

Cytomegalovirus infection in the gastrointestinal tract

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Introduction

Cytomegalovirus (CMV) infection is ubiquitous, with most infections being subclinical and asymptomatic. Within the spectrum of acquired CMV infection, CMV mononucleosis, pneumonitis, and hepatitis are the most common manifestations.¹ Gastrointestinal CMV infection occurs in two distinct clinical settings: (i) immunocompetent host; and (ii) immunocompromised patients. The purpose of this review is to analyse CMV infection of the gastrointestinal tract within the context of these two scenarios, to highlight the clinico-pathological abnormalities encountered, and to discuss briefly the diagnostic modalities available.

CMV infection in the immunocompetent

The reasons for CMV infection in apparently immunocompetent people are difficult to explain conclusively.^{2,3} It has been said that in the absence of immunosuppression CMV infections are asymptomatic.⁴ Infection has been categorised as primary when CMV infection of a seronegative person with exogenous virus occurs. The suggested methods by which CMV evades host defences include the induction of Fc receptors and the binding of β_2 microglobulin by CMV infected cells for protection against humoral immune responses.⁴⁻⁶ An important factor in the pathogenesis and expression of symptomatic disease is whether CMV infection arises from an exogenous source of virus or from reactivation of latent endogenous virus.⁷ The relatively low pathogenicity of the virus in normal subjects is testimony to the successful outcome of the interaction between the host's immune system and the virus.⁷ Although CMV frequently infects the salivary gland and the kidney, disease at these sites is not often seen.⁴ CMV infection of the liver, retina, or gut is considered to be associated with pathology in all groups in which it is observed in these sites.⁴ It has been suggested that the virus itself exerts a direct immunosuppressive action, triggering alterations in immune reactivity through a direct interaction with host lymphoid cells.⁷ Local trauma sustained during anal intercourse in two of the immunocompetent cases, described by Surawicz and Myerson,² may have a causative role. CMV infection may thus have been acquired in a similar manner to other sexually transmitted diseases, with mucosal damage providing a repository for infection.

The severity of the illness in the case reported by Blair *et al.*,³ in the absence of any

definable predisposing factor, with a rising complement fixation titre and response to antiviral treatment, indicates that CMV acted as a primary pathogen. Other reports of primary CMV colitis⁸⁻¹² have been in older patients and a degree of immunosuppression is difficult to exclude entirely. Furthermore, some of the patients described died from overwhelming disease, implying some dysfunction of the immune system. All three cases reported by Surawicz and Myerson² recovered from their episodes of CMV colitis and remained well for follow up periods of two to six years. These cases indicate that CMV was the cause of the colitis, and that the immunocompetent hosts then recovered without sequelae. Recovery was also obtained in the patient described by Blair *et al.*,³ despite the patient being severely ill with associated retinitis and hepatitis. None of the recognised and established risk factors for decreased immune function was operative in this patient. A similar clinical picture of previous good health was noted in two of three patients with CMV gastritis described by Andrade *et al.*¹³ One of the patients had received chemotherapy for Hodgkin's disease which would have accounted for depressed immunity. However, in many of the cases of primary CMV infection in so-called immunocompetent hosts, neither serological evidence (in the form of CMV viraemia) nor response to specific anti-CMV treatment is provided. The main basis for classifying these lesions as primary is because of previous "good health". Indeed, many may not truly be primary CMV infections in immunocompetent patients. Transient decreases in immunity may have been subclinical and therefore a definite predisposing condition is not readily identifiable.

Thus, CMV inducing infection in the gastrointestinal tract in the immunocompetent patient is probably a real, albeit rare, phenomenon; presentation ranges from diarrhoea, malaise, and emaciation to acute colitis. Its true incidence is difficult to ascertain, especially as many of the reported cases lack serological evidence and seem to have been self-limiting.

CMV as a secondary (opportunistic) pathogen in patients with pre-existing bowel disease

Several studies have concluded that CMV is a secondary pathogen that is superimposed on chronic, pre-existing disease in the gastrointestinal tract. Lack of CMV inclusions within

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intact endothelial cells, despite their presence in the granulation tissue of ulcers or perforations, has been construed as being consistent with "superinfection" of a damaged colon. This superinfection also results in subsequent exacerbations of the underlying primary bowel pathology.¹⁴ Even in the setting of established pre-existing idiopathic inflammatory bowel disease the presence of CMV inclusions has elicited opposing views. In an analysis of 26 patients with idiopathic inflammatory bowel disease Eyre-Brook and Dundas¹⁵ identified three patients with CMV infection. None had an associated toxic megacolon. CMV infection was not identified in a further three patients who had toxic megacolon. They concluded that CMV infection had no influence on the course of the colitis. A contrary view has also been put forward.¹⁶ An exacerbation of idiopathic inflammatory bowel disease was associated with the appearance of CMV inclusions in the colon. One of the patients in this study was being treated with steroids; stopping treatment resulted in substantial improvement.¹⁶ CMV DNA has been shown in resection and biopsy specimens from patients with ulcerative colitis and Crohn's disease.¹⁷ A higher level was detected in the former than in cases with Crohn's disease and normal control cases. The coexistence of high concentrations of CMV DNA with human herpes virus 6 and Epstein-Barr virus (EBV) DNA has led to the suggestion that these viruses may have a synergistic role in the pathogenesis of ulcerative colitis.¹⁷

Others have concluded that CMV superinfection is associated with a high mortality, frequent association with toxic megacolon, and a clinical course sufficiently severe to warrant surgery.¹⁸ Several cases of CMV vasculitis have been described in association with chronic ulcerative colitis.¹⁹⁻²³ Thus, there is overwhelming evidence to suggest that CMV is a pathogen of an already diseased bowel and can be responsible for exacerbations in the course of the disease as well as considerable morbidity.

