Systemic cytomegalovirus infection complicating ulcerative colitis: a case report and review of the literature

P J Hamlin, M N Shah, N Scott, J I Wyatt, P D Howdle

Cytomegalovirus is a common infection worldwide and in the immunocompromised individual it can be a major cause of morbidity and mortality. In patients with inflammatory bowel disease cytomegalovirus infection has been described in both immunocompetent and immunocompromised individuals. A 34 year old man with an exacerbation of his colitis was diagnosed as having both cytomegalovirus colitis and hepatitis. The diagnosis was made on the classical appearance of ‘owl’s eye’ inclusion bodies on colonic and hepatic biopsies and, in addition, viral serology and polymerase chain reaction (PCR) analysis of the cytomegalovirus DNA copy number. Fourteen days of treatment with ganciclovir led to a prompt improvement in the symptoms of colitis, resolution of the pyrexia, normalisation of the liver function tests, and clearance of the virus, as measured by a negative cytomegalovirus DNA PCR.

Cytomegalovirus infection is a potentially fatal complication of treatment induced immunosuppression in patients with inflammatory bowel disease. As in this case, infection may be systemic and not confined to the intestine. Prompt diagnosis using histology, serology, and PCR analysis allows prompt introduction of therapy and an improved prognosis.

CASE REPORT

A 34 year old Sikh was admitted with a one week history of worsening bloody diarrhoea and high fevers. He had been diagnosed with ulcerative colitis nine years previously. Colonoscopy one year previously had demonstrated a mildly active pancolitis. He had started on azathioprine nine months before admission, with regular monitoring of his full blood count and liver function tests which had remained normal. He had no other past medical history of note and no recent travel abroad. His medication on admission was prednisolone 20 mg per day, mesalazine 400 mg three times a day, and azathioprine 50 mg twice a day. He did not smoke or drink alcohol.

On clinical examination he looked well, was not jaundiced, and there was no lymphadenopathy. He had a pyrexia of 38.5°C and the only other positive finding was tenderness on palpation of the left iliac fossa.

Initial investigations revealed a normal haemoglobin concentration and platelet count but he had a mild leucopenia with a white cell count of 3.6 × 10⁹/l (3.0 × 10⁹/l neutrophils). Urea and electrolytes, glucose, and amylase were normal but he had a raised C-reactive protein (46 mg/l) and abnormal liver function tests (bilirubin 15 µmol/l, alanine transaminase 441 IU/l rising to 617 IU/l, alkaline phosphatase of 935 IU/l rising to 1164 IU/l, albumin 33 g/l). The leucopenia progressed 48 hours after admission (white cell count 2.6 × 10⁹/l, neutrophils 2.06 × 10⁹/l) and the azathioprine treatment was consequently stopped.

Blood, stool, and urine cultures were negative. A chest radiograph was normal and three early morning urine samples for acid-alcohol fast bacillus and a Heaf test were negative. Abdominal ultrasound was normal and computed tomography of the abdomen demonstrated some thickening of the intestinal mucosa from the mid-descending colon downwards but no other abnormality. In view of the abnormal liver function tests and history of ulcerative colitis, endoscopic retrograde cholangiopancreatography (ERCP) was performed to investigate the possibility of primary sclerosing cholangitis, but this was normal. The possible diagnosis of ascending cholangitis had been considered before the ERCP and, although the patient was clinically quite well, he was started on empirical intravenous cefuroxime and metronidazole 72 hours after admission. The swinging pyrexia did not respond to this therapy and antibiotic treatment was discontinued. Further negative investigations included thick/thin films for malaria, hepatitis A, B and C serology, monospot test, brucella serology, autoantibody screen, toxoplasma serology, cryptococcal antigen, and legionella serology. Viral serology 48 hours after admission was as follows: influenza A <16, influenza B <16, adenovirus 32, psittacosis <16, Q fever <16, mycoplasma <16, cytomegalovirus 8, coxiella <8, and IgG to Epstein-Barr virus nuclear antigen was positive indicating past infection. A sigmoidoscopy was performed to assess the extent of the colitis. The findings were in keeping with the observations on computed tomography of a severe colitis affecting the rectosigmoid (fig 1), with an abrupt change in the mucosa to a normal appearance in the mid-descending colon. Biopsy

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Abbreviations: PCR, polymerase chain reaction; ERCP, endoscopic retrograde cholangiopancreatography
specimens were taken to confirm the histology (see below) and the dose of mesalazine was increased to 800 mg three times a day. He was reluctant to use steroid or 5-aminosalicylate enema preparations.

In view of his persistently abnormal liver function tests a liver biopsy was done, with samples being sent for histology and microbiology.

