Cytomegalovirus colitis in pregnancy

Lantharita Charoenpong, M.D.,
Anupop Jitmuang, M.D.

ABSTRACT

We reported a case of a 38-year-old pregnant woman, GA 18 weeks, who presented with persistently mucous diarrhea, fever, abdominal cramps and generalized bowel ileus for 12 days. While ongoing gastrointestinal tract symptoms, she had premature uterine contraction and aborted the intrauterine dead fetus. Her colitis did not respond to antimicrobial agents and finally progressed to pseudo-colonic obstruction with subsequent positive stool Clostridium difficile toxin assay. Colonoscopy identified multiple punch-out ulcers, diameters varied between 0.5-2 cm, on descending colon. The ulcers had scanty positivity of cytomegalovirus by immunohistochemistry assay. She responded well to intravenous ganciclovir and was eventually discharged after 40 days of admission. (J Infect Dis Antimicrob Agents 2012;29:143-49.)

Note: This case had been presented and discussed in the Interhospital Case Conference on Infectious Disease (ICCID), 22nd December 2011, Bangkok, Thailand.

INTRODUCTION

Cytomegalovirus (CMV) is a ubiquitous virus worldwide, and causes a wide variety of clinical manifestations. The severe form mostly occurs in immunocompromised patients. CMV infection in immunocompetent host is generally asymptomatic, however it can uncommonly lead to severe complications with significant morbidity and mortality.\(^1\) Primary infection or reactivation of CMV can arise during pregnancy, which it is usually subclinical or mild disease.\(^1\) Moreover, gastrointestinal CMV infection with severe complications such as colitis with pseudo-obstruction is rarely seen in pregnancy.\(^2\) Herein, we reported a case of a pregnant woman who suffered from severe colitis with poor fetal outcome.

CASE REPORT

A 38-year-old pregnant woman, gestational age (GA) of 18\(^{th}\) week, was admitted to Siriraj Hospital, a tertiary care university hospital, owing to a 12-day history of intermittent abdominal pain, owing to a 12-day history of intermittent abdominal pain, mucous diarrhea 5-8 times per day, fever and premature uterine contraction. Initially the patient was...
hospitalized into another hospital because of premature contraction, crampy abdominal pain and diarrhea as mentioned above. The attending physicians had failed to inhibit her premature labour, and she still had severe abdominal pain, abdominal distension and high grade fever which was refractory to metronidazole and ceftriaxone therapy on the eleventh day of admission. One day before referring to Siriraj Hospital, she finally developed vaginal bleeding and prolapsed umbilical cord with visibly non viable fetus by ultrasonography.

On physical examination, temperature was 38°C, heart rate was 135/min, blood pressure was 140/80 mmHg and respiratory rate was 28/min. Patient had good color, no jaundice and mild leg edema on general appearance. Abdomen showed marked distension, absent bowel sound, tympanic on percussion, but no tenderness. Cardiothoracic system was unremarkable. Laboratory investigations revealed a hemoglobin level of 11.2 g/dL, white blood cell count of 6,200 cells/mm³ (neutrophil 86.7%, lymphocyte 9.9%, monocyte 3.1% and eosinophil 0.2%) and platelet count of 502,000/mm³. BUN and creatinine were 7.9 and 0.3 mg/dL, respectively. Hypoalbuminemia and hypoglobulinemia were 2.5 and 2.4 g/dL, respectively, with normal transaminase levels. Stool examinations revealed no white blood cells, red blood cells, and parasites including negative cultures for pathogenic bacteria. Stool *Clostridium difficile* toxin assay was positive.

