

Autoimmune Hemolytic Anemia: When is Transfusion Necessary?

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Abstract

Autoimmune hemolytic anemia is uncommon in children. We report a term male infant with autoimmune hemolytic anemia who was found to be positive for cytomegalovirus. He received steroids and two transfusions during his hospital course due to low hemoglobin levels. He did not show any signs of cardiovascular collapse. His cytomegalovirus viral count decreased without antiviral medications. He was discharged on steroids for about 3 months. We contrast this case with that of another infant male with autoimmune hemolytic anemia after a viral upper respiratory infection. In this contrasting case, the patient also had low hemoglobin levels and had no signs of cardiovascular collapse and was treated with steroids alone. In this case report we demonstrate that steroids are a suitable first line treatment for autoimmune hemolytic anemia in cases where hemoglobin is low but there are no signs of cardiovascular collapse.

Introduction

Autoimmune hemolytic anemia (AIHA) usually occurs in middle aged adults. The incidence in children is 0.81 in 100,000 under the age of 18¹. AIHA can range in its severity and may be either a primary or secondary diagnosis, associated with Non-Hodgkin Lymphoma, Evan Syndrome, and post viral infections.

Cytomegalovirus (CMV) accounts for one of the viral etiologies. CMV infection is ubiquitous and ranges in severity, primarily depending on whether the patient is immunocompromised. Infants can contract CMV transplacentally or through perinatal transmission from vaginal blood during delivery or breastfeeding. In term infants, symptoms are usually transient but can involve gastrointestinal symptoms, hepatitis, pneumonitis, and abnormal bloodwork². Preterm infants are vulnerable to severe disease by CMV and can present with sepsis, necrotizing enterocolitis, and retinopathy of prematurity³.

Patient Presentation, Diagnosis, and Outcome

Our patient is a 5-month-old African American male who was born at 39 weeks via an uncomplicated pregnancy and delivery. The patient's mother and father both have sickle cell trait. The mother's blood type is B positive. His newborn screen was unremarkable, inclusive for hemoglobinopathies and Severe Combined Immunodeficiency. The infant was discharged home on day two of life with total bilirubin level at 8.2 mg/dL. At the infant's first pediatrician's appointment, at four days of age, the patient had a total bilirubin of 17.9 mg/dL, which was below light level. On physical examination he was noted to have jaundice to level of umbilicus and scleral icterus. The infant did not have petechiae, splenomegaly, or

signs of congestive heart failure. He was feeding well with formula every three hours and having great urine and stool outputs. The BiliTool calculator showed that he did not require phototherapy (<21.5 mg/dL), escalation of care (<25 mg/dL), or exchange transfusion (<27 mg/dL). The decision was made to obtain serum bilirubin the next day.

The next day, total bilirubin level was 20.6 mg/dL, again below phototherapy threshold. Around one week of life, the child's serum bilirubin had stabilized at 12 mg/dL. While some milder jaundice remained at the infant's two-week appointment, it had completely resolved by one month of age.

At two months of age, the infant had a mild course of COVID-19 with symptoms consistent of low-grade fever, cough, congestion, and decreased appetite. At five months of age, he was seen by his pediatrician for upper respiratory symptoms and otalgia. At this visit, he was afebrile with notable jaundice, scleral icterus, and gingival pallor. Due to exam findings, patient had bloodwork drawn which showed concern for anemia since hemoglobin was 5.1 g/dL, resulting in his referral to the emergency department. In the emergency department, the patient's anemia was confirmed with a hemoglobin at 4.7 g/dL, a significant reticulocyte count, total bilirubin of 6.4 mg/dL, and direct antibody test (DAT) positive [Table 1]. A blood smear showed marked macrocytosis with polychromasia, nucleated red blood cells (RBC) and occasional schistocytes indicative of hemolytic anemia.

