Cases of the quarter

Cytomegalovirus colitis: an unusual cause of diarrhoea in the immunocompetent

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ABSTRACT Cytomegalovirus (CMV) colitis is rarely reported in the immunocompetent adult and is often associated with inflammatory bowel disease (IBD), particularly ulcerative colitis (UC). An index of suspicion in the appropriate setting is vital to diagnosing the condition. Undiagnosed CMV colitis has a significant morbidity. A review of the natural history and diagnosis of CMV is followed by a discussion of the incidence, outcome and possible treatment of CMV in the immunocompetent patient. The possible association between CMV and IBD is also reviewed, and the question of whether this should have any bearing on treatment is discussed at some length.

KEYWORDS Crohn's disease, cytomegalovirus colitis, immunocompetent, inflammatory bowel disease, ulcerative colitis

DECLARATION OF INTERESTS No conflict of interests declared.

CASE REPORT

A 72-year-old woman was admitted to hospital with lower abdominal pain and diarrhoea. She had woken up suddenly in the middle of the night with abdominal pain and an episode of loose stool associated with fresh rectal bleeding and two bouts of vomiting. Her medical history consisted of late-onset asthma diagnosed five years previously, for which she was prescribed inhalers (tiotropium, fluticasone/salmeterol and salbutamol). However, she had not been using any of these inhalers for at least a year prior to admission. The patient had never taken oral steroids for her asthma. She consumed 20 units of alcohol a week and had stopped smoking 20 years previously. There was no history of recent travel or intake of antibiotics in the last few months.

Examination revealed severe tenderness in the left flank, with localised guarding and exaggerated bowel sounds. An initial impression was made of sigmoid diverticulitis, and the patient was admitted under the surgeons.

Investigations at the time of admission revealed haemoglobin (Hb) 10.3 g/dl, white cell count 10.6 x 10⁹/l, neutrophil count 8.4 x 10⁹/l and C-reactive protein (CRP) 161 mg/l (normal <5). The patient was managed conservatively with a light diet, intravenous antibiotics and antiemetics. She continued to have loose stools, remained pyrexial and complained of left iliac fossa pain into her second hospital day. At that time her CRP was 100 mg/l. Blood and stool culture were negative. *Clostridium difficile* toxin was not detected. As the inflammatory markers did not normalise by day three and she continued to pass loose stools (more than twice a day), a computed tomography (CT) scan of the
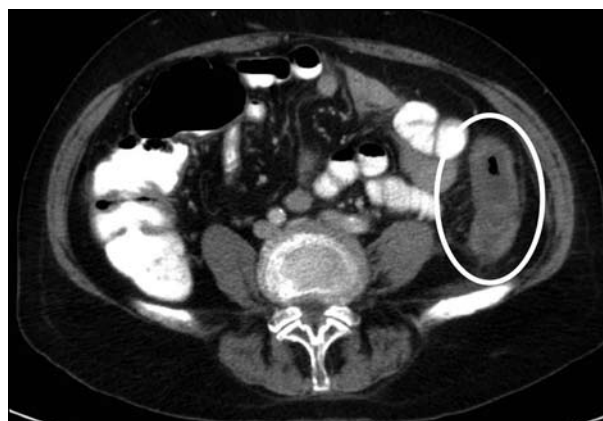

FIGURE 1 CT scan from a 72-year-old woman admitted with lower abdominal pain and an episode of loose stool, associated with fresh rectal bleeding and two bouts of vomiting. The scan shows a thickened, oedematous descending colon with a surrounding stranding of fat.

abdomen was performed to exclude diverticular abscess and other intra-abdominal pathology.

