Disseminated cytomegalovirus infection in Crohn's disease following anti-tumour necrosis factor therapy

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This case report describes a 63-year-old woman with a 15-year history of Crohn's disease. After a severe relapse with colitis she was treated with immunosuppressive agents, including an increased dosage of corticosteroids, azathioprine and a single dose of infliximab (anti-tumour necrosis factor-α). This led to a brief improvement, which was followed by worsening diarrhoea, fever and skin lesions. Biopsies from upper and lower endoscopies and from an ulcerative skin lesion revealed cytomegalovirus vasculitis in all the tissues removed. The patient improved slowly by withdrawal of the immunosuppressives and with anti-viral therapy. Whenever patients with inflammatory bowel disease deteriorate rapidly, cytomegalovirus infection should be ruled out before the immunosuppressive therapy is fortified.

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Introduction

Cytomegalovirus (CMV) is a ubiquitous herpes virus, which infects 40–100% of adults in different populations by their fourth decade of life [1,2]. In immunocompetent people the primary infection is mostly asymptomatic or mild, resembling mononucleosis. In neonates, elderly people and patients with cancer or other serious comorbidities, the disease may be more severe [3]. Clinically significant CMV infection is generally a recurrence from latent infection in immunocompromised patients, particularly those infected with HIV or transplant recipients [4].

Patients with inflammatory bowel disease (IBD) are also at higher risk of CMV infection due to their common use of immunosuppressive therapies and their altered immunity caused by malnutrition [5]. The colon is most often affected but dissemination may occur along the whole gastrointestinal tract [5]. Additional dissemination outside the gastrointestinal tract is very rare and may involve the skin, lungs, eyes or central nervous system (CNS) [3,6,7]. The mechanism of dissemination is still unclear; however, CMV vasculitis appears to play an important step in the spreading and development of organ involvement and is considered a distinct feature of disseminated disease [6,8,9].

Herein, we report a case of life-threatening disseminated CMV infection in a patient with Crohn's disease. Such a complication is very rare in Crohn's disease [5] and this is the first report of CMV vasculitis associated with seeding to the skin, complete intestinal tract and possibly the CNS.

Case report

A 63-year-old woman with Crohn's disease was admitted to hospital because of fever, diarrhoea and skin lesions. She had been in a stable condition on low-dose corticosteroids for 10 years until 1 month prior to admission, when her diarrhoea worsened. Colonoscopy revealed inflammatory lesions in the colon and ileum compatible with Crohn's disease; however, a few scattered large cells with CMV inclusion bodies were also noted. The corticosteroid dosage was increased and supplemented with azathioprine and a single dose of infliximab. After a transient improvement, the patient's diarrhoea worsened and spiking fevers developed. At the same time, she noted multiple painful skin ulcers and a papular rash along the left thoracic dermatom 12.

On admission, the patient appeared severely ill with a temperature of 38.0°C. She was oriented but had difficulty concentrating. Her hearing was impaired and, according to her husband, her short-term memory had deteriorated rapidly over the previous 2 weeks. Multiple skin ulcers were found on her left arm, both legs, back and in the perianal region (Fig. 1). The rash along dermatom 12 was characteristic for Herpes zoster. The abdomen was slightly tender but soft with active bowel sounds. Her haemoglobin level was 72 g/l and she was neutropenic with 1600 neutrophils/mm^3. The liver enzymes were normal. Upper and lower endoscopy revealed multiple oesophageal ulcers, a duodenal ulcer

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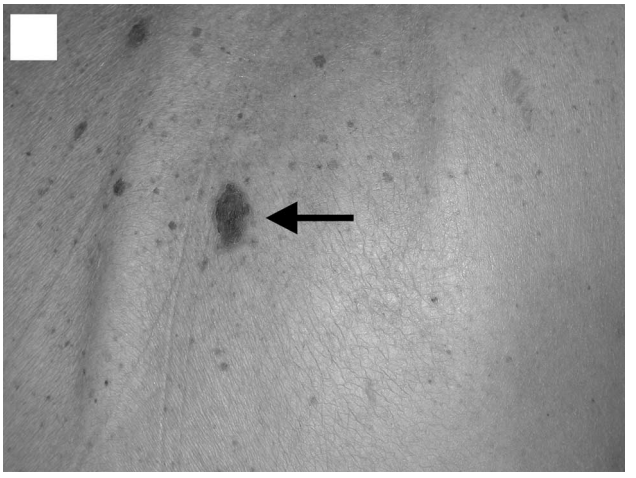
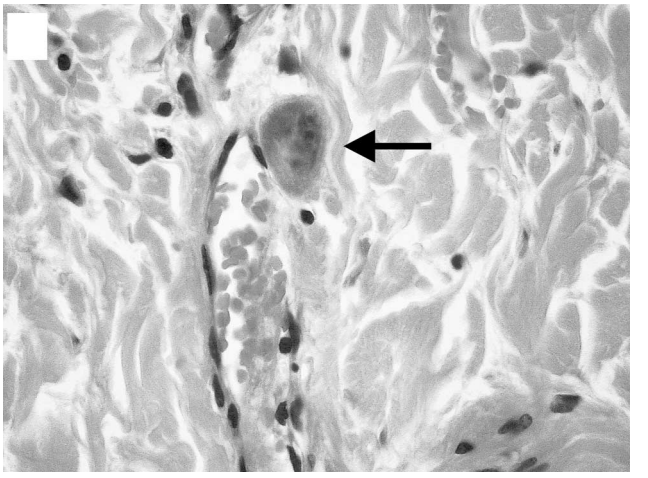
Fig. 1



Ulcerative skin lesion caused by cytomegalovirus (arrow). The margin is sharply delineated.

