Cytomegalovirus-Associated Manifestations Involving the Digestive Tract in Children With Human Immunodeficiency Virus Infection

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ABSTRACT

Objective: To study the clinical manifestations of gastrointestinal cytomegalovirus disease in children with human immunodeficiency virus infection.


Results: Six of the eight children were younger than 1 year. The most common clinical presentations were fever and chronic diarrhea. Lower gastrointestinal hemorrhage and bowel perforation were noted in four and three patients, respectively. The colon was the most commonly affected site, followed by the small bowel and esophagus. The diagnosis was established by histopathology, obtained during endoscopy and surgery.

Mucosal edema, erythema, and ulcer comprised the most common endoscopic findings. Two patients with fever, chronic diarrhea, and lower gastrointestinal bleeding developed remission after being treated with a 14-day course of ganciclovir.

Conclusion: Gastrointestinal cytomegalovirus disease can result in serious life-threatening complications, such as bowel perforation and massive gastrointestinal bleeding. Patients with chronic diarrhea and fever of unidentified cause might benefit from gastrointestinal endoscopy for early diagnosis and treatment. Although ganciclovir does not eradicate the infection and relapses are frequent, this treatment can prevent complications and reduce morbidity. JPGN 35:669–673, 2002. Key Words: Cytomegalovirus—Human immunodeficiency virus—Gastrointestinal complications—Children. © 2002 Lippincott Williams & Wilkins, Inc.

Infection by cytomegalovirus is common among the general population. Frequently, the immunocompromised host—and rarely the immunocompetent host—can present with clinical disease ranging from mild to life-threatening conditions (1). The gastrointestinal tract is one of the common systems involved during cytomegalovirus disease, usually manifested by chronic diarrhea, abdominal pain, bleeding, perforation, peritonitis, odynophagia, and bowel obstruction (1–8). The frequency of clinical cytomegalovirus disease has increased in the past two decades with the epidemic of human immunodeficiency virus (HIV) infection and the associated acquired immunodeficiency syndrome (AIDS). Here we report our experience with eight children with HIV infection and gastrointestinal cytomegalovirus disease.

PATIENTS AND METHODS

The records of patients admitted to Chiang Mai University Hospital during the period 1995 to 2001 were reviewed to identify children with the diagnosis of HIV infection and gastrointestinal cytomegalovirus disease, who presented with gastrointestinal symptoms such as chronic diarrhea, abdominal pain, dysphagia, odynophagia, and gastrointestinal bleeding. Routine stool examination, stool by concentration method for parasites, and bacterial culture were performed to identify enteric pathogens. The diagnosis of gastrointestinal cytomegalovirus disease was confirmed by histopathology, in which a demonstration of cytomegalovirus inclusion bodies in either enterocytes, stromal cells, or endothelial cells was required and further supported by an immunohistochemistry stain using polyclonal anticytomegalovirus antibody. Declination of fever, cessation of diarrhea, and no further bleeding were considered as a clinical improvement after ganciclovir treatment. Demographic, clinical, and laboratory information were retrieved in a standardized form.

RESULTS

Eight children with HIV infection and gastrointestinal cytomegalovirus disease were identified. The median age
was 4.5 months (range, 2 months to 8 years), and six were younger than 1 year. There were four boys and four girls. All acquired HIV infection perinatally; none had received antiretroviral medications before their cytomegalovirus infection, and three had developed an AIDS-defining condition (Pneumocystis carinii pneumonia, wasting syndrome, and penicilliosis, one each); two had CD4 count determined (1,080 and 490 cells/µL); viral load determination was not available. During the study period, protease inhibitors were not available, and other antiretroviral agents were rarely accessible in our hospital. Six patients presented with fever, five had a history of chronic diarrhea (≥ 3 weeks) or abdominal distention, four presented with lower gastrointestinal hemorrhage, and three presented with bowel perforation. Vomiting occurred in two subjects, odynophagia in two (one had esophageal candidiasis), and retrosternal pain in one (Table 1).

Laboratory test results showed anemia in all eight cases; the mean hemoglobin concentration was 8.2 g/dL (range, 5.2–10.2 g/dL). The mean white blood cell count was 10,600 cells × 10^9/L (range, 2,000–17,300 cells × 10^9/L). The platelet count ranged from 0.05 to 5.47 × 10^9/L, with five patients showing thrombocytopenia. Liver function test results showed hypoalbuminemia (<3.5 g/dL) in five cases, normal alanine aminotransferase concentration in all but one patient (who may have had cytomegalovirus-induced hepatitis), and hyperbilirubinemia (3.37 and 5.45 mg/dL) in two patients. Three patients with lower gastrointestinal bleeding showed prolonged partial thromboplastin time and normal prothrombin time. Serology for cytomegalovirus was obtained in five patients, immunoglobulin G was detected in five, and immunoglobulin M in none of the patients. Stool examination and culture did not show any pathogen.

