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CONCISE ARTICLE

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Ganciclovir for Severe Cytomegalovirus Primary Infection in an Immunocompetent Child

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Abstract Described here is the unusual case of a previously healthy 17-month-old girl who developed severe cytomegalovirus (CMV) disease with prolonged fever and hepatitis. The severity of her illness required hospitalization and prompted antiviral treatment. Short-term intravenous ganciclovir treatment was associated with immediate and sustained resolution of the symptoms as well as a sharp decrease of CMV viremia. This observation suggests that antiviral therapy might be considered in select cases of severe primary CMV infection in immunocompetent children.

Introduction

Primary cytomegalovirus (CMV) infection in immunocompetent children is generally a self-limited condition that does not require antiviral therapy [1]. We report here the unusual case of a breast-fed child with CMV whose infection was so severe that ganciclovir treatment was required. We also performed a literature review to collect evidence supporting the use of ganciclovir treatment in immunocompetent children.

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Case Report

A previously healthy 17-month-old girl was referred to our institution with a 4-week history of persistent fever. She had been born to a healthy mother at 38 weeks' gestation (birth weight, 2,940 g) and was still being breast-fed. At the age of 13 months, she started attending a day-care center. Three months later she was admitted to a nearby hospital with high-grade fever, a runny nose and acute bronchitis that persisted despite 8 days of antibiotic treatment.

Remarkable findings on clinical examination included fever (39°C), a truncal macular erythematous rash, cervical lymphadenopathies and splenomegaly. Laboratory tests showed anemia, leukocytosis (18.9 g/l; normal range, 4–11) with absolute lymphocytosis (12.6 g/l; normal range, 3–9.5), a moderate inflammatory state (C-reactive protein, 21 mg/l) and a slight elevation of aspartate aminotransferase levels (67 U/l; normal range, 11–42). Repeated blood, urine and stool cultures for bacteria and/or virus identification were all negative. Serological tests to detect hepatitis A, B and C, HIV, adenovirus, *Toxoplasma gondii*, *Brucella* spp. and *Borrelia burgdorferi* were all negative. Immunoglobulin (Ig)G but not IgM antibodies against HHV-6, parvovirus B19 and Epstein-Barr virus were detected, and post-vaccination serological tests for rubella and measles were positive. IgG and IgM antibodies against CMV were not detected. Tests for P24 antigenemia and Epstein-Barr virus DNA were also negative. Antigen detection (ELISA) for respiratory syncytial virus, influenza, parainfluenza and adenovirus on nasopharyngeal secretions were negative. Chest radiograph was within the normal limits and abdominal ultrasonography confirmed the splenomegaly.

Atypical Kawasaki disease was suspected, and the infant was given intravenous immunoglobulins (2 g/kg) and aspirin (80 mg/kg). Fever decreased partially and 10 days after admission the patient was released. High-grade fever rapidly relapsed, and she was referred to our hospital for further examination.

At admission, her general condition was poor; the results of the physical examination were unchanged, but liver enzymes had worsened, with elevated aspartate aminotransferase, alanine aminotransferase and GGT levels of 228 U/l (normal range, 14–50), 291 U/l (normal range, 9–42) and 370 U/l (normal range, 9–35), respectively. A liver biopsy showed a lymphohistiocytic infiltrate predominant in the portal tracts, non-caseating epithelioid cell granuloma in the lobules, and early-antigen immunostaining was positive for nuclear CMV in hepatocytes (Fig. 1). At this time, CMV pp65 antigenemia was revealed in blood leukocytes (44 positive cells/250,000 leukocytes) as was CMV DNA in plasma (3,535 copies/ml) and CMV early-antigen in urine by rapid culture. These findings prompted the diagnosis of severe primary CMV disease with associated hepatitis.

