

Intractable Diarrhea From Cytomegalovirus Enterocolitis in an Immunocompetent Infant

LeAnne M. Fox, MD*; Michael A. Gerber, MD‡; Laurie Penix, MDS§; Andrew Ricci, Jr, MD||; and Jeffrey S. Hyams, MD‡

ABSTRACT. Infection with cytomegalovirus (CMV) in infants can be congenital or perinatal. Infected infants may be asymptomatic or present with pneumonia, rash, hepatosplenomegaly, or encephalitis.¹ In the presence of an immunodeficiency, severe and sometimes fatal disease may occur. To our knowledge, CMV has not been identified previously as a cause of intractable diarrhea of infancy. We report the case of a 5-week-old immunocompetent infant with intractable diarrhea attributable to CMV-induced enterocolitis. Recognition of this infection and initiation of ganciclovir therapy was associated with a rapid improvement and resolution of the diarrhea. *Pediatrics* 1999;103(1). URL: <http://www.pediatrics.org/cgi/content/full/103/1/e10>; *cytomegalovirus, enterocolitis, intractable diarrhea.*

ABBREVIATIONS. CMV, cytomegalovirus; HIV, human immunodeficiency virus.

CASE REPORT

A previously healthy 5-week-old male infant of a normal pregnancy and delivery presented to Connecticut Children's Medical Center in July 1997 with a 24-hour history of fever (38.5°C rectal), irritability, decreased oral intake, and diarrhea. He had been born in Hartford, CT, and was breastfed exclusively from birth. Physical examination revealed a lethargic infant with a pulse of 140 beats/minute, a respiratory rate of 28/minute, a temperature of 36.6°C (rectal), a weight of 4.4 kg (50th percentile), a length of 56 cm (75th percentile), and a head circumference of 37 cm (50th percentile). Bilateral anterior cervical and supraclavicular lymphadenopathy was noted. No murmurs were heard, and his lungs were clear to auscultation. There was no organomegaly, and no rashes were present. Pertinent laboratory values included white blood count of $9.5 \times 10^9/L$ with 28% band forms; 4% neutrophils; 9% monocytes; and 56% lymphocytes with occasional reactive lymphocytes; hematocrit, 33.5%; platelet count, $540 \times 10^9/L$; serum electrolyte Na^+ ,

133 mmol/L; K^+ 4.7 mmol/L; Cl^- 103 mmol/L; HCO_3^- , 19 mmol/L; blood urea nitrogen, 1.8 mmol/L; AST, 21 U/L; ALT, 11 U/L; albumin, 4.2 g/dL; and total protein, 7.1 g/dL. Examination of the stool revealed many leukocytes and the presence of occult blood. Stool Na^+ was 97 mmol/L, stool K^+ was 10 mmol/L, and urine Na^+ was <10 mmol/L. Results of the cerebrospinal fluid examination, chest radiograph, and abdominal ultrasound all were normal. Cultures of blood, stool (*Salmonella*, *Shigella*, *Campylobacter*, *Escherichia coli* O157:H7, *Yersinia*); urine; and cerebrospinal fluid were obtained, and the patient was treated empirically with intravenously administered ampicillin and cefotaxime. Intravenous fluid support also was begun. Antimicrobial therapy was discontinued after 72 hours when all culture results were negative. Despite being given nothing by mouth, the patient's stool output continued at 90 mL/kg/day, and he lost 445 g over 7 days. Attempts to feed with a protein hydrolysate formula via continuous infusion through a nasogastric tube were unsuccessful. A central venous catheter was placed, and parenteral nutritional support was begun. Intermittent fevers to 39°C (rectal) were noted.

Endoscopic evaluation of the upper gastrointestinal tract and the rectosigmoid was performed 5 days after admission. Gastric, duodenal, and rectosigmoid biopsies revealed extensive neutrophilic inflammation and epithelial changes with nuclear enlargement suggestive of a viral cytopathic effect (Fig 1). Immunoperoxidase staining for CMV, adenovirus, and herpes simplex virus were nonreactive. One week after admission (at 7 weeks of age), the patient's serum Venereal Disease Research Laboratory test was nonreactive. IgG was 554 mg/dL, IgM was 110 mg/dL, and enumeration of T cell subsets by flow cytometry revealed normal $CD4^+$ T cells with slightly low numbers of $CD8^+$ T cells. Results of polymerase chain reaction for human immunodeficiency virus (HIV) DNA and serologic testing for HIV (enzyme-linked immunosorbent assay and Western blot) were negative at this time and when repeated at 1 year of age. Empiric therapy with intravenous immune globulin (1 g/kg) was initiated; however, the severe diarrhea continued.

