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Review

Cytomegalovirus and Inflammatory Bowel Disease: pathogenicity, diagnosis and treatment

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SUMMARY

Cytomegalovirus (CMV) infection is a common viral infection in humans. In immunocompromised patients such as transplant recipients and AIDS patients, CMV can cause severe disease, affecting multiple organs including the gastrointestinal tract. The role of CMV in patients with Inflammatory Bowel Disease (IBD) is controversial. CMV has been associated with onset of IBD, exacerbation of underlying IBD and refractoriness to medical treatment in some studies, but has been viewed as an "innocent bystander" in others. CMV infection must be distinguished from CMV disease but this may be difficult even with the newest diagnostic tests. Treatment with ganciclovir or foscarnet with or without discontinuation of immunosuppression, improves the clinical course of some IBD patients with CMV disease. Thorough clinical and laboratory evaluation is needed to identify those who will benefit from antiviral treatment until further studies reveal the exact role of CMV in the natural course of IBD.

Key Words: Cytomegalovirus, Inflammatory Bowel Disease, ulcerative colitis, Crohn's disease, CMV colitis

INTRODUCTION

Cytomegalovirus (CMV) infection is a common human viral infection, affecting 40% - 100% of adults. CMV is a member of the herpesvirus family, along with Herpes Simplex Virus-1 and -2, Ebstein-Barr Virus and Varicella-Zoster Virus. As with most of these viruses once the infection is acquired (*primary infection*), CMV remains in the host in a state of lifelong latency from which it can be reactivated.[1]

Most CMV infections are acquired either in the perinatal period and infancy or in adulthood through sexual contact. CMV targets epithelial cells lining the respiratory or gastrointestinal tract in primary infection.[2]

Primary infection in immunocompetent hosts, is usually asymptomatic or causes a mild, mononucleosis-like syndrome with fever, myalgias and pharyngitis.[3,4,5] Gastrointestinal disease due to primary infection has been described but is rare, and manifests with bloody diarrhea, tenesmus, abdominal pain, fever, anorexia, malaise and weight loss.[6] The disease usually runs a milder course in younger patients than in older ones with co-morbidities. In the elderly, it can be severe, with significant mortality.

In cases of immune deficiency (patients with AIDS, organ transplantation, cancer chemotherapy, steroids or other immunosuppressives) CMV can cause severe disease affecting the gastrointestinal tract, the lung, the retina and the liver. In the gastrointestinal tract CMV can cause colitis, oesophagitis, gastritis, ulcers, terminal ileitis, intestinal perforation and pouchitis.

In ***latent infection*** principal reservoirs of CMV are fibroblasts, myeloid cells and endothelial cells.[3] Peripheral blood monocytes constitute a major site of viral latency and triggered by secreted proinflammatory cytokines and chemokines they can differentiate into tissue macrophages, leading to CMV reactivation and probably to CMV disease.[7-9] Endothelial cells are also a common target for CMV in vivo, regardless of the organ involved.[10] The vascular endothelium represents the interface between circulating immune cells and the lamina propria of the gut and this can partially explain the role of CMV in cases of intestinal inflammation as in Inflammatory Bowel Disease (IBD).

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PATHOGENETIC MECHANISMS OF CMV

Some of the mechanisms CMV uses to avoid immune detection include inhibition of apoptosis of CMV-infected cells, blockage of antigen presentation by Major Histocompatibility Complex (MHC) molecules class I and II, protection against Natural Killer (NK) cells function, inhibition of host-produced cytokines and neutralization of host antibodies by binding to CMV-produced Fc receptors.[11-13]

The critical host defense against CMV is mediated by MHC-restricted, virus-specific, cytotoxic T-cells.[14] In immunocompromised patients the degree of impairment of T-cell function is usually related to the severity of CMV disease, while humoral immunity is usually adequate with production of anti-CMV antibodies.[4,15]

