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Cytomegalovirus Enterocolitis in Immunocompetent Young Children: A Report of Two Cases and Review of the Literature

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Abstract

Cytomegalovirus (CMV) causes significant morbidity and mortality in congenitally-infected children and immunocompromised hosts. Among healthy individuals, CMV is generally thought to cause mild, self-limited illness. CMV enterocolitis, in particular, is rarely considered among immunocompetent children presenting with diarrhea. We describe two cases of invasive CMV colitis in immunocompetent infants presenting with diarrhea, and review the literature to date on this topic. Although invasive CMV enterocolitis has been sporadically reported among immunocompetent children, it remains an under-recognized cause of infectious diarrhea in this population, and indications for antiviral therapy are lacking. We propose that CMV should be included in the differential diagnosis of intractable diarrhea in immunocompetent children.

Keywords

Cytomegalovirus; Colitis; Enterocolitis; Gastroenteritis; Pediatrics; Immunocompetent

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Introduction

Cytomegalovirus (CMV) is the leading cause of congenital deafness in children and a major source of morbidity and mortality among immunocompromised individuals [1, 2]. In immunocompetent hosts, infection is generally asymptomatic or associated with mild, self-limited mononucleosis-like picture. Although CMV colitis has been reported in a number of otherwise healthy adults, cases of CMV enterocolitis are rare among immunocompetent young children. We describe two cases of CMV colitis in apparently immunocompetent infants presenting with a spectrum of diarrheal illness, and review the literature to date on this under-recognized etiology of infectious diarrhea in children.

Case #1

An eight week old, term, breast-fed male presented with a three-day history of watery diarrhea, non-bloody, non-bilious emesis, lethargy, and decreased activity. Upon admission, he was febrile to 39.3°C, with dry mucous membranes and poor tone. He was unresponsive to stimuli, with a liver edge noted 2 cm below the costal margin, and decreased lower extremities reflexes. Initial laboratory values demonstrated leukocytosis (23,400/μL with 26% bands, 6% polymorphonuclear cells, and 34% lymphocytes), and platelets 741, 000 /mm^3 (reference range 140,000–450,000/mm^3). Urinalysis was positive for reducing substances, and a lumbar puncture demonstrated a normal CSF profile. Liver enzymes were mildly elevated (ALT 59 U/L and AST 57 U/L), and a serum C-Reactive Protein (CRP) was elevated at 11.5 mg/dl (reference range is 0–0.5 mg/dl). Blood, urine, stool, and CSF cultures were negative, as well as stool Clostridium difficile PCR. Chest and Abdominal radiographs were normal. The patient received fluid resuscitation and empiric ceftriaxone.

During admission, the patient defervesced, but diarrhea and leukocytosis (peak WBC 54,600 $\times 10^3$ / μL) continued while receiving antibiotic therapy. A peripheral smear showed toxic granulations and precursor cells, but no blast forms, and a serum LDH and uric acid were elevated at 1105 mg/dL (reference range: <285 mg/dL), and 9.3 (reference range 2.0–7.0 mg/dL), respectively. Liver function tests showed worsening hepatitis (ALT of 229 U/L and AST of 79 U/L) and CRP remained elevated (16.5 mg/dL). Fecal lactoferrin was positive and stool guaiac for occult blood was negative. Stool enterovirus and adenovirus PCR, rotavirus antigen, ova and parasites, and viral culture, CMV urine shell vial antigen, and serum HIV PCR were all negative. A Head CT was normal. Because of to his ongoing leukocytosis and malabsorption, an esophagogastroduodenoscopy (EGD) and flexible sigmoidoscopy was performed.

The patient was the product of a full term, uncomplicated pregnancy, with a birthweight of 4.25 kg (98%). He was exclusively breast fed, but had a history of poor weight gain, decreasing from the 98th to the 25th percentile by the time of presentation. There was no family history of rheumatologic disease, cancer or inflammatory disorders, nor any known history of sick contacts, pet or animal exposures, travel outside of the home, or chemical exposures since his birth.

The EGD and flexible sigmoidoscopy revealed multiple areas of colonic ulceration. Histology demonstrated a severe destructive colitis, with diffuse mucosal erosions, extensive

crypt destruction with dropout and apoptosis, inflamed granulation tissue formation within the lamina propria and viral cytopathic effect visible on hematoxilin and eosin (H&E) staining (See Figure, Supplemental Digital Content 1A, B, C). Immunohistochemical (IHC) staining for CMV demonstrated multiple CMV inclusion bodies, confirming CMV colitis (See Figure, Supplemental Digital Content 1D). A subsequent CMV plasma PCR detected 3,436 copies/milliliter[i].

