

Cytomegalovirus infection associated with ulcerative colitis in immunocompetent individuals

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Summary

Gastrointestinal infection with cytomegalovirus (CMV) is usually found in immunocompromised patients and rarely affects immunocompetent subjects. We describe two immunocompetent patients who had primary CMV infection, and in both the disease was associated with ulcerative colitis. Both patients recovered from the CMV infection spontaneously.

Keywords: cytomegalovirus infection; ulcerative colitis; immunocompetent subjects

Cytomegalovirus (CMV) is recognised as an important pathogen with a worldwide distribution. Gastrointestinal infections with CMV, especially colitis, are usually found in immunocompromised patients and rarely affect immunocompetent subjects.¹⁻⁹ CMV infection has also been related to inflammatory bowel disease (IBD), either as a precipitating factor or as a coincidental infection.¹⁰⁻¹⁵

We report two cases of immunocompetent patients with primary CMV infections. In the first case acute CMV infection was associated with exacerbation of IBD, and in the second case CMV infection coincided with the onset, and led to the diagnosis of IBD. Both patients recovered from the CMV infection spontaneously.

Case reports

Case 1

A 38-year-old woman was hospitalised because of spiking fever, dyspnoea, abdominal pain, and non-bloody diarrhoea. Eight years earlier she had been diagnosed as having ulcerative colitis; she was treated with a short course of steroids and had remained symptom-free ever since. Thirteen weeks prior to admission she had an uneventful childbirth. Seven weeks later she developed a febrile illness with watery diarrhoea. Stool cultures were positive for *Shigella mansoni*, and she was treated successfully with amoxicillin. Two weeks before admission she again developed fever up to 39.7°C, chills, weakness, dyspnoea, abdominal pain and watery diarrhoea.

Physical examination revealed an ill-looking woman with a blood pressure of 90/60 mmHg, pulse rate of 104 beats/min, and a temperature of 39°C. No lymphadenopathy was noted. Cardiac examination was normal, and decreased breathing sounds were heard over the right lung base. Abdominal examination re-

vealed an enlarged liver 2 cm below the costal margin, with a rebound tenderness over the right upper quadrant.

Laboratory investigations revealed leucocytosis of $33.1 \times 10^9/l$ with 59% polymorphonucleocytes, and 33% lymphocytes with atypical forms. Haemoglobin was 11.6 g/dl with normal platelet count. Other laboratory studies were normal except for an elevated alkaline phosphatase (262 IU/l, normal <115 IU/l) and lactate dehydrogenase (464 IU/l, normal <250 IU/l). Chest X-ray showed bilateral lung infiltrates. Electrocardiogram was normal except for sinus tachycardia.

On the second day of hospitalisation she became dyspnoeic and hypoxemic with a temperature of 39.6°C and severe abdominal pain mainly in the right upper quadrant. Physical examination noted guarding on the right upper quadrant, suggesting peritoneal inflammation. HIDA (^{99m}Tc-labeled N-substituted iminodiacetic acid) biliary scan findings were consistent with the diagnosis of cholecystitis, and intravenous antibiotics were started. Blood, urine and stool cultures remained sterile. Abdominal computed tomography (CT) scan showed thickening of the gallbladder wall as well as thickening of the colonic wall without evidence of lymphadenopathy (figure 1). Serologic tests for hepatitis B and C, human immunodeficiency (HIV), and Epstein Barr viruses were negative. Solid-phase enzyme immunoassay for IgM antibodies to CMV was highly positive (3+) on admission and decreased to (1+) over time.¹⁶ Immunofluorescence assay for IgG antibodies to CMV showed a titre of 1:160 on admission and increased to 1:320 later.¹⁷ Subsequently, CMV was detected in the urine by polymerase chain reaction and the Shell vial assay.¹⁸

Sigmoidoscopy up to 40 cm revealed oedematous, inflamed mucosa with fibrinopurulent exudate and small haemorrhages. Mucosal biopsy specimens demonstrated acute and chronic inflammatory process with crypt abscess. CMV inclusion bodies were not identified, and CMV was not detected by immunoperoxidase staining.