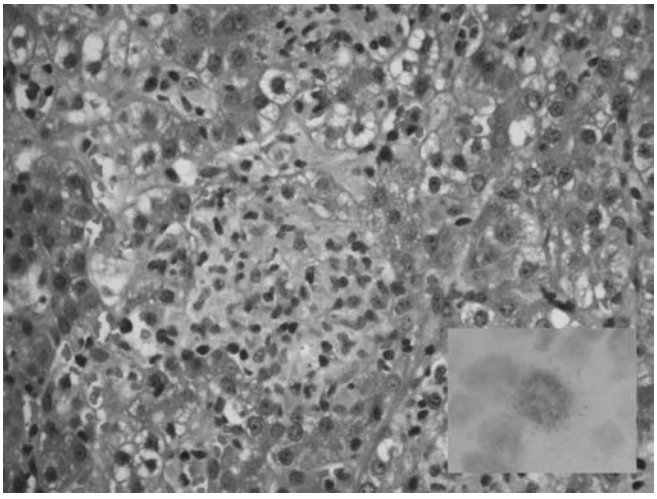

Fig. 1 Non-caseating epitheloid cell granuloma in a hepatic lobule characteristic of CMV hepatitis in an immunocompetent host (hematoxylin and eosin staining); focally positive nuclear early-antigen immunostaining in a hepatocyte (*inset*)

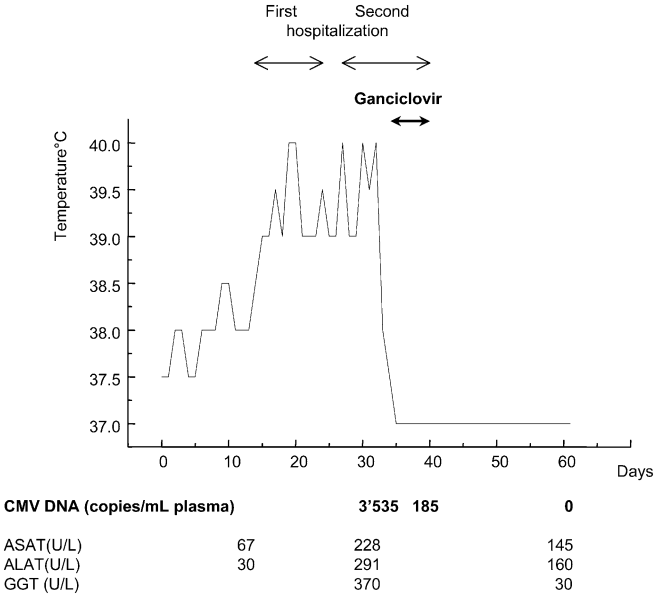

Fig. 2 Schematic presentation of the clinical and biological evolution of CMV infection in a 17-month-old patient treated with ganciclovir

Given the poor condition of the patient and the prolonged duration of symptoms, intravenous ganciclovir was introduced for 5 days (5 mg/kg b.i.d.) together with nonspecific immunoglobulin for 2 days (1 g/kg/d). Within 36 h we observed a dramatic resolution of the clinical symptoms and the fever, and 5 days later the child was discharged without further treatment (Fig. 2). Four days after the initiation of ganciclovir, pp65 antigenemia and CMV DNAemia decreased sharply to 1 positive cell/250,000 leukocytes and 185 copies/ml, respectively. At 1-month follow-up, aspartate aminotransferase and alanine aminotransferase levels were still moderately elevated at 145 and 160 U/l, respectively, GGT levels were normalized, and pp65 antigenemia and CMV DNAemia were negative.

Testing of the mother revealed her to be IgG-positive for CMV. Breast milk sampled at the time of hospitalization tested positive for CMV early-antigen but plasma was negative for CMV DNA.

Discussion

This severe case of primary CMV disease in an immunocompetent 17-month-old girl resolved with ganciclovir treatment. An unusual aspect of the case is that the child had never presented previously with a disease suggestive of an immunodeficiency. In contrast with perinatal CMV infection, which can be a severe disease [2, 3, 4, 5], CMV infection later in life is generally asymptomatic in immunocompetent children and adults. In rare cases, a self-limited mononucleosis-like syndrome with mild liver-test abnormalities can be present. Severe and prolonged disease over months and years in immunocompetent hosts is very uncommon but does exist.