A contrast CT scan of the abdomen (Figure 1) showed the large bowel from the proximal sigmoid to the splenic flexure to be diffusely abnormal, with wall thickening and a surrounding stranding of fat. The rest of the colon was normal, and there were no intra-abdominal collections. Colonoscopy revealed extensive ulceration, sloughing of mucosa, contact bleeding, mucosal oedema and erythema beginning 30 cm from the anus and extending to the splenic flexure (Figure 2). Biopsies revealed a distortion of crypt architecture and epithelial reactive changes. Several poorly formed granulomas were seen in a fragment of tissue. Within the granulation tissue, several large cells, probably macrophages and enlarged
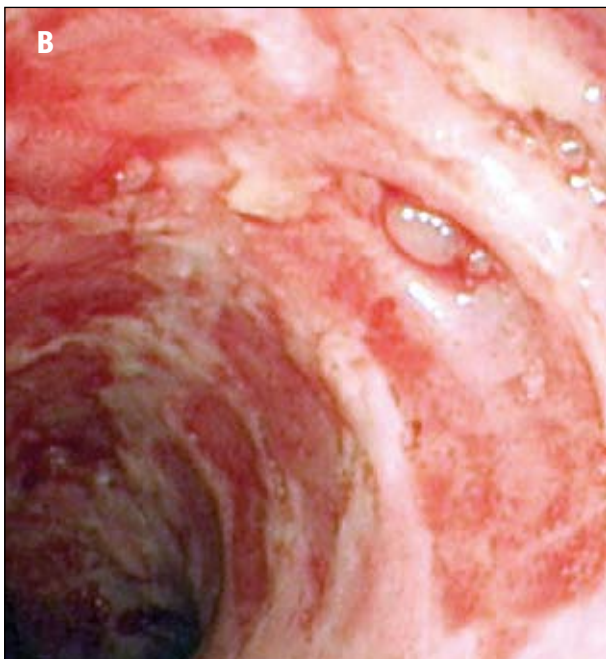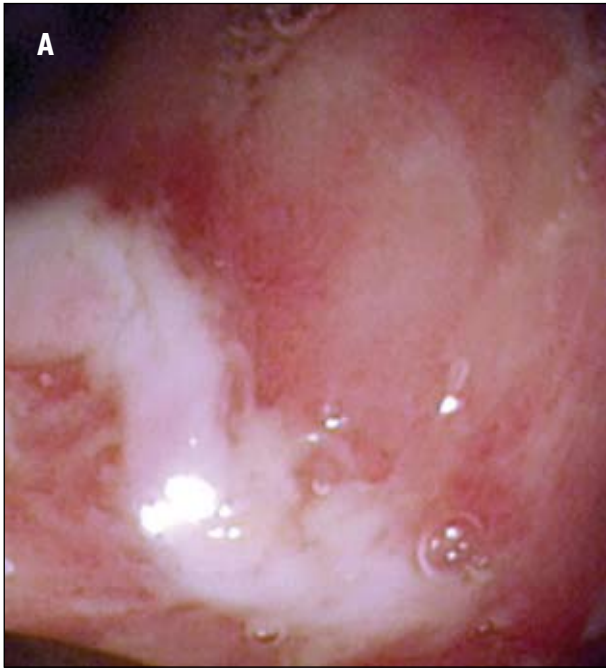
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FIGURE 2 Colonoscopy in this patient showed oedematous and haemorrhagic mucosa with sloughing and multiple deep confluent ulcers in the entire descending colon.

endothelial cells with intranuclear inclusions, were seen. A diagnosis of cytomegalovirus (CMV) colitis was suspected. Samples were sent for a second opinion to the regional referral laboratory and for immuno-histochemistry staining. The presence of immunohisto-chemical staining for CMV is shown in Figure 3. Blood was positive for CMV IgM.

By the fourth hospital day the patient's symptoms were improving and she discharged herself from hospital. When seen in the clinic three months later, she was asymptomatic. There were no further loose stools,
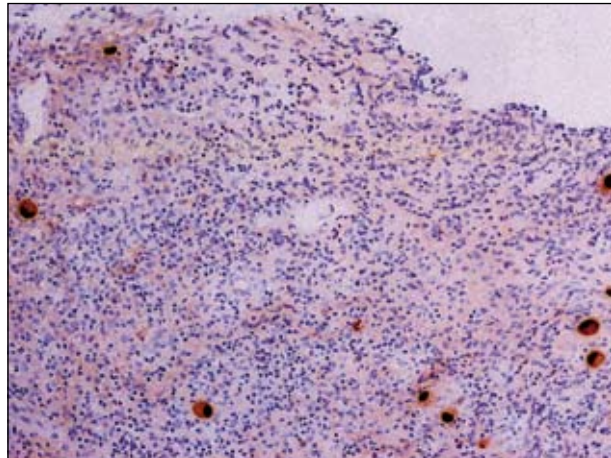

FIGURE 3 Immunohistochemical staining of the colonic biopsies revealed typical owl's-eye inclusion bodies, characteristic of CMV. (Magnification c. x100)

abdominal pain or rectal bleeding. Blood tests revealed CRP 10 mg/l, Hb 12 g/dl and white cell count 6.4×10^9/l. The patient did not wish to undergo any further blood tests or a repeat flexible sigmoidoscopy to document disease resolution.