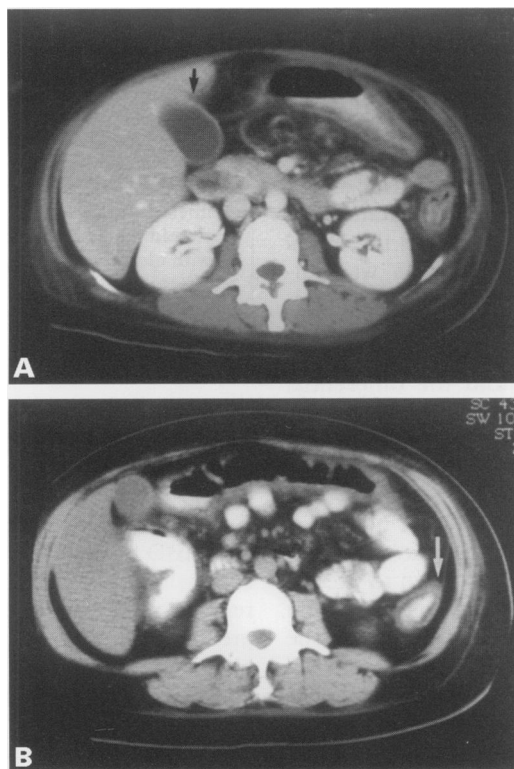
During the first 3 weeks the patient had a temperature of 38-40°C and severe watery diarrhoea. Blood counts were notable for marked leucocytosis ($20-30 \times 10^9/l$) with 30-40% lymphocytes and marked thrombocytosis (up to $1000 \times 10^9/l$). In addition, signs of malabsorption developed with hypoalbuminaemia of 2 g/dl and hypocholesterolaemia of 58 mg/dl.

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Figure 1 Abdominal CT scan showing (A) thickening of the gall-bladder wall (arrow), (B) thickening of the colonic wall (arrow)

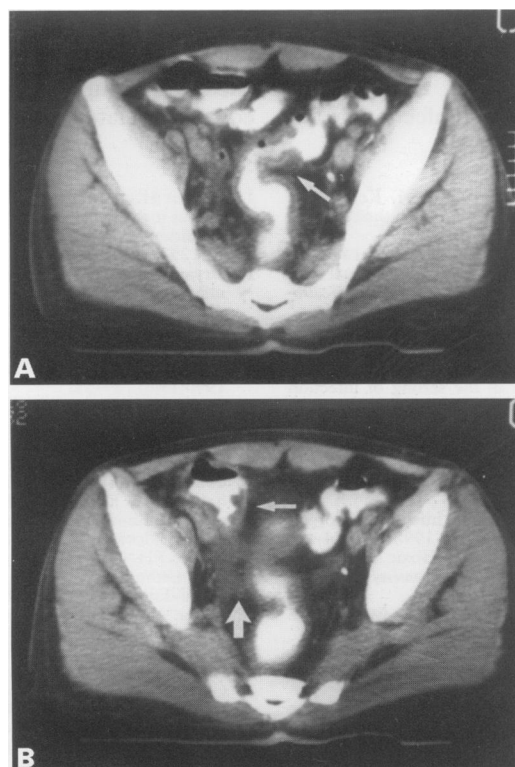


The colonic findings were compatible with exacerbation of ulcerative colitis and she was treated with 5-aminosalicylic acid (2 g/day). Her symptoms resolved completely after 2 months of treatment with no antiviral therapy or steroids.

Case 2

A 20-year-old man, who had a history of bronchial asthma and had undergone splenec-

Figure 2 CT scans showing (A) thickened wall of the colon (arrow), (B) thickened wall of the caecum (long arrow), and peritoneal fluid (short arrow)



tomy and cholecystectomy at the age 12 years because of congenital spherocytosis, was hospitalised with a febrile illness. His medications included amoxicillin, which he had been taking prophylactically since the splenectomy, and inhaled steroids during exacerbation of his asthma. Four days before admission, he developed a fever of 39.5°C with diffuse abdominal pain and a nonproductive cough. On admission, he had a temperature of 38.2°C, pulse rate of 88 beats/min, and blood pressure of 110/60 mmHg. The physical examination was otherwise unremarkable. Laboratory investigations were normal except for a leucocytosis of $12.7 \times 10^9/l$, an elevated bilirubin level of 34.2 $\mu\text{mol/l}$ and an elevated lactate dehydrogenase up to 300 IU/l. Because of his history of splenectomy he was given amoxicillin clavulonate.

