gold standard for diagnosis and has a higher sensitivity of 78-93%.^{18,19} McCurdy *et al.* recommend a flexible sigmoidoscopy with 11 biopsies in UC and colonoscopy with 16 biopsies in CD to obtain 80% chance of a single positive biopsy.²⁰

PCR DNA amplification assay in colon mucosa

Colonic mucosal biopsy tissue PCR DNA has recently been found to be useful in a French study. When done in flare up of UC or refractory disease, more than 250 CMV copies/mg had sensitivity of 100% and specificity of 66% and was predictive of resistance to steroids and advanced treatment. This cut off has also been used in other studies to treat the CMV colitis.⁵

Endoscopy

No findings on endoscopy are diagnostic of CMV infection. Punched out ulcers, longitudinal ulcers and geographic ulcers are common in CMV colitis. However, ulcers are related more to the disease than to CMV.^{16,21}

Who should be tested for CMV and which diagnostic tests should be used?

In the setting of severe disease, disease refractory to cortico steroids and in patients on immunosuppressant drugs, testing for CMV should be done. This should include histological examination of colonic biopsies and immunohistochemistry and/or blood PCR, which has been found to have good correlation with histology. The 2014 revised European Crohn's and colitis organization guidelines (on management of opportunistic infection in IBD) suggest histology with immunohistochemistry and colonic tissue PCR for the diagnosis of CMV colitis.²² These guidelines also suggest that CMV should be excluded before increasing immunosuppression.

CMV - a major player or an innocent bystander?

Several studies have looked at the association between CMV and IBD with diverse results. Pillet et al.²³ summarized the studies and found various factors that could have contributed to the varied results: Primary CMV infection had been clubbed together with reactivation, the studies had taken UC and CD together even though they had vastly different rates of CMV infection and the studies had used different diagnostic tests. There were 23 studies from 1999 to 2015, including 1208 patients with UC and 178 patients with CD. The population with UC was divergent- UC with no mention of severity, active disease, varying degree of severity of UC, refractory UC and patient with colectomy. 16 studies found CMV to have an unfavorable impact on disease status whereas 7 found no impact. The unfavorable outcome was variably defined: more steroid dependence, requirement of colectomy, avoidance of colectomy by anti viral treatment and the requirement for hospitalization. Thus, it can be concluded that CMV reactivation is a marker of poor prognosis in patients with IBD and is associated with unfavorable outcomes.

Approach to treatment in an individual patient

A recent article by Abdul-Baki Heitham *et al* outlined a treatment plan based on stratification of patients into 3 categories. Some patients have colonic CMV infection associated with viremia. This is suggestive of systemic CMV infection and warrants treatment for CMV infection. Patients without systemic viremia but features of colonic involvement in the form of punched out ulcers need CMV treatment followed by treatment for IBD in the form of medications or operative therapy. However, some patients neither have viremia nor deep colonic ulcers, and only show evidence of CMV on histology or immunohistochemistry. In this group, it is likely that they have inflammation due to activity of ulcerative colitis and CMV is likely to be innocent bystander.²⁴

McCurdy *et al.* found that patients with medically refractory disease, patients treated with immunosuppressant (not tumor necrosis factor (TNF) antagonist) and age older than 30 years were independently

associated with CMV disease. The use of TNF antagonist was not a significant factor for the development of CMV disease.²⁵

Pellet et al. suggest a quantification of CMV density in colonic tissue in patients with refractory ulcerative colitis (defined by steroid resistance or immunosuppressive treatment or anti-TNF drugs) more than 30 years of age. They divide patients into three categories - patients with no CMV in colonic tissue, patients with low-grade density (10 to 250 copies/mg tissue and less than 4 CMV inclusions in biopsy by immunohistochemistry), and patients with high-grade density (more than 250 copies/mg of tissue or more than 4 inclusions in biopsy by immunohistochemistry). Patients with low-grade density CMV associated with stigmata of severe disease (need for hospitalization and Lichtiger score more than 10) and patients with high-grade density should be treated for CMV infection.²³

What about steroids and/or immunosuppressants when CMV infection is present and needs treatment?

In the three groups described by Abdul-Baki et al., the first group of patients, who have systemic CMV infections in addition to colonic CMV infections, are usually moribund. In these patients, immunosuppressants should be stopped and steroid should be reduced. After treating CMV infection, if the IBD remains active, the patients should be treated with biologic therapy or referred for surgery. Tumor necrosis factor (TNF) antagonists do not reactivate latent CMV in CMV seropositive patients with IBD.²⁵⁻²⁷

Treatment of CMV colitis

Ganciclovir intravenously in a dose of 5 mg/kg twice a day for 2 to 3 weeks is the first line therapy. After 2 to 3 days, IV therapy can be switched to oral valganciclovir, which has excellent oral absorption. Resistance to Ganciclovir should be suspected if there is no response to treatment. Side effects of Ganciclovir include myelosuppression, rash, nausea, vomiting and headache. Intravenous Foscarnet is the second choice but is not easily available.

In summary, although there is controversy regarding the role of CMV in IBD, most studies suggest an unfavorable outcome associated with CMV infection. Patients older than 30 years, those with steroids and immunosuppressants resistance and those needing increase in dose of immunosuppressant drugs need to be investigated for CMV colitis. The recommended diagnostic tests for CMV include histological examination of colonic mucosa (H & E and immunohistochemistry), colonic mucosal biopsy PCR DNA amplification assay and blood PCR. Patients with CMV viremia and CMV colitis should be treated (immunosuppressant should be stopped and steroids should be reduced). Patients with steroid refractory disease and endoscopic ulcers should also be treated. After the treatment of CMV infection, treatment of IBD should be tailored according to the needs of the individual.

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