Three weeks after admission, the patient continued to experience daily fevers of 39°C (rectal) with worsening of the diarrhea (>90 mL/kg/day) and, consequently, repeat mucosal biopsies of the gastrointestinal tract were performed. These revealed mod-

From the *University of Connecticut School of Medicine, University of Connecticut Health Center, Farmington, Connecticut; ‡Department of Pediatrics, University of Connecticut School of Medicine, Connecticut Children's Medical Center, Hartford, Connecticut; §Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut; and ||Department of Anatomic Pathology, Hartford Hospital, Hartford, Connecticut. Received for publication Jun 26, 1998; accepted Aug 25, 1998. Address correspondence to Jeffrey S. Hyams, MD, Connecticut Children's Medical Center, 282 Washington St, Hartford, CT 06106. PEDIATRICS (ISSN 0031 4005). Copyright © 1999 by the American Academy of Pediatrics.

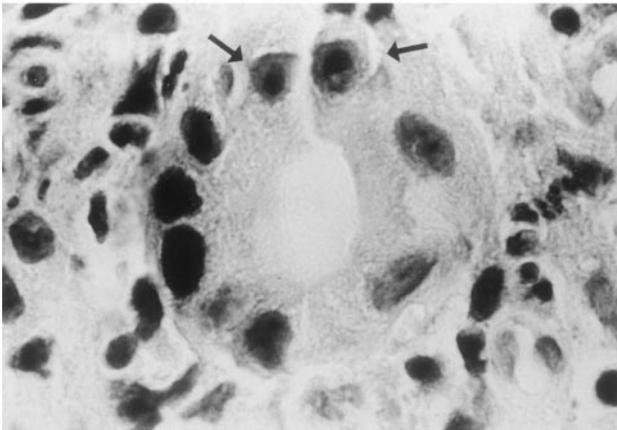
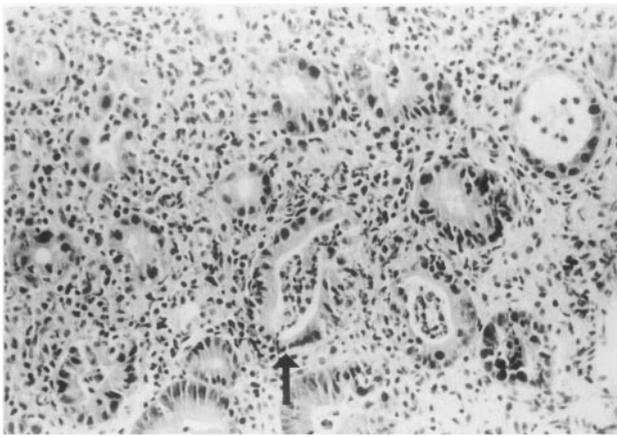


Fig 1. Top, Marked active neutrophilic colitis with crypt abscesses (arrow). Bottom, Some enlarged nuclei are suspicious for viral cytopathic effect (arrows) (original magnifications, 200× [top] and 1000× [bottom]).

erate to severe chronic active duodenitis with subtotal villus blunting and numerous nuclear and cytoplasmic inclusions characteristic of CMV enteri-

tis (Fig 2). Although numerous, the inclusions were distributed in a patchy manner in the duodenal biopsy. CMV early antigen immunostaining was focally reactive. A shell vial assay of the urine was positive for CMV early antigen, and subsequently the urine culture grew CMV. However, stool, nasopharyngeal, and rectal cultures failed to grow CMV. Ophthalmologic examination was normal, and audologic evaluation revealed normal hearing. Neurologic findings throughout the hospital course were normal, including results of cranial computed tomography. Intravenously administered ganciclovir (10 mg/kg/day) was given for 4 weeks, followed by 1 week of orally administered therapy. Within several days of initiating ganciclovir therapy, the patient became afebrile, the diarrhea decreased markedly to ~30 mL/kg/day, and enteral feeding was begun with a continuous nasogastric infusion of a low carbohydrate protein hydrolysate formula (Mead Johnson [Evansville, IN] 3232A).

Over the next 4 weeks, the enteral feedings were slowly advanced with the addition of carbohydrate and an eventual switch to Alimentum (Ross Laboratories, Columbus, OH). By 8 weeks after admission, intake was exclusively oral.

After completing the ganciclovir therapy, follow-up biopsies of the duodenum and stomach showed diminished neutrophilic inflammation in both sites, with partial restoration of the villus architecture in the duodenum. Results of repeat CMV immunostaining were negative, and no nuclear or cytoplasmic inclusions were seen. Repeat urine culture results at 6 months of age still were positive for CMV.

