INTRODUCTION

We report the case of a 6-week-old infant who presented with shock and respiratory distress due to severe anemia. He was identified as having an autoimmune hemolytic anemia despite his young age. The case highlights the importance of maintaining a broad differential, especially in very young children.

Given the severity of his presentation, an extensive workup was performed to determine the source of his critical illness and the etiology of his anemia, including evaluation for sepsis, decreased or ineffective erythrocyte production, blood loss, or erythrocyte destruction leading to his anemia. His clinical evaluation and laboratory results supported a diagnosis of warm autoimmune hemolytic anemia (AIHA). AIHA is caused by the presence of auto-antibodies (usually IgG) that develop against erythrocyte surface antigens leading to their subsequent destruction by the macrophages in the reticuloendothelial system.1 Patients presenting with AIHA have systemic symptoms of hemolysis, including pallor, jaundice, fever, and lethargy.2,3 AIHA is divided into primary AIHA when it is idiopathic with no underlying cause identified and secondary AIHA when there are known triggers for antibody development, such as malignancy, systemic illness, or drug exposure.2

Given this patient’s young age, we report this case to emphasize the need to consider this diagnosis that can be fatal due to rapid hemolysis if not recognized and treated quickly when patients present outside of expected age ranges.
A 6-week-old male born full-term via spontaneous vaginal delivery presented to Monroe Carell Jr. Children’s Hospital at Vanderbilt with jaundice and respiratory distress. His mother reported no complications during pregnancy, an uncomplicated delivery, and normal newborn nursery stay during which his newborn screen was normal and he received vitamin K. He was noted to have increasing jaundice 1 week before presentation, initially thought to be from breast milk jaundice, but it progressively worsened, and he developed pallor. The day prior to presentation, he developed difficulty feeding and decreased urine output. The day of presentation, he began to have respiratory distress prompting evaluation in the pediatric emergency department (ED) where he was pale and lethargic with decreased tone upon initial assessment. He was in significant respiratory distress (nasal flaring, retractions) with respiratory rate of 44 breaths per minute, oxygen saturation 94% on room air. He was hypothermic to 34.8°C with a pulse of 152 beats per minute.

Venous blood gas was notable for a severe lactic acidosis with a pH of 7.06, bicarbonate of 16 mmol/L, and a lactate of 18 mmol/L. His hemoglobin was noted to be 3 gm/dl on the blood gas. Complete blood count showed a hemoglobin of 3 gm/dl, hematocrit of 10%, mean corpuscular volume of 107 fl/cell, white blood cell count of 35.5 × 10^3/mcl, and platelet count of 971 × 10^3/mcl. Comprehensive metabolic panel was notable for a total bilirubin of 4.55 mg/dl, a direct bilirubin of 1.0 mg/dl, and a bicarbonate of <5 mmol/L. Due to his age and ill-appearance, blood, urine, and cerebrospinal fluid (CSF), cultures were obtained, and empiric IV antibiotics were started. A head ultrasound was performed and did not show any intracranial hemorrhage, and plain films were negative for acute findings suggestive of trauma or hemorrhage in his chest or abdomen. The patient’s mother confirmed neither she nor patient had taken any new medications.

The patient was admitted to the pediatric intensive care unit (PICU) due to the severe anemia and respiratory failure with resultant profound lactic acidosis and shock requiring intubation and mechanical ventilation. Trauma blood (type O negative) was initially ordered to prevent delay in transfusion.

Additional laboratory testing revealed an elevated reticulocyte count of 7.6% (ref range 0.5%–1.8%), a haptoglobin of <8 mg/dl (ref range 7–221 mg/dl), and an elevated lactate dehydrogenase of 616 unit/L (ref range 163–452 unit/L). His peripheral smear revealed few schistocytes or helmet cells. The red cells had normal central pallor, anisocytosis, and significant polychromasia (Figure 1A,B). He has no family history of any hematologic disorder, including thalassemia or hemolytic anemias. Type and screen demonstrated a blood type of A positive with a positive antibody screen as well as a positive Direct Antiglobulin Test (DAT) with a panagglutinin. He had no complement bound to his red blood cells (which is a surrogate marker of an IgM antibody), but he did have 4+ IgG bound to his red cells. Further antibody identification was attempted in low-ionic strength saline (LISS), which uses ionic forces to more specifically identify RBC antibodies, but his testing continued to show strong agglutination against every red blood cell consistent with a warm autoimmune antibody. Maternal blood type was A positive and a negative antibody screen was confirmed 2 days prior to delivery, and additional maternal screen was performed on the day of admission which was negative.