The endoscopic and histopathologic findings are described in Table 2. Colonoscopy, esophagogastroduodenoscopy, and flexible sigmoidoscopy were performed in four, three, and one patient, respectively. Lower endoscopy showed edema of the colonic mucosa, loss of normal vascular pattern, patchy erythema, friability, and multiple ulcers. Esophageal ulcer, esophagitis, gastritis, duodenitis, and esophageal candidiasis were observed on esophagogastroduodenoscopy. Three patients (no. 1, 3, and 8) required surgery because of jejunal perforation, massive lower gastrointestinal bleeding, and jejunal and ileal perforation (one each). The diagnosis of gastrointestinal cytomegalovirus disease was confirmed in all cases by histopathology showing typical intranuclear and intracytoplasmic inclusion bodies in epithelial (Fig. 1), stromal, and endothelial cells of the gastrointestinal tract (Fig. 2).

Three patients were treated with ganciclovir. Patient no. 5 experienced an episode of seizure secondary to cerebral infarction and refused further treatment 3 days after administration of ganciclovir. Patient no. 6 (CD4 count: 1,080 cells/µL) presented with chronic diarrhea, lower gastrointestinal bleeding, and cytomegalovirus retinitis. She was treated with intravenous ganciclovir (5 mg/kg/dose every 12 hours) for 14 days with resolution of symptoms. She was started on zidovudine (7 mg/kg twice daily) and didanosine (6 mg/kg twice daily), and follow-up colonoscopy 3 weeks later showed improvement and no evidence of cytomegalovirus cytopathic cells. Six weeks after remission, however, the patient again developed lower gastrointestinal bleeding and active cytomegalovirus retinitis. She promptly responded to a second 14-day course of ganciclovir and then developed a third relapse and was treated with a 21-day course of ganciclovir. Unfortunately, she did not improve this time and developed hepatotoxicity, prompting discontinuation of medications. Patient no. 7 (CD4 count: 490 cells/µL) also presented with cytomegalovirus retinitis and was treated with a 21-day course of intravenous ganciclovir. His fever and gastrointestinal symptoms improved, but the retinitis persisted. Six patients died (one of three that received ganciclovir and five of five that did not receive ganciclovir) of complications related to the cytomegalovirus infection (peritonitis secondary to bowel perforation in three, massive lower gastrointestinal bleeding in two, and seizures in one).

**TABLE 1. Demographic, clinical manifestations, and initial outcome**

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>67</td>
<td>103</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Vomiting</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Retrosternal pain</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bowel perforation</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ganciclovir treatment</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Initial outcome</td>
<td>Died</td>
<td>Died</td>
<td>Died</td>
<td>Died</td>
<td>Died</td>
<td>Alive</td>
<td>Alive</td>
<td>Died</td>
</tr>
</tbody>
</table>
Cytomegalovirus is one of the most common opportunistic infections among adults with HIV infection, resulting in retinitis, gastrointestinal disease, pneumonitis, encephalitis, hepatitis, and sclerosing cholangitis (1). Gastrointestinal cytomegalovirus disease is estimated to affect about 20% of adults with AIDS (9). Cytomegalovirus can involve all parts of the gastrointestinal tract, but the colon and esophagus are the most common sites (1). Reports of gastrointestinal complications in HIV-infected children have increased since pediatric gastrointestinal endoscopy has been widely used. Clinical symptoms reported in children include chronic diarrhea, abdominal pain, bleeding, and bowel obstruction (2,3,6–8). Bowel perforation, peritonitis, and odynophagia have been described mostly in adult patients (1,4,5).

In this report, chronic diarrhea and fever were the most common clinical manifestations. Inflammation of the gastrointestinal tract is responsible for these manifestations and, if untreated, ulcers eventually develop, leading to fatal complications such as gastrointestinal bleeding and perforation. One half and one third of our patients developed lower gastrointestinal bleeding and perforation, respectively. Cytomegalovirus infection of the endothelial cells and ensuing vasculitis have been postulated as playing a major role in the development of thrombosis, local ischemia, and ulceration of the gastro-

**DISCUSSION**

Cytomegalovirus is one of the most common opportunistic infections among adults with HIV infection, resulting in retinitis, gastrointestinal disease, pneumonitis, encephalitis, hepatitis, and sclerosing cholangitis (1). Gastrointestinal cytomegalovirus disease is estimated to affect about 20% of adults with AIDS (9). Cytomegalovirus can involve all parts of the gastrointestinal tract, but the colon and esophagus are the most common sites (1). Reports of gastrointestinal complications in HIV-infected children have increased since pediatric gastrointestinal endoscopy has been widely used. Clinical symptoms reported in children include chronic diarrhea, abdominal pain, bleeding, and bowel obstruction (2,3,6–8). Bowel perforation, peritonitis, and odynophagia have been described mostly in adult patients (1,4,5).

