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TOPIC HIGHLIGHT

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Cytomegalovirus and inflammatory bowel disease: Is there a link?

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Abstract

The objective of this report is to give an overall view of the epidemiological, clinical, diagnostic and therapeutic features of Cytomegalovirus (CMV) infection in inflammatory bowel disease (IBD). A review of published reports on this topic was carried out, with particular attention paid to the selection of patients included in studies and the diagnostic methods employed. CMV is frequently associated with IBD. In some cases, CMV infection is associated with a poor outcome but it is not clear which patients are more likely to be affected and in which stage of the disease. The use of anti-viral therapy in IBD is controversial and an empirical study with controls is needed. The natural history of CMV infection related to the development and treatment of IBD has not been clarified but it is important to take it in consideration because of the possibility of viral persistence in the immunocompromised host and viral interaction with the immune system.

Key words: Cytomegalovirus; Inflammatory bowel disease; Outcome

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INTRODUCTION

Cytomegalovirus (CMV) is a member of the Herpesviridae family, which includes Epstein -Barr virus (EBV), Herpes Simplex virus tipes1 and 2 (HSV-1,2), Varicella- Zoster virus, and Human Herpes virus types 6 and 7 (HHV-6,7). Similar to infection with other viruses in the family, primary infection with CMV results in the establishment of a persistent or latent infection, due to the ability of the virus to remain integrated in the DNA of host cells. The sign of a viral infection is a cytopathic effect shown by the presence of large nuclear and cytoplasmic inclusions, represented by aggregates of replicating CMV nucleoprotein cores. To avoid recognition and destruction by CD8+T lymphocytes, the virus develops the ability to evade the immune system by several mechanisms. CMV produces some proteins, such as US2, US3 and US11, that inhibit the presentation of viral antigens to T cells, blocking the class I MHC in the endoplasmic reticulum or in the cytosol. It also produces homologues to class I MHC proteins and may compete for binding and presentation of viral antigens. Once the viral DNA remains undisturbed in the infected cells, subsequent reactivation can occur in response to several stimuli, such as immunosuppressant therapy or chemotherapy[1]. The down-regulation of the cell surface markers acts on interferon-alpha/beta dependent responses by affecting several levels of IFN signal transduction and a transcription activation pathway. CMV infection leads to the activation of Nuclear Factor kappa B (NF-κB) and its translocation to the nucleus, promoting the expression of cytokines, chemokines and cellular adhesion molecules. These mechanisms are also present in inflammatory bowel disease (IBD) where there is activation of several pro-inflammatory cytokines (such as IFN-gamma), the transcription of which is regulated through nuclear transcription factors (such as Nuclear Factor kappa B) and through a signal transducer and activator of transcription (STAT family).

CMV AND IBD

The role of CMV in IBD is reviewed considering the following issues: diagnostic methods to detect the virus, prevalence of CMV in IBD according to patient selection, clinical characteristics, outcome for patients with IBD and superimposed CMV infection, role of antiviral therapy and natural history of CMV in IBD patients.

Diagnostic method

Results differ based on diagnostic method. Serology is

useful in checking for previous virus exposure and for identifying patients at risk. Since gross appearance is non-specific, a diagnosis is based on the histopathological identification of viral-infected cells in biopsied tissues, using appropriate staining Haematoxylin and Eosin (HE), Immunohistochemistry (ICH), by a dedicated pathologist. Cytomegalic cells have been revealed that are 2-or 4 fold larger (25-35 μm) than surrounding cells, containing a basophilic intranuclear inclusion (8-10 μm) that is eccentrically placed and is sometimes surrounded by a clear halo, giving it an "owl's eye" appearance. These cells also show a thickened nuclear membrane, frequently associated with smaller granular intracytoplasmatic inclusions.

Intranuclear inclusions were observed in epithelial, endothelial, stromal and smooth muscle cells.

In the gastrointestinal tract, "atypical" inclusions were also found[2]. Biopsies taken from the mucosa near or within the ulcer provided greater detection of the virus. IHC is more sensitive than HE.

