Gastrointestinal Tract Cytomegalovirus Infection with Prolonged Vomiting and Fever in an Immunocompetent Child

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Cytomegalovirus is a ubiquitous DNA herpesvirus that infects most people worldwide. The clinical picture can be varied, depending upon the age and the immune status of the host, however CMV infection generally causes very mild or inapparent illness. A healthy immune system is required to keep the virus in check. If the immune system is depressed, CMV infection may cause serious localized disease (retinitis, hepatitis, pneumonitis, colitis), or a disseminated and severe potentially fatal illness. CMV infection of the gastrointestinal tract, reported only rarely in immunocompetent individuals, is a well-recognized condition in immunosuppressed patients.

We describe CMV infection of the upper GIT and prolonged CMV viremia in an immunocompetent 14 month old child, manifesting with protracted fever, vomiting, diarrhea and weight loss.

Patient Description

A 14 month old child was admitted to our pedriatric department because of fever and persistent vomiting that began 3 weeks earlier. Pregnancy and delivery had been normal and birthweight was 3,000 g. The patient was exclusively breast fed until one month before the onset of his illness, when a cow's milk-based formula was introduced. Family history was negative for allergic diseases. The patient was well until 3 weeks prior to referral to our hospital, when he was hospitalized for 5 days in another institution because of fever, vomiting, diarrhea and dehydration. Treatment with parenteral fluids followed by oral rehydration therapy and reintroduction of his regular diet led to an apparent complete recovery. Three days later the child was readmitted to the same hospital due to recurrence of fever, vomiting and diarrhea. Administration of intravenous fluids partially ameliorated his vomiting. He was discharged after 3 days, but fever, persistent vomiting and loose stools recurred at home, and he was found to have lost 1 kg in weight. Two days later, he was referred to our hospital.

On admission, he was an ill-appearing child with obvious wasting of subcutaneous fat and muscular mass. Body temperature was 38.6°C. His weight was 9,065 g (3rd percentile), height 79 cm (12.5 percentile) and head circumference 47 cm (25ath percentile). There was no skin or lymphadenopathy. The abdomen was flat, non-tender and without palpable masses or hepatosplenomegaly. Cardiorespiratory and neurological examinations were normal. No other pathological findings were found on complete physical examination.

The laboratory data were as follows. Complete blood count and differential were normal, as were blood chemistries including kidney and liver function tests and enzymes. Urine analysis and cerebrospinal fluid were normal. Erythrocyte sedimentation rate was 10 mm/hr. Blood, urine, cerebrospinal fluid and stool cultures for bacteria, fungi and viruses were negative. Repeated stool examinations for parasites and rotavirus were negative. Stool utilization tests showed fatty acid malabsorption. Serology for *Helicobacter pylori* was negative. Serological tests for a range of pathogens, e.g. Epstein-Barr virus, *Chlamydia*, enteroviruses, adenovirus, and influenza viruses, *Brucella* and *Salmonella*, were all negative. Serum immunoglobulin G titers for CMV were positive (1:800) but IgM was negative.

After clinical observation for one week in hospital, other tests were performed for investigation of fever of unknown origin and unexplained gastrointestinal manifestations. Galliums scan, chest X-ray, abdominal ultrasonography, upper GTI barium series and cranial computerized tomography examinations were all normal. On the second week of admission active CMV infection and viremia were found by isolation of the virus in the urine and by demonstration of CMV in the blood by polymerase chain reaction. Stools were negative for CMV. Since the patient continued to vomit and had frequent soft stools, an endoscopic examination of the upper GIT was undertaken. Although the macroscopic appearance was normal, the histological examination of stomach

CMV = cytomegalovirus
GIT = gastrointestinal tract

and duodenum showed congested mucosa with mononuclear cell infiltration. Staining for *Giardia* was negative. There was no evidence for *Helicobacter pylori* gastritis. Inclusion bodies were not found, but stomach and duodenal specimens tested positive for CMV on PCR.

Investigation of humoral and cellular immunity yielded normal results: IgG 866 mg/dl, IgA 38.3 mg/dl, IgM 98 mg/dl, C_3 81 mg/dl, C_4 31 mg/dl, CD3 (mature T cells) 70%, CD16 (natural killer cells) 5%, CD19 (early B cells) 18%, CD4/CD3 37%, CD8/CD3 33%. Human immunodeficiency virus tested negative.