During the first 2 weeks of hospitalisation, abdominal pain was localised in the right lower quadrant and was associated with fever of 38–40°C, chills and abdominal guarding suggesting peritoneal signs. Laboratory evaluation showed a marked leucocytosis of up to $33 \times 10^9/l$ with 58% lymphocytes and abnormal liver function tests (bilirubin 15.4–56.4 $\mu\text{mol/l}$, lactate dehydrogenase 359–642 IU/l, aspartate transaminase 335–397 IU/l, alanine transaminase 332–360 IU/l). Repeated blood, urine and stool cultures were negative. Chest and abdominal CT scans showed marked colonic wall thickening with a small amount of peritoneal fluid (figure 2). Gallium scan showed increased isotope concentration in the right lower abdomen and over the lungs.

After 2 weeks of observation, spontaneous clinical and laboratory improvement was observed. Serological tests for hepatitis A, B and C viruses, and HIV were negative. Solid-phase enzyme immunoassay for IgM antibodies to CMV was highly positive (3+) on admission and decreased to (1+) over time. Immunofluorescence assay for IgG antibodies to CMV showed a titre of 1:160 on admission and had increased to 1:320 2 months later.

Three weeks later he again developed fever associated with mucoid and bloody diarrhoea. Blood, urine and stool cultures were negative. His blood count was normal except for a leucocytosis of $17.8 \times 10^9/l$ with 43% lymphocytes. Sigmoidoscopy showed evidence of an inflammatory process, and mucosal biopsy demonstrated an inflammatory process with crypt abscess; CMV inclusion bodies were not identified and CMV was not detected by immunoperoxidase staining. A diagnosis of ulcerative colitis was made and treatment with metronidazole and 5-aminosalicylic acid was initiated. A month later his clinical condition had improved, and during a follow-up period of 3 years he fully recovered from the CMV infection but had repeated bouts of colitis.

Discussion

CMV can affect many organs including the lungs, retina, liver, and gastrointestinal tract.¹⁹ Gastrointestinal tract disease may involve the mouth, oesophagus, stomach, small intestine and colon.¹⁹ CMV colitis is a major cause of

morbidity and mortality in immunocompromised patients but less so in immunocompetent individuals.²⁰ CMV colitis produces mucosal ulceration that can result in abdominal pain, bloody diarrhoea and even perforation, a clinical picture that resembles IBD.²¹⁻²³ Surawitz and Myerson²¹ described three cases of isolated CMV colitis with a presentation of haematochezia. In all three patients the initial differential diagnosis of the colitis was idiopathic IBD but colonic biopsies showed typical CMV inclusion bodies without any other histological features of IBD. The radiographic findings are not specific and the differential diagnosis includes granular ileocolitis and ulcerative colitis.²⁴

The link between IBD and CMV infection is unclear. Our immunocompetent individuals had CMV infection associated with ulcerative colitis. Although, the second patient had a previous splenectomy this is not known to predispose to viral infection. The first patient had a history of inactive ulcerative colitis when she presented with CMV infection. In her case the CMV infection was associated with exacerbation of silent ulcerative colitis. Several case reports have described CMV colitis in patients with IBD.^{10 11 23 25-30} In all these cases CMV inclusion bodies were detected in the colonic mucosa. Indeed, the possibility that acute CMV colitis mimics IBD cannot be excluded, however the absence of CMV inclusion bodies in mucosal biopsies make this unlikely. It has been shown that patients with ulcerative colitis are more likely to show elevated titres to CMV than normal subjects.¹⁴⁻¹⁵ Moreover, it has been suggested that resistant ulcerative colitis that requires colectomy may be related to CMV infection. Indeed, Cooper *et al*¹¹ described CMV inclusion bodies in a subgroup of patients with ulcerative colitis who underwent partial colectomy.

Our second patient had no history of ulcerative colitis. In his case CMV infection coincided with the onset, and led to the diagnosis, of acute ulcerative colitis. Although he recovered from the acute CMV infection he has

Summary points

- CMV infection may be associated with ulcerative colitis
- CMV infection associated with ulcerative colitis may occur in immunocompetent patients
- ulcerative colitis may recover when CMV infection improves
- steroid therapy is not recommended in patients with ulcerative colitis associated with CMV infection

had relapses of the ulcerative colitis. Orvar *et al*¹² described two patients in whom the primary CMV infections coincided with the onset and diagnosis of ulcerative colitis. It has been suggested that primary CMV infection precipitated IBD by enhancing surface antigen marker expression in a host predisposed to IBD.¹² It remains uncertain whether CMV merely has a predilection for inflamed mucosa or actually plays a role in the pathogenic process.

