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Postnatal Cytomegalovirus (CMV) Infection in Pediatrics: Case Report and Literature Review

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Abstract

Postnatal cytomegalovirus (CMV) infection is acquired through contact with cervical secretions during birth, breast milk, blood transfusion or bodily fluids of infected people. Breast milk is the main source of infection due to high proportion of CMV-positive women who excrete virus in milk. Postnatal CMV infection is usually asymptomatic, however, preterm infants with less protection through maternal antibodies can have a symptomatic infection. Symptomatic CMV infection includes pneumonitis, hepatitis, enteritis, lymphadenopathy, neutropenia or thrombocytopenia. Diagnosis is based on virus detection in correlation with onset of symptoms. Postnatal CMV infection usually resolves without use of antiviral treatment (Ganciclovir/Valganciclovir); antiviral treatment should be reserved for severe cases. Postnatal CMV infection is not associated with complications unlike congenital infection. We report an 8 months old male which presented a postnatal CMV infection with pneumonitis and bicytopenia (anemia and thrombocytopenia) responding favorably to treatment with ganciclovir (12 mg/kg/day) for 21 days.

Keywords: Cytomegalovirus; Postnatal infection; Ganciclovir

Introduction

CMV was isolated in 1956, but infection had been described many years before in fetal tissues with cytomegalic inclusion. CMV belongs to Herpesviridae family, Betaherpesvirinae subfamily, human herpesvirus 5 species [1]. CMV infection has high global prevalence, especially in developing countries (90%) compared with developed countries (60%) [2]. CMV is excreted in urine, saliva, vaginal secretions, semen and breast milk. Transmission can be vertical (pregnancy or birth) and horizontal, in perinatal or postnatal period. In immunocompetent persons, viral spreading is intermittent and indefinite while in immune suppressed is prolonged and constant [3].

Sources of CMV transmission are: congenital infection (intrauterine or transplacental) in 30% of pregnant women with primary infection; perinatal infection with genital secretions during birth; postnatal infection through breast milk, saliva, semen or vaginal secretions; blood transfusion from healthy donors with latent infection and solid organ transplantation [4-6]. Humoral and cellular immunity and natural killer cells are involved in infection control. CMV infection induces specific antibody formation IgM, IgA and IgG, which appear simultaneously with virus excretion (saliva and urine). Cellular immunity is critical in controlling CMV infection. Main objectives of lymphocytes T CD8+ and CD4+ are viral proteins pp65 and IE1 [7-8]. Postnatal CMV infection is asymptomatic in most cases secondary to reactivation of CMV in mothers and the child is born with protective antibodies; but, in preterm infants there is not a sufficient antibodies protection and there is an increased risk of symptomatic infection. The main risk factors are low birth weight and early postnatal CMV transmission [9].

Case Presentation

Male patient 8 months old, native and resident of Sonora, Mexico, with 8 kilograms of weight and 58 centimeters in height, both according to age. Medical history: 30 years old mother with three pregnancies born vaginally, adequate prenatal care, no TORCH report, our patient was born at 38 gestation weeks, no complications at birth with 3.8kg of weight and 51cm in height, blood group mother and newborn O (+), immunizations for hepatitis B, BCG, rotavirus and pentavalent, feeding is based in breast and formula milk with normal maturational development; denies allergies, transfusions or surgeries.

He began his condition two weeks ago with hyaline rhinorrhea, dry cough and breathing difficulty, self-medicated with paracetamol; four days after that, petechiae appear in arms and legs which spread throughout the body; he went to medical consultation where a blood count test is performed with a platelet count of 36,000 103/µl. He is sent to Cd. Obregon to start study protocol. Patient is received in emergency department where blood count is repeated with a result of 27,000103/µl platelets; hospitalization is decided at pediatric service to start study protocol with probable diagnosis of primary immune thrombocytopenia (PIT) and respiratory infection. Physical examination with normal vital signs for age; active, reactive, good hydration, jaundice, generalized petechial lesions, hyperemic pharynx, symmetrical chest with crackles on auscultation, normal heart sounds, depressible abdomen, liver with hepatomegaly of5 cm below right costal margin and splenomegaly of 3cm below left costal margin, capillary filling 2 seconds. Initial treatment with acetaminophen (15 mg/kg/dose), prednisone (2 mg/kg/day), and penicillin G crystalline.

Three days after new studies reported: HB 10.2g/dl, HT 31.9%, WBC 18.3 103/µl with lymphocytic predominance (80%), platelets 84,000 103/µl, total bilirubin (TB) 14.3 mg/dl, direct bilirubin (DB) 10.1 mg/dl, indirect bilirubin (IB) 4.2mg/dl, alkaline phosphatase

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Table 1: Postnatal diagnosis of CMV infection [21].

Studies performed on patient with suspected postnatal CMV infection • Complete physical exploration • Laboratory tests: blood count, C-reactive protein and liver function • Virology: - CMV serology - CMV quantitative PCR in blood and urine - CMV antigenemia (if quantitative PCR not available) - Culture or PCR CMV in breast milk and vaginal discharge - Culture or PCR CMV in cerebrospinal fluid, excrement, bronchoalveolar lavage or biopsy material. • Chest x-ray if respiratory deterioration • Abdominal radiograph if digestive symptoms • Abdominal ultrasound if hepatosplenomegaly, hepatitis or cholestasis
Diagnostic criteria ofpostnatal CMV infection Diagnosis is established with at least one of the following criteria: • CMV IgM seroconversion plus a positive culture or PCRafter 2 weeks of age (to rule out false positive IgM) • Culture or PCR CMV negative in the first 2 weeks of life and positive later • Culture or PCR positive after 2 weeks of life and negative CMV PCR in blood of metabolic tests
CMV: Cytomegalovirus, PCR: Polymerase Chain Reaction, IgM: immunoglobulin M.