CMV as an opportunistic pathogen in the immunocompromised

The two main clinical scenarios in which CMV acts as an opportunistic pathogen causing gastrointestinal manifestations in the immunocompromised are: (i) AIDS; and (ii) transplantation. Other causes of depressed immunity, such as iatrogenic, inherited immune deficiencies, can also result in CMV infections in the bowel.

Several reports have been published of CMV infection in the gastrointestinal tract with protean manifestations in patients with AIDS.²⁴⁻³¹ Immunosuppression once again underpins the occurrence of CMV infections of the gut in renal transplant recipients,³²⁻³⁵ those with chronic renal failure,³⁶⁻³⁷ bone marrow transplant recipients,³⁸ and liver transplant recipients.³⁹ CMV has the potential to cause infections in the gastrointestinal tract

should a patient become immunocompromised even while receiving therapeutic doses of prednisolone for the treatment of arthritis⁴⁰ or for chronic obstructive pulmonary disease.⁴¹

CMV colitis was the index diagnosis for AIDS in 11 of 44 (25%) patients analysed by Dieterich and Rahmin.³¹ Acute CMV ileocolitis is said to be the most common indication for emergency abdominal surgery in homosexuals with AIDS.⁴² Seven of 11 patients had CMV ileocolitis and CMV ileocolonic pathology was directly responsible for 70% of the deaths in patients with AIDS who underwent emergency exploratory laparotomy.⁴³ In the transplantation setting CMV infection is very common but exact figures of CMV infection alone in the gastrointestinal tract are not readily available. Bleeding caecal ulcers due to CMV have been seen in nine out of 12 renal transplant recipients with CMV infection.⁴⁴

A correct diagnosis is vital for appropriate treatment. Where there is doubt, biopsy with or without other diagnostic tests should help to resolve the dilemma.

Pathological lesions caused by CMV infection of the gastrointestinal tract

CMV can cause lesions throughout the body, from the mouth to the anus.⁴⁵⁻⁵⁸ The lesions vary but ulcerative lesions causing mainly a colitis, are the most common.

Ulcerative lesions These may take the form of punctate superficial erosions to deep penetrating ulcers. Segmental ulceration, thus mimicking Crohn's disease, has also been reported.²⁶ Deep linear ulcers within the oesophagus have been ascribed to CMV infection.⁴⁶

Perforations These can occur in any part of the gastrointestinal tract,^{43 50 53 54} but usually occur between the distal ileum and the splenic flexure.⁵⁴

Haemorrhagic proctocolitis An active colitic picture no different from that seen with other causes of proctocolitis can be obtained with CMV infection.^{36 43}

Inflammatory pseudotumour A discrete CMV induced inflammatory pseudotumour causing obstruction in the ileo-caecal region has been described.⁵⁶

Lesions mimicking neoplasia A stenosing, ulcerative CMV infection of the colon resembled a neoplasm clinically, macroscopically, and radiologically.⁵⁷ A case of gastric antral obstruction due to a mass caused by CMV infection has also been described.⁵⁸

Appendicitis Florid CMV inflammation of the appendix with a focus of perforation has been seen.^{59 60}

Toxic megacolon Not only has CMV been implicated in toxic megacolon in patients with pre-existing idiopathic inflammatory bowel disease,¹⁸ but a case of toxic megacolon primarily due to CMV infection, with florid CMV vasculitis, has also been described.⁴¹

Solitary mucosal ulcer A solitary ulcer due to CMV was noted in the ascending colon.⁴¹

Pseudomembrane formation In an analysis of six patients with AIDS and CMV colitis one case demonstrated radiological evidence of unusual caecal and ascending colon nodularity due to pseudomembrane formation.⁶¹

Pneumatosis intestinalis Pneumatosis was encountered in a renal transplant recipient and active CMV colitis was thought to have a role.⁶² Lesions of the biliary tree have also been encountered, with cholangitis, papillary stenosis, and acalculous cholecystitis all described.⁶³⁻⁶⁶

Clinical symptoms

These vary in severity, depending on the extent and type of pathological lesion, and are related to the sites of the lesions within the gut. Diarrhoea with or without blood, accompanied by fever and weight loss are the commonest constellation of symptoms in patients with AIDS.³¹ In organ transplant recipients gastrointestinal haemorrhage caused by ulceration, and occasionally perforation (usually of the right colon), are the modes of presentation.⁶⁷ The wide variety of symptoms encountered are summarised in the table.