The colonic biopsy specimens were reported as demonstrating a severe active colitis with features of idiopathic inflammatory bowel disease. However, in addition, these specimens also contained large numbers of swollen endothelial cells some of which contained inclusion bodies suggestive of cytomegalovirus infection (fig 2A). The liver biopsy histology was reported on day 14 as demonstrating a mild lobular hepatitis with one bile duct epithelial cell containing an inclusion body typical of cytomegalovirus hepatitis (fig 2B). The diagnosis of cytomegalovirus colitis and hepatitis secondary to azathioprine induced immunosuppression was made. He was started on intravenous ganciclovir (5 mg/kg) on day 16 of the admission and became (and stayed) apyrexial 48 hours later. Table 1 illustrates the cytomegalovirus titre and DNA copy number as measured by polymerase chain reaction (PCR) in relation to days from admission and initiation of antiviral therapy.

He remained apyrexial, his symptoms of colitis improved, and he was subsequently discharged home some four weeks after admission. His liver function tests and C-reactive protein were virtually normal two weeks after starting ganciclovir therapy with only a slight transaminitis (alanine aminotransferase 57 IU/l) remaining and this too had normalised by the time of his out patient review one week later.

**DISCUSSION**

There are several cases in the world wide literature of patients with established inflammatory bowel disease developing an acute exacerbation secondary to cytomegalovirus disease. The majority of cases involved patients on immune modulatory therapy before the onset of symptoms. A greater number of cases involved patients with ulcerative colitis compared with Crohn’s disease. In contrast, there is only a handful of reports of cytomegalovirus infection in patients with no previous treatment and these reports discuss patients with only colonic involvement of infection. Our case also developed a cytomegalovirus hepatitis. A mild, self limiting hepatitis complicating cytomegalovirus infection has been described in Crohn’s disease patients treated with azathioprine but not those with ulcerative colitis.

Mortality rates for patients with cytomegalovirus enterocolitis have been quoted as high as 71%. Vega *et al* reported on nine patients with moderate to severe attacks of colitis classified as steroid resistant (24 days of treatment with no improvement in inflammatory or clinical markers). All were diagnosed with cytomegalovirus infection on pathological specimens. Seven patients were treated conservatively with intravenous ganciclovir and clinical improvement was the rule. One patient needed surgery despite antiviral therapy. Two patients required surgical intervention due to toxic dilatation. Begos *et al* concluded from their investigations that patients with inflammatory bowel disease complicated by cytomegalovirus colitis had a 67% colectomy rate and 33% mortality rate. They suggest that appropriate antiviral treatment would eliminate these complications. This is supported by a recent review where aggressive medical and surgical management of these patients demonstrated mortality rates of 14.5% and 17.6% respectively.

The use of serology and parallel PCR analysis to confirm the diagnosis of cytomegalovirus infection should enable early antiviral therapy to be instituted, resulting in marked clinical improvement, as was the case in our patient. Previous reports relied heavily on biopsy evidence before the start of ganciclovir therapy (on average started on day 24*). Histology demonstrating the classical appearance of “owl’s eye” inclusion bodies is the gold standard test for cytomegalovirus diagnosis. However, recent studies using PCR have

**Table 1** Evidence for cytomegalovirus from peripheral blood

<table>
<thead>
<tr>
<th>Days after admission</th>
<th>Cytomegalovirus titre</th>
<th>Cytomegalovirus DNA copy (number/ml)</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1024 (IgM+ve)</td>
<td>49500</td>
</tr>
<tr>
<td>15 (24 hours pre-treatment)</td>
<td>66900</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>1 270</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Negative</td>
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Ganciclovir started on day 16 for 14 days.

![Figure 1](http://pmj.bmj.com/) Endoscopic appearance of the severe colitis affecting the rectosigmoid.

![Figure 2](http://pmj.bmj.com/) (A) Colonic and (B) hepatic biopsy specimens demonstrating classical cytomegalovirus inclusion bodies (arrowed).
indicated that it may be a sensitive and specific assay for diagnosis.11 12

CONCLUSION
This case report illustrates an important aetiological factor to consider in patients admitted to hospital with an acute exacerbation of ulcerative colitis who fail to respond to conventional treatment. These patients may be taking potent immunosuppressive medication and, as this case demonstrates, can develop a systemic cytomegalovirus infection. The poor prognosis seen in cytomegalovirus disease in the absence of antiviral therapy suggests rapid diagnosis and early instigation of specific treatment is important. PCR analysis can complement the information gained from biopsy evidence of inclusion bodies, but is a less invasive and more specific method.

Learning points
- Cytomegalovirus infection should be considered in patients with inflammatory bowel disease who fail to respond to conventional treatment.
- Cytomegalovirus IgM and PCR analysis of serum may allow rapid diagnosis and are less invasive diagnostic modalities than tissue biopsy.
- Treatment with ganciclovir gives rapid clinical, biochemical, and haematological response.

REFERENCES

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