Management of the child included a change of his nutrition to an elemental formula and symptomatic treatment with cisapride. After the second week, the child began to gain weight and was discharged 2 weeks later, having gained 500 g in 3 weeks. He was to receive home nasogastric elemental feeding and was followed as an outpatient in our pediatric gastroenterology unit.

One month after his discharge from hospital on elemental diet by nocturnal-nasogastric drip, he continued to vomit occasionally and had a low grade fever (38–38.2°C), but gained weight gradually and had normal stools. Histological reexamination of the upper GIT revealed mild chronic inflammatory infiltrate in the lamina propria of the stomach and duodenum. However, this time, these tissues, as well as urine and blood, were negative for CMV on PCR and on virus isolation. Over the following week the patient stopped vomiting, body temperature returned to normal, and weight gain continued at a satisfactory rate. Introducing cow's milk-based formula to his diet did not cause vomiting.

Comment

Depending upon the age and the immunological status of the host, CMV infection can cause a variety of clinical manifestations. These include congenital CMV inclusion disease, potentially devastating CMV infection of the immunocompromised host, the type of disease that follows administration of infected blood via transfusions or cardiopulmonary bypass, and CMV infection of a previously healthy individual who may develop a mononucleosis-like syndrome, occasionally with multi-organ involvement. However, the most common pattern is asymptomatic infection. In the child described here, CMV infection manifested with diarrhea and a prolonged fever, vomiting, weight loss and failure to gain weight over 2.5 months. The target organ of the CMV infection in this patient was the upper gastrointestinal tract. The diagnosis of CMV infection of the stomach and duodenum was based on the positive finding of CMV-DNA by PCR in endoscopic biopsies. Since CMV was also isolated and detected by PCR in the urine and blood, we could conclude that this child had an acute generalized CMV infection with involvement of the upper GIT. Intranuclear inclusions with a clear surrounding halo – the characteristic histologic feature of tissue CMV infection – were not observed in our patient. However, reported studies of bone marrow graft recipients [1] have demonstrated that routine histological examination is not sufficiently sensitive for the detection of CMV infection of the upper GIT, and failure to find inclusion bodies in the biopsy specimens of our patient therefore did not rule out a diagnosis of upper GIT CMV infection. Furthermore, recent studies indicate that PCR for CMV detection is a very sensitive and specific assay for the early diagnosis of CMV infection in immunocompetent and immunocompromised individuals [2].

When and how our patient acquired the CMV infection is unknown, but we assume, according to the negative IgM and high titer of IgG antibodies against CMV, that this acute generalized illness reflected a reactivation of past CMV infection.

Upper gastrointestinal involvement is rarely reported in the immunocompetent individual; regarding the pediatric age group, we found one report describing two children with Menetrier disease and evidence of CMV infection [3]. Our patient showed no features of Menterier disease. Another report described CMV colitis in an immunocompetent 5 week old infant with cow's milk allergy [4]. In our patient, since the initial symptoms of fever, vomiting and diarrhea that began 2 weeks after the introduction of a cow's milk-based formula did not resolve after substitution with an elemental diet, a diagnosis of cow's milk allergy becomes unlikely. Furthermore, biopsies from stomach and small bowel were not compatible with cow's milk allergy and there was no family history of allergy.

More recently, Fox et al. [5] described a 5 week old immunocompetent infant with intractable diarrhea attributable to CMV-induced enterocolitis. In contrast to our patient, the resolution of the intractable diarrhea was achieved only after institution of gancyclovir therapy. Another case report described the evolution of GIT dysmotility in a 30 year old immunocompetent woman with acute CMV infection of the upper GIT [6]. The protracted vomiting in our patient may indeed have been due to GIT motor dysfunction induced by the CMV infection. No clinical controlled trials have evaluated the efficacy of specific antiviral therapy for the treatment of CMV infection in immunocompetent patients and we do not believe it feasible to start with such a toxic drug without sufficient data to justify its use in immunocompetent patients.

To our knowledge, this is the first reported case of CMV infection of the upper GIT in an immunocompetent child presenting with prolonged fever, vomiting and diarrhea, which resolved without gancyclovir treatment. The upper GIT infection in our patient may have been primary, reflecting gastrointestinal involvement during systemic CMV infection. On the other hand, inflamed mucosa of the gastrointestinal tract due to (non-specific) acute gastroenteritis may be a favorable target site for CMV during coincidental viremia, resulting in localization of the CMV infection in the diseased gastrointestinal mucosa.

PCR = polymerase chain reaction

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