The association of CMV infection and ulcerative colitis raises the problem of whether or not steroids should be used. It has been shown in patients with severe ulcerative colitis, who were resistant to steroid therapy, and had CMV inclusion bodies in the mucosa, that steroid withdrawal led to a clinical and histological improvement.¹⁰⁻²⁹ It seems that cessation of corticosteroids enables the patient to overcome the CMV infection. A similar mechanism was described for chronic hepatitis B virus, in which immunosuppressive drugs were shown to enhance viral replication, while cessation of these drugs decrease its replication.^{31 32} The controversy remains as to whether steroids or immunosuppressive drugs can cause CMV superinfection with IBD exacerbation. It is noteworthy that our patients recovered from the ulcerative colitis without steroid therapy when the CMV infection improved. Thus, steroid therapy should be used with caution in patients with ulcerative colitis associated with CMV infections.

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Familial cavernous angiomas masquerading as multiple sclerosis

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Summary

We report here two cases of cavernous angioma, in the proband and her father, with quite different clinical presentations. The proband presented with a brainstem syndrome, mimicking multiple sclerosis, while the father had a history of mild epilepsy. Both patients were managed conservatively. The cases also demonstrate the utility of magnetic resonance imaging in the diagnosis of cavernous angioma.

Keywords: cavernous angiomas; multiple sclerosis; magnetic resonance imaging

Cavernous angiomas (also known as cavernomas and cavernous haemangiomas) are a form of intracranial vascular malformation that are reported to affect 0.5% of the population.¹ In up to 75% of patients the lesions are multiple. They are characterised by collections of large, abnormal vascular spaces without intervening brain parenchyma.² Up to 50% of patients with cavernous angiomas have a familial form of the disorder which is inherited in an autosomal dominant mode, with incomplete clinical penetrance.¹ The familial form may be more frequent in the Hispanic population.³ Recent genetic studies have identified linkage of this trait to chromosome 7q11.2-q21 in some families.^{1,2} Although cavernous angiomas are rarely life-threatening, they may cause significant morbidity related to their size and location.

Case reports

Case 1

A 19-year-old, right-handed woman was admitted in 1988 with a 5-day history of progressive neurological dysfunction. At the onset she had awoken with numbness of the left side of her tongue, which spread over 24 hours to affect the whole left side of her face. She sub-

sequently developed horizontal diplopia, worse on right lateral gaze, and incoordination, with a tendency to fall to the left. On the day prior to admission she had developed patchy sensory disturbance in her left arm and leg. Her medical history was unremarkable. She was taking the oral contraceptive pill. She was one of four siblings and her father had epilepsy.

On general medical examination the only findings of note were haemangiomas on the dorsum of her left hand, left calf and right thigh. Neurologically, her gait was ataxic. Fundoscopy was normal, but there were bilateral partial sixth nerve palsies, and upbeat nystagmus on upgaze. There was a left sensory trigeminal neuropathy and mild subjective blunting of hearing on the left side. In the limbs there was a mild left-sided pyramidal weakness, with subjective reduction of light touch and pin-prick distally in the left arm and leg. A diagnosis of demyelination was suspected. Visual evoked potentials were normal. A computed tomography (CT) scan of the cranium revealed two small high-density lesions in the right side of the brainstem and left putamen, thought to represent areas of haemorrhage. Cerebrospinal fluid (CSF) examination was entirely normal, with absent oligoclonal bands. The patient's condition spontaneously improved, and follow-up CT brain scan 2 weeks later showed considerable resolution of the high density lesions.

Eight months later she was re-admitted with a relapse comprising similar brainstem symptoms and signs, following a minor acute neck sprain. Cranial magnetic resonance imaging (MRI) scan revealed three separate lesions typical of cavernous angiomas, including a large lesion in the tegmentum of the midbrain, eccentrically located to the right (figure).

The patient has been managed conservatively to date. She has suffered a number of relapses referable to the brainstem cavernous angioma but has recovered to normal

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