Patients with IBD are immunosuppressed due to medications, poor nutrition and impairment of NK cells function.[16-18] CMV reactivation may be triggered by TNF-a, catecholamines and proinflammatory prostaglandins.[19] During active IBD, local expression of a wide variety of cytokines including TNF-a, IFN-γ, and IL-2 is induced, with activation of transcription factors (NF-Kb) and production of chemokines and adhesion molecules that recruit circulating monocytes and dendritic cells in the area of inflammation. There, these cells differentiate into permissive cells supporting active replication of the virus. Endothelial cells can also serve as permissive cells as they have been shown to stimulate T-cells to produce IL-2 and to proliferate. Activated T-cells consequently produce TNF-a and IFN-γ and perpetuate the inflammation process causing more injury to the gut.[20,21] These data indicate that CMV has tropism for sites of inflammation and confirm the results of clinical studies that have shown that in IBD patients with active colitis CMV is usually found in the diseased region of the gut. They also indicate that CMV replication is the result of CMV reactivation rather than primary infection.[22,23].

The role of immune suppression, especially steroids, in the reactivation of CMV in patients with IBD, remains controversial. Theoretically, all latently infected IBD patients receiving immunosuppresives frequently produce infectious virus and don't allow antiviral immune responses to develop. Reactivation of the virus was induced in animal models using whole-body irradiation, cytotoxic drugs and depletion of lymphoid cells by antibodies, but this kind of immune suppression is not used in IBD. In two recent clinical studies, corticosteroids did not seem to be a major factor in the development of CMV infection and disease in IBD patients.[24,25]

CMV AND IBD: A VICIOUS CIRCLE OF CAUSE AND EFFECT?

CMV infection must be distinguished from **CMV disease**. CMV infection refers to carriage of CMV genome and can be active or latent. In active infection there is detectable viral replication in blood or end-organs. CMV disease is the presence of CMV infection *and* clinical signs and symptoms such as fever, leukopenia or end-organ damage.

Early studies indicated that CMV infection can lead to subsequent development of IBD.[26,27] This may be possible in some susceptible patients but in most recent reports CMV colitis occured primarily in patients with pre-existing IBD.[16] There have also been reports of colitis patients with evidence of active CMV infection who improved with steroids and did not require antivirals,[28] as well as patients with active colonic CMV infection without active colitis.[29] In these cases CMV seems to behave like an innocent bystander.

As it has been mentioned before, CMV has the propensity to infect rapidly growing tissue, especially endothelial cells in granulation tissue, (22), (30), and (31). Some studies suggested that CMV represents an opportunistic infection in severely inflamed mucosa rather than a primary pathogen.[22]

The most widely held theory is that CMV infects areas of active IBD and causes further tissue injury aggravating the severity of the underlying IBD. In the majority of case-reports,[32-35] patients with severe attacks of IBD and CMV infection had significant morbidity (toxic megacolon 15%, colectomy up to 62%) and mortality (up to 44%). Antiviral treatment prevented colectomy in some but not all of the patients. In more recent series the mortality rate of CMV colitis in UC were 30% and the rate of surgery 40%.[17] CMV disease seems to be less frequent in patients with Crohn's Disease (CD) compared to patients with Ulcerative Colitis (UC).[36] The prevalence of CMV infection in steroid-refractory IBD patients, in 2 studies, was 36% and 33%, perspectively (37) – (28).

In our prospective study of 96 consecutive patients with severe, refractory UC, who underwent colectomy for their disease, two patients had serological markers of active CMV infection and were treated with antivirals, but this did not prevent colectomy. CMV was identified in the colectomy specimen of another patient without additional markers of active infection.[38] Another prospective study of unselected patients with active IBD found evidence of active CMV infection in 3/64 of patients and only one patient benefited from antiviral therapy.[39] This is in accordance with previ-

ous retrospective studies[40] that found a 4,6% prevalence of CMV enterocolitis in patients operated for UC and 0,53% - 3,4% in unselected patients with IBD.[16,41]

The true prevalence and role of CMV in patients with IBD has yet to be defined. Data of clinical trials are inconclusive or controversial, and this may be due to a number of reasons: retrospective versus prospective studies, patient selection bias (unselected versus patients with severe or steroid-refractory disease), different methods to diagnose active CMV infection and disease (see below). Some patients respond to antiviral treatment and withdrawal of immunosuppression, while in others the underlying IBD runs its course independently of the presence of CMV. It is still a challenge to differentiate the innocent bystanders from the pathogenic strains of CMV but one should keep in mind that the possible cost of delaying antiviral therapy is colectomy or even death. From this point of view most patients are finally treated with antivirals.