The CMV pp65-antigenemia assay as Polymerase Chain Reaction (PCR) DNA amplification is a sensitive, specific and rapid method for the early diagnosis of CMV infection based on immunocytochemical detection of a virus protein (pp65) in the nuclei of peripheral blood polymorphonuclear leukocytes. The advantage of this method is an early and rapid response possibility but this technique does not permit the distinction between an asymptomatic infection and an active disease. Viral load quantification may permit the observation of the infection course. PCR is a very sensitive test for the detection of CMV. In solid organ transplant patients, CMV detection can persist for months using qualitative PCR assays, despite effective antiviral therapy. Therefore, the precise amount of CMV DNA may be better determined with virological monitoring. In addition to studies using quantitative PCR in renal transplant recipients, studies on peripheral blood leukocytes suggest a cut-off of > 1000 copies/100 000 leukocytes, indicative of the development of symptomatic CMV infection after transplant[3]. A slow or absent decline in CMV DNA after the beginning of ganciclovir therapy could be an early indicator of drug resistance[4]. A PCR positive assay after ganciclovir therapy, irrespective of resolution of clinical signs and symptoms, might be an indicator that therapy should be continued[5]. Mendez *et al*[6] analyzed the early diagnosis of CMV infection using four sets of primers that were able to amplify different regions of the CMV genome. The authors demonstrated that a specific primer directed to the HIND III-X fragment region is the most sensitive primer for the early detection of CMV DNA in peripheral blood leukocytes (PBLs), providing detection 17 d before the onset of the symptoms. *In situ* hybridization and qualitative PCR in colonic biopsies seem to offer the greatest accuracy[7-9] in detecting the virus.

Quantitative PCR (viral-load) in cells from the colon[10] showed a high positive-predictive value for detecting disease and for monitoring therapeutic response. A qualitative and quantitative PCR assay for CMV DNA has been performed on human faecal specimens from immunocompromised patients[11,12].

Patient selection method

The reports on prevalence of CMV are extremely varied in regard to patient selection methodology. There is no study that gives an overall prevalence of CMV in IBD patients. Most of the studies have been carried out using a selected patient group (severe colitis, steroid-resistant colitis, urgent colectomy for colitis, patients with active disease) and different diagnostic methods were used as well for different patient group (e.g., histology, ICH, antigenemia, electron microscopy, *in situ* hybridization). Prevalence has been reported to range from 0.5 to 100% (Table 1).

Severe colitis: A group in Italy[13] studied the prevalence of CMV using rectal biopsies and HE staining, immunoperoxidase staining for CMV antigens and antigenemia pp65 (a buffy-coat preparation) on the peripheral leukocytes. The study was performed prospectively in a consecutive series of hospital admissions without waiting for a possible response to conventional therapy, in order to determine the prevalence of CMV in severe consecutive episodes of colitis. The results showed virus prevalence overall in patients with active IBD (21%). On the basis of these results the authors suggested performing a flexible proctoscopy (without air insufflation) with rectal biopsies in patients hospitalized for severe colitis flare-up, together with antigenemia on peripheral leukocytes, to determine whether the simultaneous detection of virus both in the colon mucosa and in the peripheral blood may be interpreted as the pathogenic cause.

Khishore[14] used serology, HE and PCR for CMV DNA to study a heterogeneous population, including patients with severe colitis. Thirty-six patients had severe colitis, with 8 patients (22%) shown to be CMV positive based on colonic biopsies. Moreover, the author identified clinical variables associated with a higher risk of CMV infection in IBD. These factors included female gender, pancolonic disease with active inflammation at histology, and azathioprine treatment. Using antigenemia, Wada[15] reported a prevalence of 34%, while Vega[16] reported a result of 3% in a retrospective study that used HE and ICH results.

Severe steroid-resistant colitis: Cottone *et al*[17] showed that the prevalence of CMV, studied using HE and ICH and antigenemia, was 36%. Kambham[18] obtained a similar result, using HE and ICH on colonoscopic biopsy specimens, detecting CMV in 4 of 15 steroid-resistant patients (26%). Pofelsky[19], using PCR, showed a higher prevalence (60%) compared to previous reports, and an overall prevalence of viral DNA in the colon of 38%. However, there was a poor correlation between colonic and peripheral viral load which suggests a role of local inflammation in the colon. The genotype detected was gB1, which possibly has a particular colonic tropism. On the contrary, Papadakis[20], in a retrospective study on 1895 patients, showed a low rate of 0.5% prevalence. He suggested a pathogen role for the virus based on the prompt response and clinical improvement found with antiviral treatment.

Urgent colectomy for colitis: These patients represent a subgroup in which IBD is more severe and, therefore, a higher prevalence of CMV is expected. Six studies