The patient was treated parenterally with ganciclovir for 4 weeks followed by oral valganciclovir for an additional 4 weeks. His diarrhea improvement within 72 hours of starting therapy, and his leukocytosis gradually improved with complete normalization of his white blood cell count by two weeks. Repeat plasma CMV PCR on day 14 and day 21 showed no detectable CMV DNA (<300 copies/milliliter), and his serum ALT returned to baseline by week six of therapy. An audiology test was normal. Immunology evaluation revealed normal B-Cell and T-cell subsets, as well as normal CD 11b/CD11c assay.

Case #2

A ten month old male with history of poor weight gain was admitted to our hospital with a three-week history of fever, bloody diarrhea and weight loss. He was the product of a full term, uncomplicated pregnancy and was, before this episode, tolerating a diet of formula and solid foods at home. He was otherwise fully immunized, and had no known history of sick contacts, pet or animal exposures, or foreign travel.

He was evaluated multiple times in the emergency room prior to his admission, where he was described as well appearing with good oral intake and mild weight loss. A workup, including stool bacterial cultures and an abdominal ultrasound, demonstrated no abnormality. On admission, he was afebrile and well-appearing, with mild wasting. His abdomen was soft and non-tender, with no noted hepatosplenomegaly. Initial laboratory tests showed leukocytosis (20,380 cells/μL: 3% band forms, 8% polymorphonuclear cells, 71% lymphocytes and 13% atypical lymphocytes), and a normal platelet count (340,000 cells/μL). Liver transaminases were normal; albumin and total protein were low at 2.3 g/dL (ref: 3.4–5.0) and 5.5 g/dL (ref:6.4–8.2 g/dL), respectively. CRP was mildly elevated at 2.87 mg/dL. Stool viral and bacterial cultures, enterovirus PCR, *Clostridium difficile* toxin assay, rotavirus and Giardia antigens were negative. Three ova and parasite examinations revealed few *Entamoeba coli* trophozoites by trichrome stain, which were considered clinically insignificant. Due to his failure to gain weight despite optimized caloric intake, an exploratory EGD and flexible sigmoidoscopy was performed.

On evaluation, the EGD was grossly normal, but flexible sigmoidoscopy revealed a friable colon with multiple ulcerations. On histology, colonic biopsies demonstrated multiple cytoplasmic and intranuclear viral inclusions, without evidence of crypt destruction or loss of epithelial architecture. CMV inclusions were predominantly identified in the colonic lamina propria (See Figure, Supplemental Digital Content 2A, B, C). IHC staining for CMV

[i]At the time of this clinical case, the WHO CMV PCR standard was not in use at our institution; an in- house CMV PCR plasma quantification assay was reported as copies /mL. The WHO international standard of IU/mL was implemented within one year following this case and used in case #2.

showed multiple CMV inclusion bodies, consistent with CMV infection (See Figure, Supplemental Digital Content 2D). A subsequent CMV plasma PCR detected 28,000 IU/mL.

Immunology evaluation consisting of HIV antibody, quantitative immunoglobulins, pneumococcal antibody titers, and T-cell, B-cell and NK-cell subsets, was normal. The patient did not require anti-viral therapy, and his diarrhea spontaneously resolved, with subsequent weight gain on high calorie elemental formula. A repeat plasma CMV PCR was performed one week later, and viral load decreased to of 280 IU/mL without anti-viral therapy.

Methods

We performed a literature search in Medline using PubMed through May 5, 2015, to identify cases of CMV colitis reported among immunocompetent children, utilizing the search terms “cytomegalovirus,” “immunocompetent,” “colitis,” “enterocolitis,” “infection,” “pediatric” and “children.” Articles and citations were carefully reviewed, cross referenced, and cases included if affected individuals were less than 18 years of age, demonstrated documented evidence of CMV infection by histology or tissue, stool or plasma PCR, and had clinical symptoms consistent with colitis. Non clinical (ie animal) studies, congenital infections, infections among pre-term infants, or cases of non-colonic CMV disease were excluded. Individual case data, including age, gender, birth weight, gestational age at birth, diet, white blood cell count at presentation, and immunologic workup, were collected and analyzed to characterize salient features of this cohort.

Results

We identified 93 reports of invasive CMV disease among presumably immunocompetent children. Of these, 19 reports describing a total of 21 cases met our criteria and, including the two presented here, comprise a total of 23 cases of invasive CMV enterocolitis among term, presumably immunocompetent children.