DISCUSSION

Cytomegalovirus colitis is an uncommon cause of diarrhoea in the immunocompetent, despite the high seroprevalence of CMV in the general population.[1] It occurs in 2–16% of patients receiving solid organ transplantation and in 3–5% of patients with human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS).[2]

Cytomegalovirus has three major patterns of infection.[2] The first is primary infection, in which the patient has never been exposed to the pathogen but becomes infected by another patient who is seropositive for the virus (60%). Primary infection in immunocompetent hosts causes few or no symptoms. After the initial infection, the genome of the virus persists in the host. The second pattern, reactivation, occurs in a patient who is seropositive with a latent virus that becomes reactivated if the host's immune system becomes compromised (10–20%). The third pattern, superinfection, occurs when a patient who is CMV-seropositive receives latently infected cells from another patient who is seropositive. The resulting CMV infection is from the latent donor cells, not from the recipient cells (20–40%).

Once a patient becomes infected, CMV, like other herpes viruses, can persist indefinitely in the host tissues.[3] If the host's T-cell response becomes compromised by disease or iatrogenic processes, the latent virus can reactivate and cause a variety of syndromes.[2]

The detection of CMV can be by one of several methods. Virus isolation by conventional cell culture still remains

the gold standard against which all new detection systems must be compared. The major disadvantage is the time lapse of up to six weeks between the inoculation of the clinical specimen and the appearance of virus in the culture. Sensitive methods to detect the specific circulating antibody (IgG and IgM) are routinely available and are usually the first-line investigation. Viral genome detection by polymerase chain reaction (PCR) and quantitative PCR to assess viral load and response to treatment, particularly in the immunocompromised, are now widely available and are the investigations of choice.

Direct immunofluorescent techniques and immuno-histochemical staining are also commonly used on fixed tissue sections to detect CMV antigens. Methods to detect CMV proteins (messenger matrix proteins; CMV pp65 and pp67) early (within eight hours) in a rapid culture system by fluorescent tagged monoclonal anti-bodies or messenger RNA amplification have recently been developed but are only available in referral centres.

CMV colitis in the immunocompetent

In a systematic review of all articles reporting CMV infection in immunocompetent adults from 1950 to 2007, the gastrointestinal system (colitis) and central nervous system were the most frequent sites of involvement.[3] Rafailidis and colleagues identified the gastrointestinal tract (GIT) as the primary site of involvement in about one third of all patients.[3] Cytomegalovirus infection of the GIT was classified as gastroenteritis, duodenitis, ileitis, colitis or proctitis. Symptoms observed were fever, abdominal pain, anorexia, nausea, vomiting, watery or bloody diarrhoea, haematochezia or melaena. Signs recorded on physical examination were abdominal tenderness or abnormal bowel sounds. The most common site of GIT involvement was the colon or the rectum.[3]

In their meta-analysis on the outcome of CMV colitis in immunocompetent hosts, Galiatsatos and colleagues identified only 28 cases of CMV colitis in patients with an intact immune system.[4] Most patients were older than 55 years, with an average age of 61.1 years. The fact that most patients were above the age of 55 years was thought to be a reflection of a weakened immune system as a consequence of ageing.[4] Age-related B and T cell dysfunction, impaired cytokine regulation and pertur-bation of mucosal immunity were also thought to contribute to a relative immunodeficiency in the elderly, predisposing them to various infections and inflammatory diseases.[5] In this meta-analysis, spontaneous remission occurred in 31.8%, mostly individuals under 55 years of age. Deaths occurred in patients above 55 years.[4] The extent of the disease, i.e. pan-colitis or localised colitis, was not an independent predictor of mortality in the analysis (p=0.62).[4] Advanced age, male gender, presence of immune-modulating comorbidities and the need for surgical intervention were factors negatively influencing

survival. Conversely, young, healthy patients had a good prognosis with no intervention.[4]