DIAGNOSIS OF CMV INFECTION AND DISEASE

Diagnosis of CMV is based on serology, histology, CMV culture, CMV antigen testing, CMV DNA testing and endoscopy.

CMV serology

Detection of CMV – IgM antibodies has 100% sensitivity and 99% specificity for documenting recent infection.[1] The level of IgM usually drops within 2-3 months after acute infection and is often undetectable at 12 months. In immunocompromised patients with active CMV infection, IgM may not be detected at all.[42] Detection of at least a 4-fold increase in titer of CMV - IgG specific antibodies, 2 – 4 weeks apart, indicates acute infection.[3] This is a limitation in patients evaluated for acute severe colitis because prior IgG levels are usually not available.

CMV histology

Histology has been considered the "gold-standard" for the diagnosis of CMV organ disease (eg. CMV colitis). Characteristic cytomegalic cells are seen in Hematoxylin-Eosine (H&E) staining of colonic biopsy specimens. These cells contain large nuclear inclusions sometimes surrounded by a clear halo (an "owl's eye" appearance) and smaller amphophilic cytoplasmic inclusions (FIGURE 1: CYTOMEGALIC CELLS WITH INCLUSIONS). The cells can be found in the epithelium, the lamina propria or in the endothelium. Many studies have confirmed the specificity of cytomegalic cells for diagnosing CMV[22] but sometimes these cells may be difficult to find, requiring great time and effort by the pathologist.[43] Identifying these cells is also a function of the number of biopsy specimens examined, so sampling error may reduce the sensitivity of histology (10% - 87%).[44] Immunohistochemistry (IHC) with monoclonal antibodies against CMV antigen increases the diagnostic yield compared with the classical H&E staining and has a sensitivity of approximately 93%.[44]

CMV Culture

CMV culture can be performed on blood, tissue, urine, saliva. Blood culture has a sensitivity of 45% - 78% and very high specificity for detecting disease and is more strongly associated with disease than detection in urine or saliva.[45] Culture is time-consuming (1-3 weeks) and has lower sensitivity than newer techniques (Antigen testing, PCR). Shell vial culture, a rapid viral culture, has better sensitivity but is not widely used.

CMV Antigen testing

The test detects a structural protein in leucocytes using specific monoclonal antibodies.[3] It is applied on blood or cerebrospinal fluid, has better sensitivity and the same specificity as CMV culture but is only semiquantitative, so report of results can be subjective.

CMV DNA test

PCR or hybrid capture is used to detect viral DNA in blood, plasma, leucocytes, tissue or stool. These tests can be qualitative or quantitative. Their sensitivity ranges from 64% to 100% and their specificity from 40% to 92%.[3,46] Higher CMV viral loads correlate with symptomatic disease[47] and may be useful in monitoring response to therapy, but there are some limitations especially with quantitative PCR: different blood compartments have different concentrations of CMV DNA, there are not defined cut-off values for determining CMV disease and there is lack of standardization of the process.[1] CMV DNA testing has greater than 80% concordance with CMV antigen test results.[48] Kandiel et al propose that a CMV DNA cut-off level of 25.000 copies/ mL in whole blood is a reasonable level for initiating antiviral treatment (1). A sensitive PCR essay was recently described for the detection of CMV DNA in faeces.[49]

Endoscopy

Endoscopic findings in CMV colitis can be identical to those of IBD colitis and include erythema, exudates, oedema, erosions, ulcerations, pseudotumors or even features of pseudomembranous colitis.[5,50] When biopsies are taken from mucosal lesions, especially the center of ulcer beds, the diagnostic yield of endoscopy is increased.[5] CMV may

exclusively affect the right colon[51] but may also be found in macroscopically normal-appearing mucosa.[16]

