Brief Communication

Hemolytic anemia in an immunocompetent infant due to acute cytomegalovirus infection

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Cytomegalovirus (CMV) infection is a very common source of infection, whether symptomatic or asymptomatic. In immunocompromised patients, CMV infection can lead to severe clinical manifestations related to direct viral cytotoxic effect on specific organs and tissues (gastrointestinal tract, central nervous system, retina, respiratory tract, and hematopoietic system).[1] On the contrary, in immunocompetent patients, primary CMV infection can present merely as a viral illness, or will mimic infectious mononucleosis infection. In general, CMV infections are not rare, and the worldwide prevalence ranges from 60-100%.[2] Most CMV hemolytic anemia case reports are in adults.

A 2-month-old female baby was brought to our emergency department due to fever for one week.

In addition, the patient presented with intermittent, dry cough, and runny nose for one week. There was no history of vomiting but she had diarrhea with an average of 4 times per day. The patient's mother described the diarrhea as non-bloody and non-mucousy. There was also a history of decreased urine output, and the urine color was described as dark yellow. Past medical history and family history, including the mother's prenatal care was unremarkable. Immunizations are up-to-date, and the development is adequate. On admission to the ward, the vital signs were as follows: temperature -37.8°C; pulse 150/min; blood pressure 73/45 mm Hg, respiratory rate 34/min, head circumference 37.5 cm (22.3 percentile); weight 4.4 kg (25th percentile); length 54 cm (75th percentile). The infant looked pale, irritable, and crying with sunken eyes. Her skin had normal skin texture, no rashes, no hypo- or hyper-pigmentation; her capillary refill was 3 seconds. Her head was nondysmorphic, with anterior fontanelle 4x4 cm flat, and depressed. For ear, nose, and throat: there was cerumen impaction in both ears; normal throat; dry mucous membranes; and no cleft palate. The neck was supple with no lymphadenopathy. Her chest had a normal shape with good air entry bilateral, no retractions, wheezing, or crackles. In terms of her cardiovascular system, the peripheral pulses were palpable, femoral pulses synchronous with brachial pulses; regular rate and rhythm, and soft 2/6 physiologic systolic murmur best heard in the left second intercostal space. The abdomen was not distended; symmetrical in contour; soft with no apparent tenderness; with no organomegaly or palpable masses; and with positive bowel sounds. The external genital was normal. In terms of the neurological exam, the patient was awake, mild irritable, pupils were reactive to light, cranial nerves were grossly intact and there was no nystagmus.

Initial laboratory results. The following are the results: blood group O^+; direct Comb's test negative; white blood cell (WBC) 35600/ul; red blood cell (RBC) 2000000/ul; hemoglobin 4.9 g/dl; hematocrit 17.4%; mean corpuscles volume 83.7 fl; mean corpuscular hemoglobin 28.2 g/dl; red cell distribution width 34.9%; and platelets 204000/ul. For neutrophils 18%; lymphocyte 71%; monocytes 11%; and reticulocyte count 9.38%. Serum glucose, blood urea nitrogen, creatinine, calcium, sodium, potassium, chloride, total protein, ammonia, folate, ferritin, uric acid, hemoglobin electrophoresis, glucose-6-phosphate dehydrogenase, and albumin were normal. The total bilirubin was 35 umol/L; alkaline phosphatase 422 U/L, ALT (alanine aminotransferase) 422 U/L, and AST (aspartate aminotransferase) 532 U/L. Urine analyses were within normal limits. Prothrombin time was 10.6 seconds (10-14.3) activated partial thromboplastin time was 19.7 seconds (normal value 32-55.2), and the International Normalized Ratio (INR) was 1. The cerebrospinal fluid protein and glucose levels were within the acceptable range, and the CSF gram stain, viral polymerase chain reaction (PCR) and culture were negative. The blood and urine cultures were negative. The haptoglobin was <3 mg/dl. Further investigations including peripheral smear and blood virology showed positive CMV immunoglobulin (Ig)M, and positive CMV IgG with CMV PCR in blood (39889 copies/ml). The Epstein-Barr virus and adenovirus PCR were negative in the blood. In the peripheral smear, there was marked anemia with reticulocytosis, mild hypochromia, microcytosis, marked anisopoikilocytosis with many macrocytes, some tear drops, frequent schistocytes, few spherocytes, and moderate thrombocytopenia. The neonatal screen was normal. The respiratory virology panel was negative; stool occult blood was negative; stool culture was negative; and the stool was negative for rotavirus and adenovirus.

Course of hospitalization. The patient was transfused with packed RBC 15 mg/kg, and started on ganciclovir. The patient was hemolyzing during the course of treatment and required a second pack of RBC transfusion and hemolysis was eventually stopped once the blood CMV virology PCR level became negative. At discharge, the patient's hemoglobin was 9.5 g/dl, hematocrit 27.1%, and reticulocytes count 2.5%. Two

days previous to discharge, the hemoglobin level was 9.6 g/dl. Dehydration was corrected, and the patient was discharged in good condition.

Follow up. The parents failed to return to the clinic in one week as recommended, but repeat hemoglobin 3 months later was recorded as 12.6 g/dl.

The CMV has several strains, and it is only the human strain that can cause human disease. There are many modes of transmission including vertical (from mother to fetus, or infant), horizontal (from person to person via contact with virus containing secretions), and via blood, or blood derivatives transfusion.[3] Molecular diagnostic methods, such as PCR that are not universally available appear to be sensitive in ruling out the disease.[4] In most health centers, CMV infection is diagnosed by viral isolation in tissue cells (urine, leukocytes, pharynx, semen, human milk, and body fluids), direct visualization of viral inclusion bodies, and serologic methods like latex agglutination, enzyme immunoassay, indirect hemagglutination, and fluorescence assays.[3] Rafailidis et al[5] reviewed the evidence associated with severe manifestations of CMV infection in apparently immunocompetent patients, retrieving 89 articles reporting on severe CMV infection in 290 immunocompetent adults, in which 5 were found to have hemolytic anemia. The CMV disease treatment in children is ganciclovir (5 mg/kg per dose IV every 12 hours for 2-3 weeks, depending on the clinical and virological response),[3] valganciclovir is an option for CMV treatment. However, the literature targets the patient's pre- and post-organ transplantation. The dose (in mg) is calculated as follows: 7 × body surface area x creatinine clearance. The recommended regimen is once a day within 10 days of transplantation until 100 days post-transplantation. It is crucial to mention that before prescribing any medication, we should weigh the benefits against the potential risks and toxicity of the therapy. While adverse effects were not reported in the reviewed cases, we should be aware that ganciclovir can cause myelosuppression, central nervous system disorders, hepatotoxicity, irreversible infertility (inhibition of spermatogenesis), or teratogenesis, whereas foscarnet can cause disturbances in mineral and electrolyte homeostasis, as well as nephrotoxicity.[5]

In conclusion, after reviewing textbooks and articles, hemolysis appears to be a rare complication of CMV infection in the immunocompetent child, and the mechanisms responsible for it remains obscure. Guidelines for treatment have yet to be established, and the effectiveness of antiviral therapy has not been proven. In this report, an unusual case of primary CMV infection manifested by severe hemolysis in an immunocompetent infant is presented. In view of the only culprit agent in our patient being CMV, and due to an adequate response to ganciclovir suggests that virological mechanism is probably responsible for hemolysis. Further research is needed to find the exact mechanism responsible for the hemolysis due to CMV and guidelines for treatment should be established.

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