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**TABLE 2. Endoscopic and histopathologic findings**

<table>
<thead>
<tr>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endoscopic procedure</strong></td>
<td>Colonoscopy</td>
<td>EGD and colonoscopy</td>
<td>EGD and flexible sigmoidoscopy</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td><strong>Endoscopic findings</strong></td>
<td>Mucosal edema and ulcer at ileum</td>
<td>Esophageal ulcer, esophagitis, gastritis, duodenitis, colonic mucosal edema, erythema, friability, and ulcers</td>
<td>Esophageal candidiasis, colonic mucosal edema, erythema, friability, and rectal ulcers</td>
<td>Edema, patchy erythema, multiple ulcers with yellow exudate</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td>Mucosal edema, erosion, ulceration with mononuclear inflammatory cell infiltrate; positive CMV inclusion bodies in the endothelial, epithelial, and stromal cells</td>
<td>Open ulceration with fibrous tissue containing fibrin-deposited vasculitis; mucosal edema with chronic inflammatory cell infiltrate; cryptitis; positive CMV inclusion bodies in the endothelial and stromal cells</td>
<td>Necrotic exudates and inflamed mucosa with formation of crypt abscess; positive CMV inclusion bodies in the endothelial and stromal cells</td>
<td>Mucosal edema; positive CMV inclusion bodies in the endothelial, epithelial, and stromal cells</td>
</tr>
<tr>
<td><strong>Immunohistochemical stain for polyclonal antibody to CMV</strong></td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

EGD, esophagogastroduodenoscopy. Note: Case 1, 2, and 8 presented with bowel perforation and underwent surgery without endoscopy, and all had histopathologic confirmation of gastrointestinal CMV disease.

**FIG. 1.** High-power magnification of the colonic crypt shows degenerated crypt lined by irregular-bordered absorptive cells bearing foamy cytoplasm and distorted nuclei. One enterocyte displays glassy nuclei and perinuclear clear zone, almost surrounded by typical cytoplasmic eosinophilic inclusion.
intestinal mucosa (4,8). The histopathologic findings in our cases support this hypothesis because all sections had evidence of cytomegalovirus inclusions in the endothelial cells. Primary cytomegalovirus infection of the epithelial cells of the gastrointestinal tract can also result in mucosal erosion and ulceration (5). Although *Salmonella* and *Cryptosporidium* were the enteric pathogens in our HIV-infected pediatric population, they rarely caused intestinal bleeding (10).

The serology for cytomegalovirus is of little help in our children because of their age and immune impairment. Gross endoscopic abnormalities noted herein are similar to those previously reported, including mucosal edema, erythema, friability, hemorrhage, erosion, and ulcer of the colon, esophagus, and stomach (1). Even in cases with normal gross endoscopic findings, it is advisable to obtain random biopsy specimens because, as reported by Dieterich et al. (9), nearly 25% can have evidence of cytomegalovirus infection on histopathology.

Because of nonspecific symptoms and endoscopic findings, confirmation of cytomegalovirus infection necessarily requires detection of typical intranuclear and intracytoplasmic inclusion bodies in biopsy specimens. Immunohistochemistry for cytomegalovirus-specific antigens may increase sensitivity. Both techniques require endoscopy and gastrointestinal biopsy. Hence, endoscopy with biopsy are crucial for HIV-infected children presenting with chronic diarrhea and fever whose routine laboratory investigations fail to identify any causative agent. These procedures should be expedited in patients with lower gastrointestinal bleeding.

Although rare, gastrointestinal cytomegalovirus disease also has been reported in immunocompetent individuals. These patients usually have underlying gastrointestinal conditions such as Menetrier disease (11), cow’s milk allergy (12), and ulcerative colitis (13). Interestingly, Fox et al. (14) recently reported an immunocompetent infant with cytomegalovirus enterocolitis. In general, the clinical manifestations are similar to those described among immunocompromised hosts, but they tend to resolve without specific therapy, and episodes of relapse have not been reported (11–13).

Surgical intervention is indicated for patients with bowel perforation. For other instances of cytomegalovirus disease, successful medical treatment has been reported with the use of ganciclovir alone (1,3,15–17). Maintenance therapy is well established for cytomegalovirus retinitis but not for gastrointestinal cytomegalovirus disease (17). Currently, restoration of the immune system by antiretroviral treatment has the best chances in preventing relapses. Before the widespread use of antiretroviral therapy, patients with AIDS who had gastrointestinal cytomegalovirus disease would relapse within 3 to 4 months (15,17). In the event of relapse, a second course of treatment with ganciclovir or other alternative drug such as foscarnet has been suggested for adult patients with AIDS (17).

Although cytomegalovirus disease in HIV-infected adults occurs usually in patients with marked immunosuppression, one of our infants did not have evidence of severe immunosuppression. This observation probably reflects the poor correlation seen in infants between the number of CD4 T lymphocytes and their functional immune status. This fact has been well demonstrated by the development of opportunistic infections such as *P. carinii* pneumonia (18).

In summary, gastrointestinal cytomegalovirus disease is not uncommon in HIV-infected children. It can result in serious life-threatening complications such as bowel perforation and massive gastrointestinal bleeding. The early use of gastrointestinal endoscopy in patients with an unidentified cause of chronic diarrhea and fever, particularly in patients with lower gastrointestinal bleeding, can establish the diagnosis and prompt initiation of ap-
propriate treatment. Although the use of ganciclovir does not eradicate the infection and relapses frequently occur, this treatment can prevent complications and reduce morbidity.

REFERENCES