Table 1 Prevalence data according to population and methodology of the study

Author (year of publication)	Population characteristics	Diagnostic assay	Study type	Prevalence
Criscuoli (2004)	42 pts with severe colitis	HE-ICH on rectal biopsy + antigenemia pp65	prospective	21%
Kishore (2004)	63 pts with severe colitis (36 steroid resistant)	Serology-HE and qualitative PCR	prospective	16% 22%
Wada (2003)	47 pts with severe colitis	Antigenemia	prospective	34%
de Saussure (2004)	64 pts with active colitis	Serology-viremia-antigenemia- HE-ICH	prospective	1.5%-6%
Vega (1999)	267 active colitis	HE-ICH	retrospective	3%
Pofelski (2005)	48 pts severe colitis	Quantitative PCR on colonic biopsies	retrospective/ prospective	38% 60%
Kambham (2004)	40 pts steroid resistant (25 operated on for colectomy)	HE-ICH	retrospective	Overall 25% Operated on pts 24%
Papadakis (2001)	1895 steroid resistant pts	HE	retrospective	0.5%
Cottone (2001)	19 Steroid resistant pts	HE-ICH on rectal biopsy + antigenemia pp65	prospective	36%
Maconi (2005)	77 pts operated on for colectomy	HE-ICH on surgical specimen	prospective	22% overall 27% steroid resistant
Takahashi (2004)	69 surgical specimen of IBD pts	HE-ICH on biopsy and surgical specimen	retrospective	11.5%
Alcalà (2000)	39 pts operated on for colectomy	HE + ICH	retrospective	18%
Eire-Brook (1986)	26 pts operated on for colectomy	Light and electron microscopy- ICH	retrospective	11.5%
Cooper (1977)	46 pts operated on for colectomy	HE	retrospective	13%
Rahbar (2003)	23 pts with IBD (13 UC-10 CD)	ICH+ *in situ* hybridization	prospective	92/100%
Wakefield (1992)	50 pts with IBD (29 CD-21 UC)	qualitative PCR	prospective	66/81%

(two older studies using HE and four recent studies using ICH) have been reported on surgical specimens from patients with colitis who were not responsive to medical therapy[6,21-25]. These studies showed an overall prevalence (11.5%-27%) that is similar to reports in other studies. In the subgroup of steroid-resistant patients, Kambham and Maconi reported a similar prevalence of 25%-27%.

Patients with active disease: Rahbar[7] has estimated virus prevalence in intestinal biopsies from IBD patients both using ICH and *in situ* hybridisation. The latter showed detection in over 90% of ulcerative colitis (UC) patients, and in 100% of patients with Crohn's disease (CD). Since the presence of the virus does not necessarily mean active infection, the authors looked at viral replication by CMVea (early antigen) and CMVla (late antigen) by immunohistochemistry, and they obtained a similar result (85% *vs* 100% for UC *vs* CD, respectively) using CMVea.

Other authors have used an immunoperoxidase technique, using a monoclonal antibody against CMV, to demonstrate early CMV infection in cells of colonic specimens in cases showing few cytopathic cells at histological examination. On the contrary, the DNA *in situ* hybridization technique was less helpful in establishing a diagnosis of early infection[8].

A study that used PCR showed positive detection in about 66% of CD patients, 81% in UC patients, and 29% in controls[9].

CMV and acquired immunodeficiency syndromes or immunosuppressive therapy

The gastrointestinal system is a common site of CMV infection, especially in AIDS patients. Any tract can be affected, with preference to oesophagus and colonic mucosa (especially right colon) rather than ileum, considering the pouch mucosa are morphologically similar to colon mucosa[26]. The syndrome begins with a watery diarrhoea due to an inflammatory response, that quickly turns into bloody diarrhoea due to ulcerative changes in the colonic mucosa. The endothelial cells are a site of CMV detection both in a latent state and active replication state[27]. This explains why CMV vasculitis is a common manifestation of viral disease localized in different organs (bowel, retina, brain) and that vascular damage is responsible for thrombosis[28] and atherosclerosis. In the bowel, vasculitis may cause ischemia and transmural necrosis with an increased risk of toxic megacolon and perforation.

A recent meta-analysis[29] on the outcome of CMV colitis in an immunocompetent host reviewed 44 cases (of which 16 had coexisting immune-modulating morbidities such as diabetes, malignancy or renal failure). The conclusion of this analysis was that CMV colitis is found more frequently in elderly patients in whom the disease had a severe course and where there was a high mortality rate. On the contrary, younger patients (< 55 years) had a significant rate of spontaneous recovery, with 42% of patients diagnosed with subsequent IBD after resolution of CMV infection. Ng[30] carried out a retrospective analysis on patients without apparent causes for immunodeficiency but who were mainly elderly and were admitted to hospital with bloody diarrhoea. The mortality rate reported was 40% which was thought to be related to co-morbidity

IBD and superimposed CMV infection: When the syndrome appears with a pre-existing inflammatory disease, IBD may be more aggressive. The clinical outcome of IBD with superimposed CMV is not well understood. The first report about the possible role of cytomegalovirus in IBD dates to 1961 when Powell[31] described a case of ulcerative colitis and cytomegalic inclusion disease. After many sporadic reports over the last decade, the topic has

regained attention due to more frequent publications of case-reports or small series studies in which the virus provided a worsening prognosis influence, sometimes promoting disease initiation or otherwise acting as a bystander[9].