The authors suggested that the presumed benefit of treatment with specific antiviral agents should be reserved for severe CMV infections in immunocompetent patients after weighing the risks of potential toxicity of these drugs.[4] They recommended the need for further randomised trials to evaluate the use of antiviral agents for treating serious CMV infections in the immuno-competent adult.[4] The use of antiviral agents in the treatment of CMV was reviewed in this journal in 2001.[6]

CMV colitis and inflammatory bowel disease

Since Powell et al. first reported CMV inclusion disease in a case of ulcerative colitis (UC) in 1961,[7] the association of CMV with inflammatory bowel disease (IBD) has been very controversial. Strong immunosuppressive therapy may increase the opportunity for CMV infection in IBD. However, it is still unclear whether CMV infection has an active role in IBD or whether it exists co-incidentally.[8] A study by Kuwabara and colleagues showed that IBD, particularly UC, was strongly associated with CMV colitis.[8] The degree of CMV colitis, as assessed by the number of immunohistochemically stained cells in a biopsy section, was higher in severe UC than in patients with moderate UC or Crohn's disease (CD). The prevalence of CMV colitis in CD was much less than in UC.[8,9] Retrospective studies have shown that in UC, CMV infection can be present in 5–21% of the surgically resected specimens.[9] Recent prospective studies have shown 25–81% of steroid-refractory UC patients to harbour the virus.[10] Steroid resistance is also reported to be one of the characteristics of UC associated with CMV infection.[11]

The issue of whether CMV infection directly influences IBD or is co-incidental remains unclear. Eyre-Brook et al. reported that CMV infection is of little significance to the course of IBD and that administration of acyclovir for CMV infection did not alter the course of the disease.[12] However, ganciclovir has greater efficacy, and Wada et al. have found it to be effective in 67% of patients with CMV infection.[11] They also reported an improvement of UC on steroid withdrawal in steroid-resistant UC.[11] This suggests a direct influence of CMV in the deterioration of patients with IBD. Kishore and colleagues, however, are of the opinion that reactivation of CMV in immunosuppressed patients with IBD is due to the development of secondary CMV colitis, rather than its primary role in the aetiology of IBD.[13] Tumour necrosis factor – alpha and interferon gamma, which are elevated in patients with IBD – are thought to cause the reactivation of latent CMV infection,[14] which in turn causes the liberation of pro-inflammatory cytokines such as interleukin 6 that might cause an exacerbation of IBD.[15]

At best, the questions as to whether IBD is the true cause of colitis, and whether CMV can only superinfect

an already inflamed mucosa or causes or triggers IBD, remain unsettled.[3] Some researchers have suggested that viral proteins of CMV may trigger IBD in susceptible individuals by upregulating the immune system and inducing MHC class I surface antigen expression.[16,17] In patients with long-standing IBD, particularly on immunosuppressive medications, CMV has been associated with relapses, medically refractory disease and a more severe clinical course.[18,19]

In a study by Kishore and colleagues, the outcome of medical treatment for IBD in patients with CMV infection was worse than for those without CMV.[13] Patients with CMV often required colectomy and died.[13] The authors suggest that, as CMV colitis is known to cause toxic megacolon and colonic perforation and can also progress as a result of immunosuppressive therapy in IBD, a certain population of patients should be screened for CMV. We agree with Bloomfeld that patients with steroid-refractory UC or steroid-dependent UC, particularly with active pancolitis, should be screened for CMV infection before increasing dosage or adding new drugs.[20]

However, there is no consensus on the treatment of active CMV infection in IBD patients. Considering the high risk of immunosuppression in IBD patients, one may believe that a therapeutic strategy towards combating CMV infection is warranted.[13] With the currently available data, a reduction in immunosuppression and steroids is unlikely to be acceptable in the presence of active IBD.[14] Antiviral agents such as ganciclovir and val-ganciclovir seem to be the only potential option left for such patients. Only few anecdotal case reports and uncontrolled series support this view.[19] Further randomised controlled trials are needed to answer this question conclusively.

CONCLUSION

Our patient highlights a rare cause of diarrhoea in the immunocompetent adult. Our report discusses its association with IBD and raises some unresolved issues with regards to its management.

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