Due to ongoing concern for hemolysis and need for transfusions, he was started on 2 mg/kg/day intravenous (IV) methylprednisolone divided every 12 h. He was ultimately transfused with a total of 25 ml/kg of packed red blood cells (pRBCs) in small aliquots during his PICU admission increasing his hemoglobin to 8.2 gm/dl and
allowing transfer to the floor once he was extubated to room air.

Additional testing for congenital hematologic conditions (Band 3 testing for hereditary spherocytosis, glucose-6-phosphate-dehydrogenase [G6PD] enzyme qualitative testing), autoimmune conditions (ANA panel), immunodeficiency syndromes (quantitative immunoglobulins, T&B-cell subsets), genetic conditions (urine organic acids and acylcarnitine profiles), bacterial infections (blood, urine, and CSF cultures), and viral infections (Epstein Barr virus, cytomegalovirus, parvovirus, hepatitis, and CSF meningitis/encephalitis) all returned negative.

He continued to require daily pRBC transfusions to maintain a hemoglobin goal of greater than 7 gm/dl, and his steroids were gradually transitioned to an oral regimen. He received one dose of IV immunoglobulin (IVIg) when transfusion requirements did not decrease with steroids alone. Frequency between pRBC transfusions slowly improved. His hemolysis worsened with any wean of his steroids, and thus, a very long steroid taper was initiated. Due to his inability to wean steroid further and worsening complications from steroid therapy (severe hypertension requiring multiple anti-hypertensive medications for several weeks), he also received rituximab. After four IV doses of rituximab 375 mg/m², his steroids were able to be further decreased. He was able to wean off steroids completely after 4.5 months and remains stable now 18 months after his initial presentation.

3 | DISCUSSION

The 6-week-old term male patient described above presented with jaundice and respiratory distress and was found to have severe anemia secondary to autoimmune destruction of his red blood cells at body temperature, or warm autoimmune hemolytic anemia. AIHA should considered in the differential for patients with anemia, but rarely is it the cause of illness in a patient this young. Therefore, it was critical on presentation to consider other reasons for his anemia given the severity of his presentation. With a patient presenting at this age with any sort of distress, bacterial or viral infection leading to sepsis should be at the top of the differential diagnosis. Cultures (blood, urine, and CSF) and infectious evaluation with empiric antibiotics are important while further diagnostic workup is ongoing. Additional diagnostic considerations for severe anemia include undiagnosed congenital liver pathologies or blood loss from trauma (accidental or non-accidental). Extensive evaluation did not reveal any other causes leading to his clinical presentation.

Despite his age, the clinical diagnosis that fit the severity of his anemia and his blood bank testing findings is warm AIHA, and no obvious trigger such as infections or medications were identified. He was critically ill at time of presentation, which was quickly recognized by the ED and PICU allowing for supportive care.

Recognition of the patient’s respiratory distress progression into respiratory failure required emergent response with type O negative (trauma) blood for initial transfusion to improve his oxygen carrying capacity rapidly. Though the preference is to transfuse crossmatched pRBCs, in this case, waiting for the type and screen would have delayed necessary care by at least an hour and likely longer due to the presence of a panagglutinin. Subsequently, RBC phenotyping was performed for the Rh and Kell antigens to best provide pRBCs for him most similar to his own, though the product would be considered the least compatible as opposed to truly crossmatched. He was provided with phenotypically matched (E and K1 negative) pRBCs, which reduces the potential for future antibody development by mimicking the antigens present on the patient’s own RBCs.

The laboratory findings in this case were most consistent with ongoing hemolysis. It is important to note that haptoglobin is a less reliable marker of hemolysis in infants less than 3 months of age since it is not synthesized in the liver reliably, although it is a common component of an evaluation for hemolysis in patients of all ages.

