Case Report

# A case of autoimmune hemolytic anemia with anti-D specificity in a 1-year-old child

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Although antibodies to antigens in the Rh blood group system are common causes of warm autoimmune hemolytic anemia, specificity for only the D antigen is rare in autoimmune hemolysis in pediatric patients. This case reports an anti-D associated with severe hemolytic anemia (Hb = 2.1 g/dL) in a previously healthy 14-month-old child who presented with a 3-day history of low-grade fevers and vomiting. Because of his severe anemia, on admission to the hospital he was found to have altered mental status, metabolic acidosis, abnormal liver function tests, and a severe coagulopathy. He was successfully resuscitated with uncrossmatched units of group O, D– blood, and after corticosteroid therapy he had complete resolution of his anti-D-mediated hemolysis. ***Immunohematology* 2013;29:15-18.**

**Key Words:** autoimmune hemolytic anemia, pediatrics, anti-D

Autoimmune hemolytic anemia (AIHA) is the pathological destruction of red blood cells (RBCs) by antibodies produced against self-erythrocyte surface antigens. Its prevalence is estimated to be approximately 1 to 3 per 100,000 per year, although it may be lower in pediatric patients.[1–4] Warm AIHA is usually caused by immunoglobulin G (IgG) antibodies that bind to RBC antigens and result in erythrophagocytosis by splenic macrophages or hepatic Kupffer cells. In many cases, antigen specificity cannot be determined, or patients express pan-reactivity across antigen groups. However, there have been reports of specificity to as many as 50 RBC antigens with anti-e being one of the most common specificities cited in reviews.[4–6]

AIHA can be either a primary or a secondary disease, usually as a result of an underlying autoimmune disease, primary immunodeficiency, or lymphoid malignancy; it can present in a known primary process or as part of its initial presentation.[4,7,8] In adult patients primary AIHA represents approximately 60 percent of cases.[9] In case series of pediatric patients, the proportion of patients with primary AIHA has ranged from 7 to 64 percent.[4,5,10] This case of AIHA is unusual because of the D specificity of the autoantibody and its occurrence in a 14-month-old child without an underlying immune or autoimmune disorder and with no long-term sequelae.

## Case Report

A previously healthy 14-month-old white male born after a term pregnancy without perinatal problems and with no prior history of blood transfusion presented to the emergency department with lethargy and jaundice. He had a history of low-grade fevers, vomiting, and fatigue for 3 days before presentation. On the day of admission he was noted to have occasional episodes of shallow breathing with decreased responsiveness. His vital signs showed he was tachycardic, normotensive, and not hypoxic. He was noted to be pale, jaundiced, and responsive to painful stimulus only. In addition, he was found to have an intermittent gallop and hepatosplenomegaly.

His initial blood work showed he was severely anemic with a hemoglobin (Hb) of 2.1 g/dL, hematocrit (Hct) of 7.1 percent, and an elevated reticulocyte count of 32 percent. His white blood cell count was elevated, and his platelet count was normal. The pertinent laboratory evaluations are summarized in Table 1. In addition to his severe anemia, the patient had a bilirubin that was greater than 3 times the upper limit of normal and a lactate dehydrogenase, which is a marker for rapid cell turnover, that was almost 6 times the upper limit of normal. The results were consistent with the diagnosis of an acute hemolytic anemia.

Further laboratory testing demonstrated significant end-organ ischemia secondary to his severe anemia. He was acidotic on admission, with a pH of 7.19. He had evidence of prerenal insufficiency and hepatic dysfunction with elevated hepatocellular enzymes. Although he did not have any clinical signs of bleeding, he had a prolonged prothrombin time, but a normal partial thromboplastin time. Further evaluation of coagulation factors demonstrated a deficiency in factors II, V, and VII, an elevated factor VIII, and normal fibrinogen. His D dimer was 1390 ng/mL. Although there was evidence of activation of coagulation, the patient did not have severe consumption, and his coagulopathy was most likely attributable to decreased hepatic synthesis. Vitamin K deficiency could not be documented.