The diagnosis was confirmed by histology (IHC or viral inclusions) in 16/24 cases (67%), tissue PCR in 3 cases (Cases 5, 14, 16), stool PCR in 2 cases (cases 13, 15), and blood PCR alone in 2 cases (cases 6, 17). Children diagnosed by serum CMV PCR demonstrated positive CMV IgM at the time of diarrhea, and in the treated case (case 6), dramatic clinical improvement within 2 days of antiviral therapy. One child (case 9) was diagnosed by CMV IHC of a gastric biopsy; however, given the secretory nature of his diarrhea, enteric involvement was deemed to be highly likely.

Patient characteristics are reported in Table 1. The majority of cases were identified among young, male infants (median age at presentation 2.5 months) with no history of intrauterine growth retardation, prematurity, or prior infectious history. The majority of patients (72%) were exclusively breast fed at the time of illness, three had associated cow’s milk protein allergy (CMPA) at the time of presentation, and four had a documented history of poor weight gain prior to their illness.

Clinical characteristics at the time of presentation included marked leukocytosis and thrombocytosis (Table 2). Median WBC at presentation was 19.4×10^3 cells/μL (Interquartile range 14.4×10^3, 27.0×10^3), with leukocytosis (WBC >15,000) noted in 12/17 (71%) of individuals. Median platelet count was 545×10^3 cells/μL (IQR 205×10^3, 685×10^3) with thrombocytosis (platelet count> 140,000/μL) observed in 12/18 (63%) of individuals. Patients presented with loose watery (50%), as well as bloody, diarrhea (50%), with a mean symptom duration of 13 days (median 7 days) at the time of presentation (range1 – 90d). All patients were admitted, and thirteen individuals (59%) received antiviral therapy, with the majority of patients (82%) recovering completely. Significant complications (perforation, colonic stricture) were reported in three patients, and one infant, who was diagnosed at autopsy, died (18).

Discussion

Cytomegalovirus (CMV) is a ubiquitous double stranded DNA virus, and a cause of significant morbidity and mortality among congenitally infected children and immunocompromised hosts [2]. Among apparently immunocompetent children, post natal CMV infection is generally considered to be asymptomatic in the neonate, and is occasionally associated with a mononucleosis-like syndrome of fever, malaise, and mild hepatitis in older individuals [1, 3]. While in recent years, an increasing number of invasive CMV infections have been recognized among apparently immunocompetent adults, as well as in preterm infants presenting with necrotizing enterocolitis (NEC), CMV infection is rarely considered as a cause of infectious diarrhea in otherwise healthy children [4, 5].

Post-natal CMV enterocolitis was first described in 1996 by Huang et al, in a 42 day old term, formula fed female who presented with three days of fever and diarrhea, and subsequently developed ileal perforation [6]. Since then, a steadily increasing number of cases of CMV colitis have been reported (Table 1). While these reports demonstrate a spectrum of clinical illness across a range of ages from 6 weeks to 14 months, the majority of affected individuals we identified (including our first case above) were male, breast fed, and young (<=3m). Among such individuals, leukocytosis and thrombocytosis were common, and antiviral therapy frequently employed. In contrast, older individuals (>3m) we identified (including our case #2) presented with chronic, intractable diarrhea (mean duration 41 d) without thrombocytosis, and generally did not require antiviral therapy.

Among infants we identified with invasive CMV colitis, a significant proportion (72%) were breast fed, and in at least one case, CMV infection via breast milk was confirmed through sequencing of maternal breast milk and infant colonic CMV isolates [7]. CMV shedding in breast milk has been well documented among seropositive mothers, with maternal shedding estimates ranging from 37%–96%, and asymptomatic infant transmission occurring in up to 58% of cases [8–11]. However, in contrast to breast-milk CMV exposed preterm infants, in whom subsequent infection can manifest as a variety of illnesses ranging from acute enterocolitis to sepsis like syndrome, invasive CMV colitis has not been previously associated with breast milk transmission in term, immunocompetent infants [11–16]. While infection via breast milk leading to colitis was credibly demonstrated in only one case in our review, given the high proportion of breast fed infants represented in the infected group, and

the lack of routine testing for CMV in breast milk, it is possible that breast milk transmitted CMV played a role in additional cases as well [7].

Other potential modes of infection include exposure at the time of delivery through viral shedding within the birth canal, as well as asymptomatic congenital infection, and post-natal horizontal transmission [1]. However, despite previously reported infection rates of 27–56% among infants vaginally exposed to CMV, the degree of CMV shedding in the birth canal has been shown to be negligible in comparison to breast milk, and is not considered a major source of post-natal CMV infection [8, 14, 17]. In addition, while it is impossible to rule out asymptomatic congenital infection in the absence of routine CMV testing at birth, it is notable that no sequelae of congenital infection (low birth weight, microcephaly, or hearing loss) were noted in any of the cases, and that the median time to presentation of 2 months in our cohort was almost identical to the incubation period (42 d) reported among extremely low birthweight (ELBW) infants with proven post-natal CMV disease [14]. In addition, in contrast to congenital and pre-term cases of CMV infection, identified cases tended to demonstrate elevated platelet counts, and not thrombocytopenia as is typically observed in those settings. Finally, as horizontal CMV transmission, including toddler to toddler transmission, remains a leading mode of infection among young children, potential infection from childcare or other household contacts should also be considered, though no such contacts were identified in our case [18].