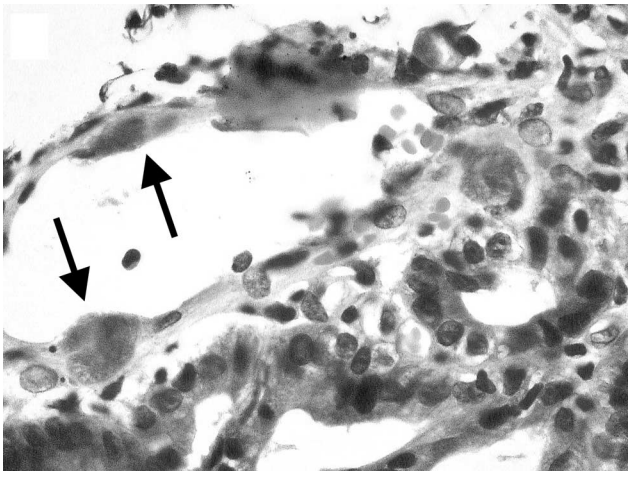
Fig. 3



CMV vasculitis in the skin. Note the CMV-infected endothelial cell of a large capillary (arrow). Haematoxylin and eosin stain; original magnification × 200.

and severe haemorrhagic ileocolitis. Numerous inclusion bodies typical for CMV were seen within the endothelial cells of the small vessels of the oesophagus, stomach, ileum and colon (Fig. 2). A biopsy of a skin lesion showed endothelial CMV inclusions with local inflammation and necrosis (Fig. 3). Immunoglobulin M (IgM) serum antibody titres against CMV were positive; those for immunoglobulin G (IgG) were negative. A magnetic resonance imaging head scan revealed no abnormalities. A lumbar puncture was normal; however, polymerase chain reaction (PCR) was positive for CMV.

Fig. 2



CMV vasculitis in the stomach. CMV-infected cells are giant with intramuscular and intrazytoplasmatic inclusion bodies (arrows). Haematoxylin and eosin stain; original magnification × 200.

The patient's corticosteroids were tapered rapidly and azathioprine was stopped. Foscarnet was initiated and was later switched to ganciclovir after recovery of the neutrophils. Intravenous metronidazole and ciprofloxacin were begun and parenteral nutrition was started. The skin lesions healed within 8 weeks. The patient's diarrhoea and impaired cerebral function improved very slowly. After 8 weeks she was discharged to a rehabilitation hospital from where she returned home in a stable condition 1 month later.

Discussion

In immunocompromized patients, CMV most often affects the gastrointestinal tract, in particular the colon. CMV infection is also known to complicate the course of IBD, in particular ulcerative colitis [5]. In a study by Cottone *et al*., CMV was diagnosed in the rectal specimens as well as by buffy coat preparation in 36% of patients with refractory IBD disease [10].

To our knowledge, dissemination to the whole gastrointestinal tract, skin and possibly CNS has not been described previously. Because of positive cerebrospinal fluid PCR for CMV and deterioration of short-term memory, we presumed simultaneous CNS infection. But PCR results may be false positive in this case due to contamination because skin infection was already present when the lumbar puncture was performed.

Widespread dissemination as seen in this case appears to be caused by fortified immunosuppressive therapy (azathioprine plus a single dose of infliximab) at a time when CMV inclusion bodies were already present in the gastrointestinal tract. It is therefore essential to

exclude CMV infection in corticosteroid-resistant flares of IBD and to avoid increasing immunosuppression, which might cause widespread dissemination. Meticulous evaluation, prompt antiviral therapy and withdrawal of immunosuppressive treatment may avoid complications and mortality [5].

Vascular pathology may play a crucial role when multiorgan involvement is present [6,8,9]. This patient presented with CMV vasculitis in all the tissues removed. It has been proposed that the dissemination of CMV from the gastrointestinal tract is facilitated by vasculitis with damage of the microvascular endothelium, which allows CMV to circulate within the shed endothelial cells [8,9].

Although CMV infection is a frequent cause of severe colitis in IBD patients, dissemination outside the gastrointestinal tract is very rare.

In conclusion, antiviral therapy should be initiated and immunosuppressive agents discontinued in IBD patients with severe refractory colitis and CMV-infected cells in the intestinal tract [5,10].

Acknowledgement

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