The coincidental detection of primary CMV infection at the first appearance of IBD is reported in some case-reports[32,33], underlining the ability of CMV proteins to enhance pro-inflammatory cytokines that are able to maintain a local colonic inflammation with an immune response. In other conditions the latent virus could exacerbate[34-36] pre-existing colitis after immunosuppressive situations. Experimental studies have shown that highly proliferating cells, like those in the granulation tissue, around inflammation or in ulcer depth, are easily objects of CMV infection. In this situation the virus could reach the mucosa by monocytes and then colonize the mucosa, acquiring particular affinity for the inflamed mucosa.

This is evidenced by the fact that super-infection with pre-existing colitis causes worsening of symptoms, with a severe course of disease that rarely strikes suddenly, with high prevalence of toxic megacolon and surgical intervention[10,11,33]. In this case, since steroids or immunosuppressive therapy can lead to the flare-up of CMV infection, the outcome for patients with an acute attack is likely to be poor. A case of disseminated (whole gastrointestinal tract, skin and central nervous system) CMV infection has been reported in Crohn's disease after anti-TNF therapy[37]. The mechanism of dissemination is likely to be related to vascular damage that allows a viral circulation within the shed endothelial cells.

The literature contains many case reports of CMV infection in steroid-naïve patients or immunocompetent hosts with IBD. Rachima[38] reported two cases of CMV infection diagnosed by high titres of IgM antibodies to CMV (solid-phase enzyme immunoassay) but without histological detection on colonic biopsies. A high prevalence of CMV IgG antibody in patients with ulcerative colitis, compared to normal controls and to patients with active Crohn's disease, permits the hypothesis of a possible role for the virus to exacerbate the inflammatory disease and therefore its pathogenicity. Although clinically significant CMV infection occurs in individuals with acquired immunodeficiency syndrome or due to immunosuppressive therapy, the same inflammatory disease could be considered a booster of viral infection with local factors, even without previous immunosuppressive therapy.

Antiviral treatment: A review of the literature does not affirm that antiviral treatment is mandatory when CMV is detected in biopsy specimens or in peripheral blood, however, some authors are favourable to the use of antiviral treatment[2-9]. Eddleston[39] proposes the consideration of antiviral therapy in immunocompetent patients with multiple organ disease, taking into consideration the poor prognosis with widespread CMV disease. Pfau considers Ganciclovir as a beneficial treatment that significantly decreases the mortality rate and the request for surgery. Eire-Brook considers CMV as a bystander and refuses to allow any antiviral treatment during an acute flare-up of IBD.

It is difficult to draw conclusions about the role of antiviral therapy on the basis of the available evidence. Severe steroid-resistant colitis is the setting in which the role of antiviral therapy should mainly be considered. According to some reports, antiviral therapy treatment was useful, whereas in others it was useless. A controlled study is necessary to answer this question, however a large number of patients would be needed for such a trial and it would therefore be necessary to involve many centres using homogeneous diagnostic methods.

Natural history of CMV infection: No studies have reported on the natural history of CMV infection. It is not known whether the virus remains in the colon after an acute attack or spontaneously disappears. It is also not known whether there is a high incidence of relapse when the virus remains in the colon. Furthermore, it is not clear whether the virus plays a role in risk for cancer and lymphoma of IBD. For many years, the involvement of Human Herpes Virus (EBV, HHV-8) has been well known in the pathogenesis of some tumours, while there is little knowledge about the potential oncogenetic role of CMV.

A study performed using ICH, *in situ* hybridisation and PCR on pathological specimens of colorectal polyps, adeno-carcinomas and normal mucosa, reported an immunoreactivity of at least 80% in the colorectal polyps and carcinoma both for an immediate early gene product (IE1-72) and for a delayed early gene product (pp65), and acid nucleics. Moreover, detected cyclo-oxigenase -2 in the same site of virus detection may play an important oncogenetic role in the development of human colorectal cancer. The virus could activate cellular proto-oncogenes, kinases and transcription factors implicated in tumour-cell survival pathways[40].

On the contrary, a more recent study[41] using similar methods did not find nuclear immunoreactivity for CMV proteins and DNA, but found focal cytoplasmic positivity in normal colonic mucosa as well, demonstrating no evidence of association. Adani[42] reported a case of severe ulcerative colitis with superimposed colonic CMV infection without peripheral involvement that was associated with colorectal high-grade B-cell non Hodgkin's lymphoma (MALT type). More frequent association is reported between CMV pneumonitis and non-Hodgkin's lymphoma. Both cases were associated with previous immunosuppressive treatment, which is a well-known promoting factor.

CONCLUSION

In general the role of CMV in IBD remains unclear. On the basis of the current evidence,in our opinion, in active severe IBD CMV, if is detected in the colonic biopsies together at the presence of antigenemia, should be treated with antiviral drugs. There is certainly a pathogenic role of CMV in immunosuppressed transplant patients and in patients with AIDS where treatment is mandatory.

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