**Table 1.** Selected abnormal laboratory values in this patient consistent with a brisk hemolytic process and end-organ ischemia caused by severe anemia

| Laboratory test | Patient's results | Normal range |
|---|---|---|
| Complete blood count | | |
| White blood cells (WBC) | 39.4 × $10^3$/μL | 5–13 × $10^3$/μL |
| Hemoglobin (Hb) | 2.1 g/dL | 9.5–14 g/dL |
| Hematocrit (Hct) | 7.1% | 30–41% |
| Platelet count | 376 × $10^3$/μL | 150–500 × $10^3$/μL |
| Reticulocyte count | 32% | 0.56–2.72% |
| Blood chemistries | | |
| Venous blood gas | | |
| pH | 7.19 | 7.32–7.42 |
| $PCO_2$ | 19 mm Hg | 40–50 mm Hg |
| Bicarbonate ($HCO_3$) | 7 mEq/L | 22–25 mEq/L |
| Glucose | 36 mg/dL | 60–105 mg/dL |
| Blood urea nitrogen (BUN) | 50 mg/dL | 6–17 mg/dL |
| Creatinine | 0.7 mg/dL | 0.2–0.6 mg/dL |
| Lactate dehydrogenase (LDH) | 2042 U/L | 150–360 U/L |
| Liver function tests | | |
| Bilirubin (total) | 3.7 mg/dL | 0.2–1.2 mg/dL |
| Aspartate transaminase (AST, SGOT) | 1388 U/L | 20–60 U/L |
| Alanine transaminase (ALT, SGPT) | 689 U/L | 0–33 U/L |
| Coagulation tests | | |
| Prothrombin time (PT) | 49 seconds | 10.8–13.8 seconds |
| Partial thromboplastin time (PTT) | 27 seconds | 25.4–35 seconds |
| Factor II | 38% | 50–150% |
| PIVKA II | 0 U/dL | 0 U/dL |
| Factor V | 14% | 63–116% |
| Factor VII | 4% | 52–120% |
| Factor VIII | 363% | 58–132% |
| Fibrinogen | 276 mg/dL | 202–404 mg/dL |
| D dimer | 1390 ng/mL | >255 ng/mL |

PIVKA II =protein-induced by vitamin K absence or antagonist II.

He was resuscitated with both crystalloid fluids and emergency units of unmatched, group O, D– packed RBCs. After this resuscitation the patient's mental status and cardiovascular status improved. His renal and liver function tests improved, and he had prompt resolution of his metabolic acidosis.

Further testing showed that the patient was group B, D+ with warm-reacting autoantibodies. His direct antiglobulin test (DAT) was 2+ positive for IgG, and an eluate from the cells demonstrated anti-D specificity and no reactivity with D+ LW– RBCs. Extended Rh phenotype by serology indicated that the patient was D+, C–/c+, E+/e– (likely $R_2R_2$); however DNA testing revealed that the patient's genotype was D heterozygote, C–/c+, and E+/e+ (likely $R_2r$). There was no evidence of anti-C/c or anti-E/e alloantibodies or autoantibodies. Sequencing of his *RHD* gene showed he was negative for the RHD-inactivating pseudogene and had none of the 18 most common partial D genotypes. The discrepancy between his positive e genotype and negative phenotype for e is likely caused by an altered *RHCE* gene, although complete sequencing could not be performed.

After his initial resuscitation, the patient's hemoglobin remained stable with no additional evidence of hemolysis, and he did not require any additional RBC transfusions. On the day of admission, he was started on a 10-day course of prednisone (2 mg/kg per day) and was successfully tapered off the medication without recrudescence of his hemolysis. Infectious disease testing was performed, including a respiratory virus direct stain for adenovirus, influenza A and B, parainfluenza 1 through 3, and respiratory syncytial virus, which was negative. There was no evidence of current or prior infection with Epstein-Barr virus. The patient had no underlying conditions such as another autoimmune disorder (negative antinuclear antibody), immunodeficiency (normal serum immunoglobulins), or malignancy, making this a primary AIHA.