In an extensive review of the medical literature, we found descriptions of 34 cases of severe CMV disease in immunocompetent adults [6] and only six cases in immunocompetent children [5, 7]. Of these six children, five were aged 1–5 years and one was aged 8 months. All of them presented with CMV hepatitis that lasted for weeks or months; one case resulted in death. Our patient presented with severe and prolonged disease with proven CMV hepatitis and required hospitalization. Congenital immune dysfunction was not documented and was very unlikely in the absence of previous infections and laboratory abnormalities. Due to the recently administered intravenous immunoglobulin perfusion, we could not accurately quantify the different immunoglobulin classes.

Since primary CMV infection in immunocompetent hosts is generally self-limited, no specific antiviral therapy is usually required. However, antiviral therapy can be beneficial in immunocompetent hosts, including adults, with severe acute or persistent CMV infection, as reported in a limited number of cases [3, 5, 6]. For example, nine immunocompetent infants and children aged 20 days to 33 months each received a 2-week-course of intravenous ganciclovir (n=6) in association with anti-CMV immunoglobulin (n=2) or anti-CMV immunoglobulin alone (n=1) for severe CMV disease [3, 5]. Isolated or combined ganciclovir treatment was effective in resolving either hepatitis or CMV-related symptoms in these patients.

In our patient, the symptoms and duration of the primary CMV infection were severe enough for antiviral therapy to be considered, with fever persisting for more than 4 weeks after symptom onset. However, in contrast with the prolonged course of ganciclovir reported in the previous cases, the treatment administered to our patient was limited to 5 days, which proved effective in resolving fever and hepatitis and correlated with a dramatic decrease of viremia. This was confirmed by the absence of clinical relapse and the negative CMV DNAemia result obtained 1 month later.

It is worth noting that oral valganciclovir is now available and might be an alternative to intravenous therapy, although no post-licensing data are actually available for infants. It must be kept in mind, however, that the large majority of cases do not require treatment and the bone marrow and gonadal toxicities associated with ganciclovir must be taken into account. Kimberlin et al. [8] reported that almost two-thirds of ganciclovir-treated infants with congenital CMV disease involving the central nervous system had significant neutropenia. In this respect, foscanavir, which has less gonadal toxicities, might be an alternative for treatment. Thus, ganciclovir treatment of immunocompetent children should be reserved for highly selected cases only.

Breast-feeding (vertical transmission) and day-care-center attendance (horizontal transmission) are the two major sources of postnatal CMV acquisition [1]. Localized reactivation and intermittent excretion of CMV in the breast milk of postpartum IgG-positive women are common and can last for up to 6 months [9, 10, 11]. CMV virions have been detected by culture in the breast milk of 32% to 50% of IgG-positive women [1, 10, 11, 12]. The rate of mother-to-child transmission averages 30% to 40%, and the risk is higher when the duration of breast-feeding is longer [1, 11]. CMV infection of the infant usually ensues between birth and 8 months of age and is generally self-limited, except in preterm and low-birth-weight neonates [4, 11, 13]. Day-care-center attendance is the other important means by which children acquire postnatal CMV infection [14]. Chronic shedding of high quantities of CMV into saliva and urine facilitates horizontal transmission between toddlers aged 1–3 years but, as with vertical transmission, the subsequent CMV infection is generally subclinical [1, 14].

In the case presented here, we considered vertical transmission to be the likely source of CMV transmission since CMV culture of the mother's breast milk was positive concomitant to the child's severe CMV disease. However, since molecular identity testing was not performed to compare the CMV strains obtained from the child and the mother's breast milk, this hypothesis cannot be definitely confirmed. In addition, CMV transmission by breast-feeding so late in life is unusual and we did not find any similar reports in the current literature. Another likely source of CMV acquisition in our patient could be horizontal transmission via the saliva of an infected child attending the same day-care center.

The case presented here shows that primary CMV infection can lead to severe and prolonged disease, not only in neonates and high-risk infants, but in immunocompetent older children as well. Our observation suggests that antiviral therapy can shorten the duration of disease and might be considered in selected cases.

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