Ceftriaxone 2 g once daily and metronidazole 500 mg every 8 hours were continued intravenously and misoprostal vaginal suppository for fetal evacuation. The following day the dead fetus was aborted vaginally with no gross anomalies. The placenta demonstrated appropriate villous maturation for GA, focal retroplacental, subchorionic hemorrhage and three-vessel cord without funisitis or demonstrated organism. Film acute abdomen series showed generalized small bowel and large bowel dilatation without step ladder pattern and abnormal free air as shown in Figure1. Computerized tomography of abdomen as shown in Figure 2 revealed markedly generalized dilatation of small and large bowels without definite point of obstruction. The maximal diameter of small bowel loop and cecum were 5 cm and 7 cm, respectively, with moderate amount of ascites also noted. Colitis with pseudo-colonic obstruction and coincidental *C. difficile* associated diarrhea (CDAD) were primarily diagnosed and oral vancomycin 250 mg every 6 hours was administered. Because of a slight improvement, a repeated CT of abdomen on day 9 of therapy was performed. The result showed no significant change and no complications such as ischemic colitis and perforation. Colonoscopy performed on the eleventh day of treatment identified multiple punch-out ulcers, diameters varied between 0.5-2 cm, with normal intervened mucosa on descending colon approximately 50 cm proximal to anus. Colonic ulcer biopsies demonstrated ulcerated mucosa with suppurative pseudomembranes and no granulomas seen. There were few positivities of intranuclear CMV particles by immunohistochemistry method, suspicious for CMV colitis. Nonetheless, CMV viral load was undetectable (< 600 copies/mL). Intravenous ganciclovir 300 mg every 12 hours was commenced and the patient responded well to the antiviral therapy. Fever and gastrointestinal symptoms were resolved within 2 weeks of treatment, including follow-up abdominal CT. Following colonoscopy found only two areas of abnormal mucosa with healed granulation tissue, and negative for CMV immunostaining technique after 3-week ganciclovir treatment. The patient received ganciclovir for four weeks and metronidazole and vancomycin for two weeks. She was clinically stable and eventually discharged after 40 days of admission.
Figure 1. Film acute abdomen series showed generalized small bowel and large bowel dilatation without step ladder pattern and abnormal free air.

Figure 2. Computerized tomography of abdomen revealed markedly generalized dilatation of small and large bowels without definite point of obstruction, the maximal diameter of small bowel loop and cecum were 5 cm and 7 cm (white arrow) respectively, moderate amount of ascites also noted.
DISCUSSION

Cytomegalovirus (CMV) is a well-recognized pathogen, with 40 to 100% of general population having positive serology. It is a member of the Herpesviridae family, which also includes Epstein–Barr, herpes simplex, varicella zoster, and human herpesviruses 6 to 8. CMV is excreted in body fluids including saliva, respiratory secretions, urine, blood, breast milk, and semen. It is transmitted via multiple routes such as sexual transmission, blood or tissue exposure, perinatal transmission and close personal contact. Serological studies have shown a bimodal peak of infection, the first of which is in early childhood, and the second in young adulthood.

Clinically significant disease, whether primary or reactivation, is typically seen in immunocompromised individuals, such as AIDS, organ transplanted patients, and post chemotherapy patients. In these hosts, CMV disease usually presents with specific organ involvement e.g. eyes, lungs, gastrointestinal tract, and is usually associated with a poor prognosis. Whereas pneumonitis is more common in bone marrow transplant patients, retinitis and gastrointestinal disease are usually seen in AIDS patients.

In normal host, primary infection is usually asymptomatic but can produce a syndrome similar to infectious mononucleosis. CMV remains latent within the host and can reactivate later in life. However, organ specific disease can occur in the setting of primary infection. In a systematic review of the literature regarding serious manifestations of CMV infection in apparently immunocompetent individuals, published between 1950 and 2007, we retrieved 89 articles reporting on severe CMV infection in 290 immunocompetent adults. The gastrointestinal tract and the central nervous system were the most frequent sites of severe CMV infection. Gastrointestinal CMV infection manifests as colitis, esophagogastroenteritis, ileitis, proctitis or exacerbation of inflammatory bowel disease. This patient presented with fever, abdominal pain and mucous diarrhea which those symptoms were compatible with inflammatory gastrointestinal process which is a pathophysiology of this condition. Pathological findings of CMV colitis are intestinal ulcerations, erosions, and mucosal hemorrhage which colon and esophagus are the most common sites of infection. However, the pathogenesis is poorly understood.