At 4 months of age, repeated enumeration of peripheral blood lymphocyte subsets by flow cytometry revealed normal numbers of both CD4⁺ and CD8⁺ T cells (Table 1), as well as normal ratio of

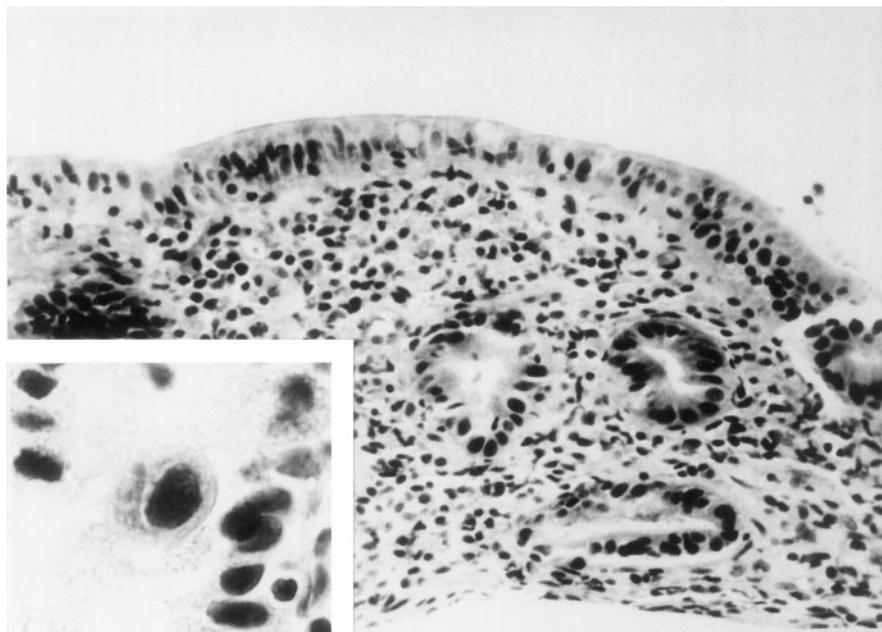


Fig 2. Active duodenitis with total villus atrophy without crypt hyperplasia. Inset, Characteristic CMV inclusions in nucleus and cytoplasm (original magnifications 200× and 500× [inset]).

naive CD45RA and memory CD45RO subsets of CD4 T cells for age (CD4⁺ CD45RA⁺ 2344 and CD4⁺ CD45RO⁺ 697 cells/58 L). At 6 months of age, in vitro lymphocyte proliferation studies were performed on the patient's peripheral blood as well as on that of an adult control subject. The patient's lymphocytes demonstrated an excellent polyclonal proliferation in response to mitogens but failed to recognize *Candida albicans* or tetanus antigens. The patient was seen again for follow-up evaluation at 12 months of age, at which time his growth and development appeared to be entirely normal.

DISCUSSION

To our knowledge, this is the first reported case of CMV-induced enterocolitis in an immunocompetent infant presenting with intractable diarrhea.

It is unclear whether this infant had a congenital or perinatal CMV infection. Congenital CMV infection occurs in ~1% of newborns in the United States, and most infants with congenital CMV infection are asymptomatic. Approximately 10% of neonates with congenital CMV infection have findings such as hepatosplenomegaly, pneumonitis, jaundice, petechiae, purpura, and the development of severe central nervous system sequelae such as mental retardation, sensorineural hearing loss, cerebral palsy, seizures, and visual defects.^{2,3} Perinatal infection with CMV, often acquired through genital tract secretions at delivery or transmitted through breast milk, usually is asymptomatic but can present with pneumonitis, lymphadenopathy, and hepatosplenomegaly.³ Because this patient presented at 5 weeks of age, we were unable to determine whether this case represented a congenital or perinatal CMV infection.

Gastrointestinal infections caused by CMV can be an important problem in the immunocompromised child. Complications of gastrointestinal CMV infections in these individuals include perforation, hemorrhage, and ulceration, and have occurred after heart, liver, and renal transplantation.⁴ CMV infection of the gastrointestinal tract in children with acquired immunodeficiency syndrome can be associated with chronic diarrhea, ulcerations, transmural inflammation, vasculitis, hemorrhage, perforations, and intestinal obstruction.⁵ Extensive immunologic evaluation of this patient, including lymphocyte subset enumeration and in vitro lymphocyte studies, revealed no evidence of a congenital immunodeficiency. Failure of this 6-month-old's lymphocytes to proliferate in response to *C albicans* and tetanus antigens is likely attributable to immaturity of his cell-mediated immune response as well as to antigenic naivete. Antigen-specific proliferative responses, as well as intradermal delayed-type hypersensitivity responses, may be difficult to detect in immunocompetent children younger than 1 year of age.⁶