In summary, although there are several methods for diagnosing CMV infection it is not yet clear which patients have actually CMV disease that will respond to antiviral therapy. Hommes et al. proposed in a recent review (21) a schematic representation of CMV activation and replication during active IBD, describing 3 phases of CMV action in IBD: the *initiation phase* (IgG positive, PCR negative, Biopsy negative), the *reactivation phase* (IgG positive, PCR negative, Biopsy positive) during which reactivation of CMV is restricted to the inflamed bowel section and the *consolidation* phase (IgG positive, PCR positive, Biopsy positive) during which active replication takes place in endothelial cells and this possibly aggravates the inflammatory response. Viral particles are shed into the circulation as well as the lumen of the gut. From a clinical point of view, it is suggested that IBD patients with refractoriness to treatment, those with systemic symptoms and signs (high fever, dyspnea, lymphadenopathy, splenomegaly, leukopenia), those with worsening of clinical symptoms after an initial improvement while on immunosuppression, when other pathogens have been ruled out they should be tested for CMV and be offered antiviral treatment.[16] Combined detection of CMV in blood and on histological examination may indicate more severe disease course as well as possible benefit from treatment.[28] However, some patients may simply respond to steroids and other immunosuppressives or may undergo colectomy despite efficient antiviral treatment.

TREATMENT OF CMV COLITIS

Ganciclovir is a nucleoside analog structurally similar to acyclovir that inhibits viral DNA polymerase. It is given at a dose of 5mg/Kg intravenously every 12 hours for a period of 2-3 weeks. After 3-5 days of intravenous administration, the patient can be switched to oral ganciclovir. The most frequent side effects of ganciclovir are neutropenia, thrombocytopenia, rash, hypotension, nausea, vomiting and headache.[43]

In cases of intolerance or lack of efficacy, *foscarnet* is the alternative choice. Foscarnet is an inhibitor of DNA polymerases of all herpes viruses and unlike ganciclovir does not require phosphorylation to be activated. It is administered intravenously at a dose of 90mg/Kg every 12 hours for 2-3 weeks. Toxicity of foscarnet includes renal insufficiency, central nervous system side effects, hypomagnesaemia, hypocalcaemia, hypophosphataemia and anaemia.[4]

In a recent review, Kandiel et al propose that patients admitted with severe flares of IBD, should be started on parenteral steroids and if there is no improvement after 2-3 days, they should undergo sigmoidoscopy with biopsies and blood testing (CMV DNA) to search for CMV. If these tests are positive and the patient is steroid refractory after 5-7 days of treatment, ganciclovir should be administered. If the patient's clinical condition is declining prior to 5 days of intravenous steroids and tests are positive for CMV, ganciclovir should be started earlier.[1]

Colitis remission rates after antiviral treatment in IBD patients with CMV infection range from 67% to 100% (28), (37), (16), (41). Relapse is possible but data are lacking in IBD patients. Improvement of colitis symptoms coincides with resolution of detectable CMV infection.

CONCLUSIONS

The role of CMV infection in patients with IBD has not yet been clearly defined. In the majority of published studies CMV is considered to act like a true pathogen, complicating the course of IBD and adding to morbidity, while in others CMV does not seem to alter the natural course of the underlying IBD. CMV infection does not always mean CMV disease. Detection of CMV DNA in blood is the most sensitive diagnostic test available, but due to lack of optimal cut-off values to determine CMV disease, it has low specificity. Histology remains a cornerstone in the diagnosis of CMV colitis. CMV histological disease or antigenemia are not always associated with steroid-resistance.

Prospective studies are needed to find the true prevalence of CMV in IBD patients and to determine the subgroups of patients that will benefit from specific treatment. Ganciclovir is the first-line treatment for CMV colitis and is given for 2-3 weeks. Resolution of detectable CMV infection after antiviral therapy has been associated with clinical improvement and prevention of colectomy in some but not all of the patients with severe or refractory IBD.

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