Samples from the patient exhibited a weakly positive DAT for 2 to 3 months after his initial presentation. Subsequently, the DAT became negative, and he had complete resolution of his hemolysis 1 year after his initial presentation without evidence of any autoimmune or immune disorders.

## Discussion

AIHA is caused by antibodies to a specific antigen on the patient's own erythrocytes, resulting in either intravascular or extravascular hemolysis. Warm AIHA is caused by IgG antibodies and results in antibody-mediated erythrophagocytosis by splenic macrophages. Cold AIHA is caused by IgM antibodies and results in intravascular hemolysis secondary to complement fixation on the RBC surface. The thermal amplitude of the antibodies determines their clinical significance; cold agglutinins that are reactive at temperatures lower than body temperature are generally of little clinical significance. Biphasic IgG antibodies that bind RBCs at colder temperatures and then fix complement in warmer temperatures cause paroxysmal cold hemoglobinuria (PCH).

The incidence of both warm and cold AIHA increases with patient age. But in pediatric patients the highest incidence of cold AIHA, including cold agglutinin syndrome and PCH, is in patients younger than the age of 4, likely because of their association with common childhood infections such as viral respiratory infections and *Mycoplasma pneumoniae*.[9] In most case series, warm AIHA constitutes about 60 percent of the cases in pediatric patients.[10] Some series report that primary AIHA is more common, whereas others demonstrate that secondary AIHA is more common in pediatric patients.[5,9,10]

One of the largest series showed that the majority of cases of AIHA are caused by warm antibodies, 64 percent, versus 26 percent attributable to cold antibody and 10 percent attributable to mixed antibodies (n = 100).[10] This series also demonstrated that approximately half of the patients (54%) had an underlying disease process such as autoimmune disease, idiopathic thrombocytopenia, neoplasia, or hemoglobinopathy, whereas the remaining 46 percent of patients had primary (idiopathic) AIHA. The most common autoimmune disorders associated with AIHA include lupus, Evan's syndrome, autoimmune lymphoproliferative syndrome (ALPS), and other immunodeficiencies. The majority of patients with warm antibody disease, 59 percent (38/64), had primary AIHA,[10] similar to a series of 26 children in India that showed that 65 percent had primary AIHA.[11] Children with primary AIHA are more likely than adults to have a self-resolving, relatively short course (less than 6 months). Patients who present at younger than 2 years and older than 12 years are at risk for a chronic course.[12]

The discrepancy between the patient's e negative phenotype and e positive genotype likely represents an altered *RHCE* gene. This altered gene may place the patient at a higher risk of developing alloantibodies to the e antigen; however, it should not play a role in the development of autoantibodies to D. D is the most immunogenic antigen when development of alloantibodies occurs after an exposure; however, it is not commonly associated with autoantibody development. Antibodies against antigens in the Rh system, such as anti-e, anti-E, and anti-c, are most commonly implicated in warm AIHA.[2–5,10,11,13,14] Patients frequently have multiple anti-Rh antibodies or panreactive Rh antibodies, but having only anti-D is rare in AIHA.[15]

There are case reports of patients developing anti-D after solid-organ transplant, although these are not true autoantibodies as they were passively transferred by donor lymphocytes.[16] Autoantibodies to D have been found in the setting of myelodysplasia[17] and as a paraneoplastic syndrome associated with breast carcinoma and ovarian teratoma.[18,19] There was an additional case report of IgM anti-D in the setting of non-Hodgkin lymphoma.[20] To date, there is only one case of primary AIHA caused by anti-D in an adult patient.[15] To our knowledge, the case presented here is a unique case of primary AIHA with an IgG antibody toward the D antigen in a pediatric patient.

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