Another key component of this case is the balance of the volume of blood required for diagnostic testing and maintaining the patient’s oxygen carrying capacity while awaiting pRBC transfusion. Tests that will change clinical management are the highest priority, followed by tests that will be affected by transfusion of blood products. In the neonatal period and early infancy, hemolytic disease of the fetus and newborn (HDFN) should be considered high on the differential for a patient with hemolysis. HDFN is most commonly due to ABO or Rh incompatibility where maternal antibodies cross the placenta and can target fetal cells with different antigen patterns but can also be due to minor red blood cell antigen incompatibility. Our patient’s blood type matched his mother who had multiple negative antibody screens, making this less likely. The antibody screen evaluates for circulating antibodies and the DAT is used to assess if antibodies are bound to red blood cells. Further attempts to identify specific antibodies present are done with an antibody identification test, but when patients have a strong panagglutinin (4+ agglutination in all screening cells, meaning the serum shows agglutination with every red blood cell tested), the specific antibody is often unable to be identified due to the inability to separate the antibody from the RBCs to the level required for identification, as was the case for this patient.

Because it is atypical for infants to develop autoantibodies, antibodies identified on an infant’s type and screen
are usually maternal IgG antibodies (like anti-D) that have been passively acquired through the placenta. The negative maternal screen from prior to delivery and upon patient’s admission confirms that his mother did not have evidence of a minor red blood cell antibody, thus suggesting the antibody leading to his clinically significant hemolysis was indeed an autoantibody despite his young age.

Warm AIHA is a rare disorder in children, with an estimate of 0.4 cases per 100,000 person-years and is even rarer in young infants. Given the rarity of this disease in pediatric populations, there are limited diagnostic and treatment recommendations, and most information is based on the case reports. Initial treatment with corticosteroids has been widely practiced.6,7 Their initial mechanism of action is to block the phagocytic Fc receptor, leading to decreased red cell destruction within 24–48 h.1 A later effect of corticosteroids is decreased autoantibody production, a slow wean off corticosteroids over weeks to months is initiated.1,7 Approximately 80% of patients will respond initially to corticosteroids.1,3,8 However, corticosteroids are known to have numerous complications, especially with prolonged use. Growth suppression, osteoporosis, immune suppression, and hypertension (as seen in this case) are all seen in pediatric patients on glucocorticoids.9

There is no consensus on the best treatment for steroid-refractory pediatric cases of warm AIHA. A variety of approaches have been tried, including immunosuppressive drugs, cytotoxic agents, androgens, and splenectomy.1,6 Emerging evidence in adults has suggested that rituximab, a monoclonal antibody against the CD20 antigen on B lymphoblasts has been effective in patients with warm AIHA. Pediatric data are limited, although a 2017 French cohort looked at 61 pediatric patients with various AIHA syndromes, including Evans syndrome, treated with rituximab, which showed an overall response rate of 75%.10 Younger patients less than 12 months (only 10 infants in this cohort) were shown to have a sustained response after treatment with rituximab and six of these 10 infants were able to completely discontinue steroids.10

4 | CONCLUSION

While a rare diagnosis in the pediatric population, the non-specific presentation of warm AIHA can lead to it being easily overlooked. Given the severity of the symptoms and potential for brisk hemolysis, these patients can rapidly become critically ill. Mortality rates are estimated to be around 10% in pediatric patients.3 Therefore, we felt this was an important case to describe, educating pediatric providers of the potential for AIHA to develop even in very young infant.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

Drs. Walker, Ransom, Sood, Andrews, and Smith drafted, reviewed, and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ETHICAL APPROVAL

The article was written and submitted for publication following written permission from the patient’s family.

CONSENT

Published with written consent of the patient.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current.

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How to cite this article: Walker SC, Ransom M, Sood S, Andrews J, Smith CM. Respiratory failure and shock in an infant with severe anemia. *Clin Case Rep*. 2021;9:e04852. [https://doi.org/10.1002/ccr3.4852](https://doi.org/10.1002/ccr3.4852)