The infant's folate and vitamin B12 levels were both unremarkable. His blood type was confirmed as B positive, ruling out ABO incompatibility. He was given methylprednisolone and a 15 mL/kg transfusion of packed red blood cells (pRBC) without complications. Decision to transfuse was made based on critically low hemoglobin level, however patient was not symptomatic. Six hours post

transfusion, hemoglobin levels improved to 8.7 g/dL, total bilirubin was 9.7 mg/dL and lactate dehydrogenase (LDH) was 916.

On day three after presentation, his hemoglobin was stable at 7.6 g/dL, total bilirubin at 4.5 mg/dL, and LDH was 780. As the etiology list continued to expand, investigations included an abdominal ultrasound which showed hepatomegaly, cholestasis, and gallstones. A quantitative immunoglobulin study showed low IgM at 15 and normal IgG and IgA. Patient was transitioned to oral steroids and started on intravenous immunoglobulins 1 gram per kg for further immune suppression. On day four after presentation, the infant's hemoglobin was 6.9 g/dL with a negative hemoglobin electrophoresis and stable bilirubin and LDH levels. On day six after presentation, infant's hemoglobin dropped to 6.5g/dL and he was again transfused pRBCs at 10mL/kg. Again, he did not show symptoms of his anemia. Patient's post transfusion hemoglobin was 9.9 g/dL and he was discharged home to continue oral steroids for two weeks with a plan for close follow up with hematology.

At five months of age, 2 days after discharge, the infant was readmitted for concerning bilirubin levels (direct 10.4 mg/dL; total bilirubin 14.6 mg/dL). He was given ursodiol and prednisolone. Two days later, his total bilirubin improved to 2.4 mg/dL. Clinical suspicion pointed to stone passage. Due to elevated liver enzymes, aspartate transaminase (AST) of 442 and alanine transaminase (ALT) of 919, patient had a liver biopsy. The biopsy showed nonspecific findings of mild portal and lobular inflammation, and a trichome stain showed no fibrosis. However, a viral stain showed multiple immune-positive cells consistent with CMV hepatitis.

Infant was discharged four days later with a hemoglobin of 9 g/dL, total bilirubin of 2.1 mg/dL, and LDH of 510. A

Table 1. Laboratory workup during admission.

Lab Test	Value	Reference Range
Red blood cells (RBC)	1.37 M/uL	2.70 - 4.90 M/uL
Hemoglobin	4.7 g/dL	9.0 - 14.0 g/dL
Hematocrit	17.9 %	28.0 - 42.0 %
Mean corpuscular volume (MCV)	131 fL	74 - 115 fL
Mean corpuscular hemoglobin concentration (MCHC)	26.3 g/dL	29.0 - 37.0 g/dL
RDW	18.9 %	11.5 - 14.5 %
Platelet	255 K/uL	150 - 450 K/uL
Total bilirubin	6.4 mg/dL	0.1 - 1.0 mg/dL
AST	56 U/L	10 - 40 U/L
Iron	205 ug/dL	45 - 160 ug/dL
Saturated Iron	81 %	20 - 50%
Reticulocytes	>23%	0.4- 2.0%
Direct antiglobulin test (Coombs)	Positive	
Lactate Dehydrogenase (LDH)	698	110 - 260 U/L
Anti-neutrophil Antibody (ANA)	Negative	

quantitative CMV polymerase chain reaction (PCR) showed viremia with 20,701 copies of CMV. Patient continued taking steroids until 8 months of age, approximately 3 months from initial presentations. Steroids were tapered from 2.5 mg/kg to 0.25 mg/kg before discontinuing. No other medications, including antivirals were added. Infant is now 11 months of age and has not shown any sequela at this time. At 10 months of age, he had a hemoglobin of 12.3 g/dL, reticulocytes 2%, DAT positive, and CMV PCR was 189 copies.

