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Cytomegalovirus Infection and Severe Anemia in Infants: Case Report of Two Infants and Review of Literature

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Abstract

Cytomegalovirus (CMV) infection presenting as severe anemia in infancy is rare. AIHA is a severe hematological manifestation of CMV infection. AIHA is an erythrocyte (RBC) hematologic disorder that is rarely seen in infants and young children. Most cases are associated with viral or bacterial infection, but the immunologic events leading to hemolysis are poorly understood. We report two cases of infants who presented with severe anemia and CMV infection. The first infant had chronic refractory mixed AIHA and the second infant had anemia directly attributable to CMV infection.

Introduction

Cytomegalovirus (CMV) infection presenting as severe anemia in infancy is rare. Auto-Immune Hemolytic Anemia (AIHA) is characterized by the presence of auto antibodies that bind to RBC membranes and lead to their premature destruction. It can be classified as primary or secondary AIHA. The latter is due to lymphoproliferative and autoimmune diseases, drugs, and severe injuries. Bacteria and viruses can be associated with AIHA in children [1,2]. Amongst its various hematological manifestations, *Cytomegalovirus* (CMV) can cause transient neutropenia with thrombocytopenia or more severe, such as AIHA and pancytopenia. We report two cases of infants who presented with severe anemia, thrombocytopenia, and CMV infection. The first infant had chronic refractory mixed AIHA and the second infant had severe anemia and thrombocytopenia directly attributable to CMV infection.

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Case Series

Case 1

A six-month-old male child born out of third-degree consanguineous marriage presented with new onset progressive paleness of the body and worsening respiratory difficulty in the last 20 days. He received 7 aliquots of packed RBC every 2 to 3 days in the past 20 days and was started on syrup prednisolone at 2 mg/kg/day with no response. His physical examination was remarkable for severe tachypnea (54/min), tachycardia (166/min), pallor, icterus with moderate hepatosplenomegaly. CBC at admission showed severe anemia with thrombocytopenia with a hemoglobin of 3.1 g/dl with a platelet count of 43,000/μL. The corrected total leukocyte count was 18,600/μL with 30% neutrophils, 68% lymphocytes, and 2% myelocytes and metamyelocytes each. Peripheral smear showed numerous spherocytes with reticulocytosis of 23%. There was indirect hyperbilirubinemia, LDH was 2150 U/L and Direct Coombs Test (DCT) was strongly positive (4+). DCT positivity was due to IgG (titer ≥ 1000) of subclasses IgG1 (titer >100) & IgG3 (titer >100) coating the red cells along with C3d, a very weak coating with IgM was also seen. A diagnosis of AIHA was made. Serologic and virologic testing revealed CMV IgM and CMV IgG positive. CMV PCR blood and urine showed 200 copies and 2120 copies, respectively. Flow cytometry for double negative TCRαβ+ T cells was negative.

He was started on intravenous ganciclovir (dose calculated as 3 × BSA × Creatinine clearance) daily for 10 days. He also received IVIg at 1g/kg daily for 2 doses with methylprednisolone at 2 mg/kg for 3 days followed by prednisone at 2 mg/kg for 2 weeks followed by a slow taper of 0.25 mg/kg/week. At discharge he was shifted to Valganciclovir. His hemolysis continued with persistent requirement of blood transfusion. He had a poor response to steroids and was started on weekly rituximab at 375 mg/m^2. Peripheral blood PCR for CMV DNA came negative after 3 weeks of valganciclovir. His hemoglobin stabilized at 10.8 g/dl, platelet count normalized, LDH was 568 U/l, and bilirubin was