Gastrointestinal infections caused by CMV also have been reported in immunocompetent patients with underlying gastrointestinal disease. For example, an association between Menetrier's disease and CMV infection has been reported.⁷ A 12-month-old girl with intussusception and intestinal perforation

in association with CMV enteritis of the ileum has been described,⁸ as well as a case of a 5-week-old immunocompetent infant with cow milk allergy and CMV colitis in which the child thrived and developed normally without any specific treatment for the CMV infection.⁹

Ganciclovir, a guanosine analog that selectively inhibits CMV DNA polymerase, is the antiviral agent used to treat immunocompromised patients with active CMV infection. Ganciclovir has proven efficacious in treating and preventing CMV infection in transplant recipients, yet little data about the use of ganciclovir in the pediatric age group exist.¹⁰ Whitley and associates¹¹ report a phase II study of ganciclovir in 42 neonates with symptomatic congenital CMV infection, and the dosage of ganciclovir and duration of therapy used in our case were based on that study. Treatment with ganciclovir was associated with a clinical and histologic response with decreased stool output, increased oral intake, weight gain, and histopathologic improvement. Although the most appropriate regimen of ganciclovir administration for isolated CMV enterocolitis in an immunocompetent infant has yet to be determined, the current recommendation for the treatment of CMV enterocolitis in patients with HIV/acquired immunodeficiency syndrome is 3 to 6 weeks.¹²

In summary, we report a case of isolated CMV enterocolitis developing at 5 weeks of age in an immunocompetent infant. CMV should be considered in the differential diagnosis of enterocolitis and intractable diarrhea of infancy.

REFERENCES

1. Alford CA, Britt WJ. Cytomegalovirus. In: Fields BN, Knipe DM, eds. *Virology*. 2nd ed. New York, NY: Raven Press; 1990:1981-2010
2. Boppana SB, Fowler KB, Vaid Y, et al. Neuroradiographic findings in the newborn period and long-term outcome in children with symptomatic congenital cytomegalovirus infection. *Pediatrics*. 1997;99:409-414
3. Stagno S. Cytomegalovirus. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 4th ed. Philadelphia, PA: WB Saunders; 1995:312-353
4. Proujansky R, Orenstein SR, Kocoshis SA, Yunis EJ, Starzl TE. Cytomegalovirus gastroenteritis after liver transplantation. *J Pediatr*. 1988; 113:700-703
5. Kahn E. Gastrointestinal manifestations in pediatric AIDS. *Pediatr Pathol Lab Med*. 1997;17:171-208
6. Clerici ML, DePalma E, Roilides R, Baker R, Shearer GM. Analysis of T helper and antigen-presenting cell functions in cord blood and peripheral blood leukocytes from healthy children of different ages. *J Clin Invest*. 1993;91:2829-2836
7. Eisentat DD, Griffiths AM, Cutz E, Petric M, Drumm B. Acute cytomegalovirus infection in a child with Menetrier's disease. *Gastroenterology*. 1995;109:592-595
8. Zupancic JA, Pennie RA, Issenman R. Intussusception in a child with cytomegalovirus infection. *Pediatr Infect Dis J*. 1994;13:548-549
9. Jonkhof-Slok TW, Veenhoven RH, de Graeff-Meeder ER, Buller HA. An immunocompetent infant with cow's milk allergy and cytomegalovirus colitis. *Eur J Pediatr*. 1997;156:528-529
10. Canpolat C, Culbert S, Gardner M, Whimbey E, Tarrand J, Chan KW. Ganciclovir prophylaxis for cytomegalovirus infection in pediatric allogeneic bone marrow transplant recipients. *Bone Marrow Transplant*. 1996;17:589-593
11. Whitley RJ, Cloud G, Gruber W, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. *J Infect Dis*. 1997;175:1080-1086
12. Whitley RJ, Jacobson MA, Friedberg DN, et al. Guidelines for the treatment of cytomegalovirus disease in patients with AIDS in the era of potent antiretroviral therapy. *Arch Intern Med*. 1998;158:957-969

Intractable Diarrhea From Cytomegalovirus Enterocolitis in an Immunocompetent Infant

LeAnne M. Fox, Michael A. Gerber, Laurie Penix, Andrew Ricci Jr and Jeffrey S. Hyams

Pediatrics 1999;103:e10

DOI: 10.1542/peds.103.1.e10

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/103/1/e10>

References

This article cites 10 articles, 1 of which you can access for free at:
<http://pediatrics.aappublications.org/content/103/1/e10#BIBL>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Intractable Diarrhea From Cytomegalovirus Enterocolitis in an Immunocompetent Infant

LeAnne M. Fox, Michael A. Gerber, Laurie Penix, Andrew Ricci Jr and Jeffrey S. Hyams

Pediatrics 1999;103:e10

DOI: 10.1542/peds.103.1.e10

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/103/1/e10>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 1999 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