(AP) 794 IU/l, alanine aminotransferase (ALT) 154 IU/l; aspartate aminotransferase (AST) 199 IU/l; cytomegalovirus (CMV) IgM 25.20U/ml. Imaging studies: normal hepatic ultrasonography, computed tomography without calcifications, chest radiography with air trapping and parahilar infiltrators. Normal ophthalmologic evaluation, no corioretinitis. Polymerase Chain Reaction (PCR) for Parvovirus, Epstein bar and CMV is requested; actual treatment with antipyretic, steroid and antibiotic.

Five days after hospitalization still have jaundice, petechiae and hepatosplenomegaly, on this day starts with dyspnea which disappear to applying oxygen with nasal cannula (3 liters per minute). Control laboratories with persistent cholestasis: ALT 417 IU/l, AST 270 IU/l, AP 800 IU/l, TB 15.5 mg/dl, DB 11.5 mg/dl and IB 4.0 mg/dl. Blood count: HB 10.0g/dl, WBC 21,200 103/µl with lymphocytic predominance (85%), platelets 85,000 103/µl. RT-PCR in blood positive to CMV with viral titer of 148,357 copies/ml. Diagnosis of pneumonitis secondary to postnatal CMV infection (IgM and PCR +) is established. Treatment is changed to Ganciclovir at dose of 12 mg/kg/day for 21 days with remission of respiratory symptoms (day 5), cholestasis (day 9) and a progressive normalization of transaminases and hematologic (day 18) and. There was not adverse effects associated with Ganciclovir. Breast milk was not suspended during treatment.

Discussion

Symptomatic CMV infection may manifest as pneumonitis, hepatitis, enteritis, lymphadenopathy or aseptic meningitis. Pneumonitis presents similar to other types of atypical pneumonia symptoms, course is usually afebrile, with increased secretions of upper respiratory tract, tachypnea, cough and need for supplemental oxygen as happened in our patient [10]. Clinical course is often prolonged, occasionally requiring mechanical ventilation. Hepatitis is manifested by hepatosplenomegaly, jaundice and elevation of transaminases; our patient presented the above described alterations with improvement when starting antiviral treatment. Severe cases have been reported with systemic involvement, portal hypertension and progression to cirrhosis [11].

Our patient hadrespiratory infection and petechiae which is expected. From analytical point of view, CMV infection can appear with neutropenia, lymphocytosis, thrombocytopenia, anemia and cholestasis. These findings disappear gradually in coming weeks such as happened in this case, although postnatal CMV infection is one of the most common causes of prolonged neutropenia [12]. Mortality in postnatal CMV infection is low, in clinical cases of last decade only four deaths are related to CMV infection [13]. Diagnosis is based on virus isolation or genome identification by PCR in biological samples. Detection of anti-CMV IgG antibodies translates transplacental transmission of maternal antibodies. Determination of IgM antibodies may be useful, but absence does not discard infection and presence does not confirm [14].

Classically, diagnosis has been made by urine or saliva culture; this practice has been replaced by technique of "shell vial" a method of rapid isolation or PCR, which have the advantage of short time it takes to get results (24-48 hrs) [15]. In our case diagnosis was performed using serology (IgM +) and PCR (Table 1). Quantitative PCR performed is useful for identifying patients with higher viral titer (increased risk of severe involvement) and to measure the progress of infection [16]. Evidence of antiviral treatment effectiveness is limited and is based on clinical cases. The drug most commonly used is intravenous ganciclovir at doses of 12 mg/kg/day twice daily for at least 2 weeks. With clinical improvement, treatment can last 1-2 weeks if symptoms are not resolved [17]. Ganciclovir has adverse effects; the most common is granulocytopenia [18]. In treated patients, blood counts should be performed weeklyto identify analytic alterations. In our case, treatment was continued for 21 days with satisfactory results without adverse effects.

Valganciclovir is an alternative treatment, a recent study has established that a dose of 16 mg/kg orally are equivalent to 6 mg/kg intravenous of Ganciclovir, main adverse effects are neutropenia, anemia and diarrhea [19]. Intravenous immunoglobulin is used to reduce risk of infection but there is not clearly evidence to recommend as prevention treatment [20].

Conclusion

Lack of knowledge, multiple forms of presentation, differential diagnosis of a congenital or postnatal infection, numerous diagnostic procedures and indications for treatment or prophylaxis became to CMV infection in a challenge for physicians. There are multiple differential diagnostic, however, in all pediatric patients with petechiae, hepatosplenomegaly and jaundice is recommend discard a CMV infection due to highly prevalent. Although breast milk is the

main source of postnatal CMV infection is recommended to continue with this practice because it is not a contraindication. Diagnosis must be confirmed by culture, PCR or IgM antibody positivity as set out in diagnostic criteria (Table 1). Routine prenatal CMV screening is not recommended, only in high-risk pregnant women through IgM and IgG. We recommend treatment with Ganciclovir or Valganciclovir in severe cases because in literature and present case effect is beneficial with a minimum three weeks treatment in postnatal CMV infection at doses of 12 mg/kg/day. Finally, although there are no reports of complications in postnatal CMV infection we recommend a follow-up to school age by high viral titer.

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