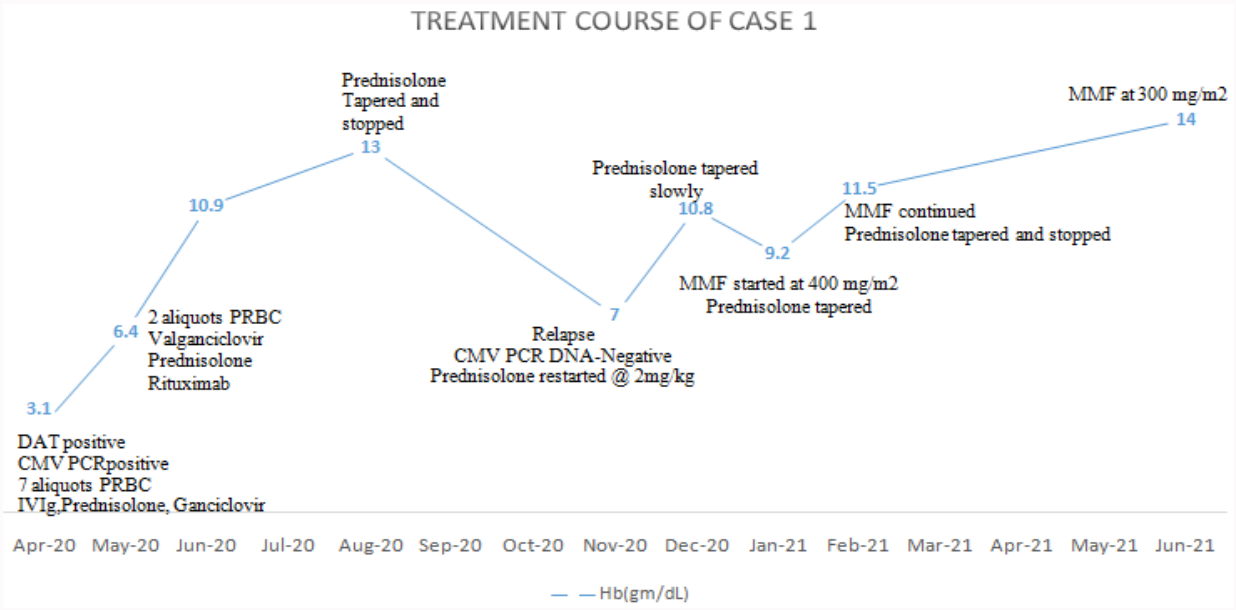

Figure 1: Depicts the treatment course of case 1.
DAT: Direct Antiglobulin Test; PRBC: Packed Red Blood Cells; IVIg: Intravenous Immunoglobulin; MMF: Mycophenolate Mofetil

0.8 mg/dl after 3 weeks of rituximab. Steroids were slowly tapered and stopped as he was in complete remission. He relapsed after 2 months of stopping steroids and 6 months after rituximab therapy. He was restarted on steroids followed by mycophenolate mofetil at a dose of 400 mg/m^2 as the steroid sparing agent. He started responding within 1 month and the steroids were tapered slowly and stopped. At his last visit to the OPD in June 2021, he was 1 year and 8 months of age, his parameters were- hemoglobin 14 g/dl, LDH 368U/L, bilirubin 0.53 mg/dl. MMF is planned to be tapered slowly (Figure 1).

Case 2

A five-month-old male child was symptomatic from 2 months of age with pallor, decreased activity with decreased feeding. There was no history of fever, jaundice, or any bleeding. He had received 4 PRBC transfusions in the past 2 months. On examination he had pallor with moderate hepatosplenomegaly. Blood investigations revealed hemoglobin of 3.9 g/dl, normal total leukocyte count of 17100/µL, platelet count of 23,000/µL, and absolute reticulocyte count 45,000/µL. His serum bilirubin was 2.3 mg/dl, with indirect bilirubin 1.3 mg/dl, LDH was 590 U/L. DCT was negative. A bone marrow biopsy was done and revealed marked erythroid hyperplasia with unremarkable megakaryocytes and myeloid cells.

Presence of anemia with hepatosplenomegaly with hepatitis with marked erythroid hyperplasia in bone marrow, differential of thalassemia; CDA and infection related (TORCH) was kept. TORCH profile was positive for CMV IgM and IgG antibodies. CMV PCR revealed 2130 copies/µL. A diagnosis of CMV infection causing recurrent anemia was made. He was started on ganciclovir and received it for 18 days. He became transfusion independent and his liver and spleen regressed on ganciclovir.

Discussion

In this case series, we report two infants both with CMV infection with severe anemia, thrombocytopenia, and moderate hepatosplenomegaly. The cause of anemia in case 1 was mixed autoimmune hemolytic anemia and on the other hand, the cause of anemia in case 2 was attributed directly to CMV infection. In both these cases, thrombocytopenia improved with treatment of CMV infection. The mixed AIHA in case 1 was steroid refractory and required rituximab as secondary treatment, further during the course, relapsed and required steroid sparing immunosuppressive therapy (mycophenolate mofetil). We would be discussing case 1 in detail.

Heisel et al. [1] evaluated prognostic factors in childhood AIHA and concluded that there are two distinct varieties of AIHA in children, the acute disease generally occurred in 2 to 12 years of age, had a sudden onset of symptoms, showed low reticulocyte counts and had normal platelet counts. This acute disease variety responded well to steroids and the disease resolved within 6 months without mortality. On the other hand, children with chronic AIHA were generally less than 2 or greater than 12 years of age, had a more prolonged onset of symptoms, had increased reticulocyte counts, and had decreased platelet counts. These children with the chronic variety had a variable response to steroids, frequently requiring other modalities of treatment and had a mortality of 25%. It also seems to be the scenario as in case number 1, he had a poor response to steroids and relapsed 6 months after Rituximab, warranting maintenance of second line steroid sparing immunosuppressive therapy.