Finally, given the relative infrequency of postnatal CMV colitis despite a high reported rate of asymptomatic post-natal CMV infection among term infants, we found the high proportion of male infants in our cohort to be peculiar, and potentially suggestive of subtle differences among host immune defenses (X-linked or otherwise) against CMV [8, 19]. Recently, components of the innate immune system including toll-like receptor-2 and 4 (TLR-2, 4), and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) have been demonstrated to regulate host innate responses to CMV, and it is possible that among susceptible individuals, variations in these or other similar protein encoding genes may increase the risk of invasive CMV infection [19–21]. While no immune deficiencies were identified in our cases, it is likely that such subtle immune defects may have played a role in their illnesses, and that similar presentations likely warrant further genomic investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Reported cases of invasive CMV enterocolitisin immunocompetent infants. GCV, ganciclovir; VGCV, valganciclovir; TPN, total parenteral nutrition.

Case	Author	Year	Age (m)	Gender	Breast Fed	Bloody Stool	Ganciclovir	Outcome / Complications
1	Huang [1]	1996	1.5	F	No	No	No	Ileal perforation
2	Jonkhoff [2]	1997	1.5	M	No	Yes	No	Recovered without therapy
3	Quiros-Tejeira [3]	1999	2	M	Yes	No	Yes	2 weeks GCV, Recovered
4	Fox [4]	1999	1	M	Yes	Yes	Yes	4 weeks GCV, recovered.
5	Shinawi [5]	2001	14	M	No	NA	No	Recovered without GCV therapy
6	Iwanaga [6]	2003	2	F	Yes	No	Yes	2 weeks GCV, Recovered
7	Rongkavilit [7]	2004	2	M	Yes	No	Yes	3 weeks GCV, Recovered
8	Hinds [8]	2004	2	M	Yes	Yes	No	3 weeks TPN, Recovered without GCV
9	Shimizu [9]	2005	12	M	Yes	No	No	Prolonged TPN with pancreatitis and pseudocyst. Recovered without GCV
10	Buonomo [10]	2006	7	M	Yes	Yes	Yes	5 weeks VGC, Recovered
11	Abdulhannan [11]	2008	3	F	Yes	Yes	Yes	2 weeks GCV, recovered
12	Ramos-Boluda [12]	2009	2	M	Yes	Yes	Yes	2 weeks GCV, recovered
13	Nigro[i*] [13]	2009	3	M	N/A	Yes	Yes	8 weeks OGCV, recovered
14	Nigro[*] [13]	2009	2	M	N/A	No	Yes	8 weeks OGCV, recovered
15	Nigro[*] [13]	2009	3	F	N/A	No	Yes	8 weeks OGCV, recovered
16	Gupta [14]	2010	1	NA	No	NA	Yes	6 weeks GCV, recovered
17	Rogalidou [15]	2010	3	M	No	Yes	No	Recovered without GCV therapy
18	Tzialla [16]	2010	21d	F	Yes	No	Yes	Colonic Stricture, recovered with GCV × 6 weeks
19	Refai [17]	2012	2	F	Yes	No	No	Died
20	Louazon [18]	2014	2	M	Yes	Yes	No	Recovered without GCV therapy
21	Novakova [19]	2014	2	M	Yes	Yes	Yes	Colonic Stenosis
22	Sue	2015	2	M	Yes	No	Yes	4 weeks GCV + 4 weeks VGC, recovered
23	Sue	2015	10	M	No	No	No	Recovered without GCV therapy
Totals	---	---	**2**	**M (76%)**	**72%**	**45%**	**61%**	**Complications (22%)**

[i]*Infants reported by Nigro in a case series; although 2 M / 1F were reported, gender was not specifically assigned to specific cases. Weights between 3.34–3.4kg were reported but not assigned, and age at admission was designated at 2 – 3 months but also not specifically assigned.

Table 2

Characteristics of immunocompetent children with invasive CMV enterocolitis.

Characteristic	Median	Interquartile Range
Age (months)	2	2, 3
Birthweight (grams)	3350	2900, 3690
White Blood Count (× 10^3 cell/μL)	19.4	14.4, 27.0
Platelets (× 10^3 cell/μL)	545	205, 686
Duration of Diarrhea at presentation (days)	7	3, 12