Diagnosis of CMV infection of the gastrointestinal tract

Light microscopy remains one of the major diagnostic tools for the diagnosis of CMV, but this is not always possible because classic inclusions are not always found.⁶⁸ Therefore, microscopy should be coupled with some of the other diagnostic tests available.

SEROLOGY

Viral serology is relatively cheap and minimally invasive. Current infection is suggested by a high titre of IgM antibodies or by a rising IgG titre, with IgM being most suggestive of primary, rather than reactivated, infection. Measurement and interpretation of rising antibody titres may be difficult in some circumstances, particularly in the context of the immunosuppressed, and histological techniques may be more appropriate.

CULTURE

The virus may be isolated in cell cultures of human embryo fibroblasts.⁶⁹ Successful virus isolation does not, however, imply active CMV disease, as the virus is excreted for months, even years, after a primary infection. A better estimate of the pathogenetic effects of CMV may be made using histological methods.

Clinical symptoms

| | |
|---|------------------------------------------------------|
| 1 | Diarrhoea: watery, bloody, intractable, intermittent |
| 2 | Abdominal pain |
| 3 | Abdominal distension: with paralytic ileus |
| 4 | Acute abdomen |
| 5 | Haematochezia |
| 6 | Haematemesis |
| 7 | Dysphagia |
| 8 | Fever |
| 9 | Weight loss |

CMV ANTIGENAEMIA

This is a sensitive and specific diagnostic tool that permits rapid and early diagnosis of active CMV infection.⁷⁰ It is restricted to the early—intermediate stage of the CMV infection cycle and is confined to circulating leucocytes, particularly neutrophils and monocytes. CMV antigenaemia is a useful marker of disease activity, may help in decisions regarding specific chemotherapy, and in monitoring the results of such treatment.

HISTOLOGY AND IMMUNOHISTOLOGY

“Owl’s eye” intranuclear inclusions are the hallmark of CMV in routine haematoxylin and eosin histological preparations. These may be found in vascular endothelial cells, mucosal epithelial cells, and connective tissue stromal cells. The presence of such inclusions in biopsy tissue may be the first indication of previously unsuspected CMV infection. The inclusions can usually be regarded as strong evidence of the presence of CMV, although occasional difficulties can arise in distinguishing CMV from other herpes viruses. Atypical CMV inclusions have been described, and are said to be particularly numerous in cases of AIDS.⁶⁸ When the diagnosis is uncertain, immunohistochemical methods can be useful in confirming the presence of CMV.

Antibodies to CMV antigens for use in immunohistology are widely available and may be used on both frozen and formalin fixed material.⁷¹ In cases of florid infection immunohistochemistry is usually unnecessary. However, immunohistology is usually more sensitive than simple visual identification of inclusions and may therefore detect the virus in cases where it would otherwise be missed.

Most of the antigens used for immunohistochemical detection of CMV are replication cycle specific in that the antigen may not be expressed by infected cells except during certain parts of the viral replication cycle.^{71 72} More sensitive techniques of viral detection depend on the identification of viral nucleic acid, which is present in any infected cell.

DETECTION OF VIRAL NUCLEIC ACID

The polymerase chain reaction (PCR) has been widely used to demonstrate CMV nucleic acid in human tissues. This technique has the theoretical sensitivity to detect a single copy of the viral nucleic acid in a tissue sample. Not surprisingly, such a sensitive assay has demonstrated virus at a far higher rate than histological methods.¹⁷ Like all herpes viruses, CMV is capable of lifelong latency once infection has occurred. Probably because of this the virus is frequently demonstrated in normal tissue,¹⁷ and there are considerable difficulties in attributing pathogenicity to CMV when detected in this way.

Currently, PCR technology does not permit visualisation of the tissue being investigated, as this needs to be homogenised to release the nucleic acids. In situ hybridisation using non-radioactive probes is a technique

which has the theoretical sensitivity to detect viral DNA in single cells while allowing the histological context of the infected cells to be appreciated.⁷³ In the gastrointestinal tract, as elsewhere, the relevance of the presence of CMV in the absence of an inflammatory response is likely to remain a matter of some controversy.

Management of CMV infections in the gut

Once CMV has been established as the cause of the gastrointestinal symptoms, specific antiviral treatment is available. Gastro-intestinal CMV disease responds well to ganciclovir, regardless of the cause of the underlying immunosuppression.⁷⁴ In 35 of 42 (83%) patients gastrointestinal CMV improved or stabilised after administration of ganciclovir.⁷⁴ Four transplant recipients with CMV induced gut disease also experienced improvement or stabilisation.⁷⁵ Clinical improvement in 75% of patients with AIDS has also been reported.⁵¹

A series of 66 patients with AIDS and first episode gastrointestinal CMV disease were treated with foscarnet as first line treatment for two to four weeks.⁴⁸ Seventy seven per cent of patients with oesophagitis and 57% of those with colitis responded clinically and endoscopically in three weeks. Thus, foscarnet is an effective first line treatment for gastrointestinal CMV infection. This view has been endorsed by others.⁴⁹

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