To our knowledge, there are a few reported cases of CMV colitis in pregnancy. We searched literature for case reports of CMV colitis in pregnancy through the databases of the PubMed. Search terms applied were “cytomegalovirus”, “CMV”, “pregnancy”, “immunocompetent”, “colitis”, “enterocolitis” and “gastrointestinal tract infection”, in various combinations and limited to those written in English. We found only 4 cases of CMV colitis in pregnancy including our case report, all were summarized in Table 1. Most of the patients had CMV infection between 2nd and 3rd trimester and primary infections were postulated according to serological tests. During this period of pregnancy, Th2 and Th3 responses are enhanced, whereas Th1 cytokines (i.e., IL-12 and IFN-γ), which are potentially detrimental to the foreign fetus, are suppressed. The cell mediated immunity are relatively defected, pregnant women are at high risk to be infected by intracellular organisms and have severe manifestations, corresponding to the presented case. However, the patient’s serology for CMV infection was not done, thus we could not prove the primary infection. From the case series, all pregnant women presented with inflammatory diarrhea for more than 1 week, most of them, including the patient, had intrauterine fetal death. The patient’s fetus had no gross anomaly and the fetal pathology and immunohistochemistry were not investigated. Hence we did not know whether the fetal
Table 1. Summary of case reports of cytomegalovirus colitis in pregnancy.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>GA (weeks)</th>
<th>Type of infection</th>
<th>Symptoms</th>
<th>Methods of diagnosis</th>
<th>Treatments</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>39&lt;sup&gt;13&lt;/sup&gt;</td>
<td>33</td>
<td>Primary</td>
<td>Onset: 1 week Bloody diarrhea, abdominal pain, fever</td>
<td>Serum CMV IgM &gt; 1:1,024, negative CMV IgG Viral culture&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Supportive therapy</td>
<td>Congenital CMV infection IBD</td>
</tr>
<tr>
<td>22&lt;sup&gt;7&lt;/sup&gt;</td>
<td>28</td>
<td>Primary</td>
<td>Onset: 16 days Bloody diarrhea, fever, vomiting, gastrointestinal bleeding, toxic megacolon and impending bowel perforation</td>
<td>CMV IgM- positive Histopathology&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ganciclovir</td>
<td>DFIU Resolution</td>
</tr>
<tr>
<td>22&lt;sup&gt;14&lt;/sup&gt;</td>
<td>31</td>
<td>Primary&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Onset: 1 week Fever, abdominal pain, vomiting, abdominal distension, toxic megacolon and mesenteric vein thrombosis</td>
<td>Serology&lt;sup&gt;d&lt;/sup&gt; PCR CMV&lt;sup&gt;e&lt;/sup&gt; CMV pp65 Ag&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Ganciclovir</td>
<td>DFIU Resolution</td>
</tr>
<tr>
<td>38 (case report)</td>
<td>18</td>
<td>Unknown</td>
<td>Onset: 12 days Mucous diarrhea, fever, abdominal pain, severe bowel ileus, and pseudo-obstruction</td>
<td>Immunohistochemistry&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Ganciclovir</td>
<td>DFIU Resolution</td>
</tr>
</tbody>
</table>

CMV: cytomegalovirus, DFIU: dead fetus in utero, GA: gestational age, IBD: inflammatory bowel disease, PCR: polymerase chain reaction

<sup>a</sup> from urine,
<sup>b</sup> CMV inclusions in endothelial cells,
<sup>c</sup> assumed from clinical syndrome and laboratory tests,
<sup>d</sup> the authors did not specify method and type of serology,
<sup>e</sup> the authors did not specify type of specimens,
<sup>f</sup> from colonic biopsies
death was related to intrauterine CMV infection. Severe CMV colitis can complicate by profuse bleeding necessitating resection, toxic megacolon, and bowel perforation, potentially contributing to fetal loss.8

Gold standard for the diagnosis of CMV disease is histopathological finding of typical intranuclear and/or intracytoplasmic inclusion body or cytomegalic change of infected cell. However, viral inclusion cannot be easily seen. Ismail HK et al found that the specificity and sensitivity of histopathological diagnosis were 100% and 23.2 %, respectively.9 Kandiel A et al reported the sensitivity of immunohistochemistry (IHC) for detecting CMV infection was higher compared to histopathological diagnosis, approximate 78-93%, and specificity was 92-100%.10 That was the reason why the presented case could not be found a cytopathic change of CMV colitis into histopathologic sections, but was diagnosed by IHC. Furthermore combination of histopathology and IHC were able to increase sensitivity and specificity.11

Most reported cases received intravenous ganciclovir for at least 2 weeks, including this patient, with good clinical outcomes, except one patient who was subsequently diagnosed with inflammatory bowel disease. Most patients had severe complications similar to this patient, and her clinical course became worse from colonic pseudo-obstruction probably as a result of delayed diagnosis.

In another study of CMV colitis in immunocompetent hosts, 44 patients were identified. CMV colitis mainly involved and correlated with worse outcome in older patients with some comorbidities, and patients with immune-modulating diseases, e.g. diabetes mellitus, lymphoproliferative and non-hematological malignancies, renal failure, autoimmune disease and pregnancy.12 In pregnant patients, the maternal and fetal outcome was associated with severity of disease and delayed diagnosis similar to the presented case. Whenever a pregnant woman has a problem with prolonged inflammatory diarrhea, clinical suspicion and early diagnosis of CMV colitis are the main modules to improve pregnancy outcome.

**Conclusion**

Although CMV infection usually occurs in immunocompromised patients such as AIDS patients and transplant recipients, one should also keep in mind the possibility of CMV infection in non-immunocompromised patients. A pregnant woman with persistent inflammatory diarrhea, CMV colitis should be considered in differential diagnosis. Clinical suspicion, early diagnosis and treatment are major roles to improve outcome.

**References**

8. Klauber E, Briski LE, Khatib R. Cytomegalovirus