Literature was reviewed regarding CMV as the cause of AIHA in children. In the largest series of pediatric AIHA patients, Aladjidi et al. [3], we evaluated 265 children with AIHA and reported 6 patients with *Cytomegalovirus* as the causative agent for AIHA. Naithani et al. [4], reported 26 patients (range, 0.2 to 17 years) with AIHA. Secondary AIHA was seen in 9 (35%) patients, with only 1 patient with CMV as the etiology. Thatikonda et al. [5], in their study evaluating 50 childhood AIHA patients, CMV was the causative etiology in 1 patient only. In a study by Fan et al. [6], 7 patients out of 68 cases were EBV/CMV positive. Few case reports of CMV with AIHA are reported [7,8]. All these studies suggest that CMV is a rare cause of AIHA in children. Comparing with adults, Rafailidis et al. [9], we performed a systematic review of 290 immunocompetent patients with severe CMV infection, 25 patients were found to have various

hematological manifestations among them only five were found to have hemolytic anemia, so AIHA secondary to CMV infection is a rare event in adults.

Efficacy of Rituximab in steroid refractory AIHA in children has been reported in small case series. Zecca et al. [10], reported data of fifteen children (range, 0.3 to 14 years) with AIHA who were given rituximab, 375 mg/m^2/dose for a median of 3 weekly doses. Three responders relapsed at 7, 8 and 10 months after rituximab infusion. Quartier et al. [11] reported five children with refractory idiopathic AIHA who received rituximab. All children remained in complete remission for 15 to 22 months after receiving rituximab. In adult patients, the median duration of response after Rituximab is 20 months. In our case number 1, the infant started responding to rituximab after the 3rd weekly dose but relapsed after 6 months. Rituximab use is associated with absence of circulating B cells and hypogammaglobulinemia, which have implications for vaccine efficacy especially in infants. Ideally inactivated vaccines should be completed at least 1 week prior, and any live-attenuated vaccines should be completed a minimum of 4 weeks prior to commencing treatment. Due to lack of immune cell function, all future immunizations should be withheld whilst on rituximab. Post the completion of rituximab therapy, immunoglobulin and B-cell levels should be checked every 3 months. Once both levels have returned to normal AND ≥ 6 months post treatment has lapsed (whichever is later), immunization with both inactivated and live-attenuated vaccines can recommence [12].

According to the guidelines from AIEOP for second-line treatment in warm AIHA pediatric patients [13], second-line treatment options for steroid dependence on a dose of prednisone ≥ 0.1 mg/kg/day to 0.2 mg/kg/day, include rituximab, immunosuppressive drugs, splenectomy, alemtuzumab and hematopoietic stem cell transplantation. Immunosuppressive drugs, with the exception of cyclophosphamide, are an appropriate second-line treatment, as they can be used as steroid-protective drugs in steroid-dependent patients. Given that these drugs require a long time to elicit a response, in fact, they should be infused early with the help of powerful drugs, such as steroids. Mycophenolate mofetil, a potent inhibitor of the enzyme containing 5'-monophosphate dehydrogenase, is the most widely indicated in steroid-dependent patients to reduce the dose of steroids. Panigrahi et al. [14] reported in 3 pediatric AIHA patients that MMF appears to be an effective and well-tolerated adjunct immunosuppressant that allows for rapid weaning of steroid usage, minimal adverse side effects to the patients, and long-term stabilization of counts. Therefore, this novel combination therapy may be an excellent alternative for the treatment of persistent or chronic autoimmune cytopenia's in the pediatric population. In our patient, MMF with steroids was started and the patient achieved complete response on MMF and steroids could be tapered. He tolerated MMF and had no side effects and remains in complete remission.

Conclusion

CMV infection should be considered when evaluating patients with severe anemia and thrombocytopenia. AIHA may be primary or secondary to other diseases, including infections, autoimmune disorders, and malignancies. The mixed AIHA in our case was secondary to CMV infection. It was steroid refractory and relapsed after 6 months of rituximab therapy and received MMF as the steroid sparing immunosuppressive therapy. The patient had no side effects to MMF. MMF may be an excellent alternative for the treatment of chronic AIHA in pediatric patients. Vaccination should be carefully planned in children, especially infants receiving rituximab.

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