Contrasting Case

In a contrasting case, a two-and-a-half-year-old African American male with sickle cell trait, presented with pallor and jaundice and preceding viral upper respiratory infection. This case presented before the COVID-19 pandemic. On physical exam, he was pale, jaundiced, and had splenomegaly without evidence of congestive heart failure. His hemoglobin was 3.1 g/dL with normal white blood cells and platelets. On blood smear he had microspherocytes with polychromasia. Like the patient above, he was found to be DAT positive and ANA negative. He was treated with oral steroids and did not receive blood transfusions. He demonstrated a quick response to steroids he required tapering a continued low dose for 3 months.

Discussion

The current literature on AIHA in pediatric populations emphasizes the importance of early diagnosis with DAT and indirect antiglobulin testing and first line treatment with glucocorticoids⁴. The goals of steroid therapy are to decrease hemolysis and increase the tolerability of possible packed red blood cell transfusion. In most cases, steroids result in a response rate of up to 80%⁴. Steroids should then be gradually tapered from 4-6 months after improvement in hemoglobin levels⁴. Those with poor response to steroids can receive intravenous immunoglobulin, with increased benefits in individuals who show hepatomegaly and pretreatment hemoglobin less than 7g/dL⁵. A study by Mayo Clinic reported a relapse rate of 21.4% in children with AIHA in the first year after completing an initial steroid course⁶. Rare and severe cases may go on to requiring anti-CD20 monoclonal antibody. For patients with chronic AIHA, splenectomy can be of great benefit⁷.

Current literature also suggests that transfusion therapy should be avoided unless the patient's course is severe and hemoglobin levels are below 6 g/dL⁸. The primary issue with transfusion therapy is that autoantibodies cause a reduced survival rate of the transfused red blood cell. Administration of steroids prior to transfusion to decrease antibody development is still debated, neither validated nor contraindicated⁸. Leukocyte depleted packed red cells are currently recommended for AIHA patients to lower the risk of febrile non-hemolytic reactions⁸.

Transfusion should be restricted to cases who are in imminent danger of cardiovascular collapse. As always, benefit needs to outweigh the risk of further hemolysis with worsening anemia and acute renal failure from cell-free hemoglobin induced endothelial and tissue damage.

Though possible, it is difficult to conclusively state that the Coombs positive hemolytic anemia in this instance was caused by the concurrent CMV infection. Viral illnesses can cause AIHA to develop, and once the illness resolves the AIHA usually does as well. There have been a few case reports describing AIHA caused by CMV in pediatric patients, though there are no clear management principles. A few case reports describe patients with severe CMV and AIHA symptoms and complications that needed to be resolved with antiviral therapies, whereas other describe less severe symptoms that are either resolved primarily with glucocorticoids or no therapy at all^{9,10}. Furthermore, the patient had a viral upper respiratory infection and COVID-19 prior to his hospitalization due to AIHA. There are a few case reports describing pediatric patients with COVID-19 induced AIHA who showed response to steroids and IVIG within one month of treatment^{11,12}.

The two cases highlight differences in management of AIHA in children. Both patients initially presented with low hemoglobin, normal platelet levels, were DAT positive and ANA negative. Both patients presented after upper respiratory infection signs, though the first case may have also had his case of AIHA in conjunction with CMV infection, and thus his disease etiology is less clear. The first case shows that low hemoglobin from AIHA was treated with transfusions in addition to steroids, though the patient did not show any signs of cardiovascular collapse as well.

The contrasting case shows that steroids can be an effective first line treatment for AIHA even if hemoglobin levels are low, considering that the patient did not have any further signs of cardiovascular collapse.

Conclusion

We report a case of AIHA in an infant that demonstrates varied practice in the management of AIHA. We showed potential complications associated with the disease treatment, specifically the risks associated with use of blood transfusions. Steroids are a suitable first line treatment for AIHA, regardless of hemoglobin results, especially when the anemia is otherwise asymptomatic.

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Conflict of interest

We have no conflicts of interest to disclose.

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