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A case of autoimmune hemolytic anemia with anti-D specificity in a one-year-old

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Abstract

While antibodies to antigens in the Rh group 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 who presented with a three-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, Rh-negative blood, and following corticosteroid therapy he had complete resolution of his anti-D-mediated hemolysis.

Keywords

autoimmune hemolytic anemia; pediatrics; anti-D

Introduction

Autoimmune hemolytic anemia (AIHA) is the pathological destruction of red blood cells (RBCs) by antibodies produced against self erythrocyte surface antigens. Its incidence is estimated to be approximately 1-3 per 100,000 per year, though the incidence may be lower in pediatric patients.[1-4] Warm AIHA is usually caused by IgG antibodies that bind to RBC antigens and result in erythrophagocytosis by splenic macrophages or hepatic Kupfer cells. In many cases, antigen specificity cannot be determined, or they express pan-reactivity

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across antigen groups. However, there have been reports of specificity to as many as 50 RBC antigens with anti-e being seen commonly in some reviews[4-6].

AIHA can either be a primary or secondary disease, usually due to 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% of cases.[9] In case series of pediatric patients, the proportion of patients with of primary AIHA has ranged from 7-64%.[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 without an underlying immune or autoimmune disorder and with no long-term sequelae.

Case Report

A previously healthy 14-month-old Caucasian male born after a term pregnancy without perinatal problems 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 three days prior to 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 (Table 1, normal range in parentheses) showed he was severely anemic with a hemoglobin (Hb) of 2.1 g/dL, hematocrit (Hct) of 7.1%, and an elevated reticulocyte count of 32%. His white blood cell count was elevated, and his platelet count was normal. A summary of pertinent laboratory evaluations is 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 pre-renal insufficiency and hepatic dysfunction with elevated hepatocellular enzymes. While 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 and 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 due to decreased hepatic synthesis. Vitamin K deficiency could not be documented.

He was resuscitated with both crystalloid fluids and emergency units of unmatched, Group O negative packed red blood cells (RBCs). Following 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, Rh (D) positive positive with warm-reacting autoantibodies. His direct antibody 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 allo- or autoantibodies. Sequencing of his *RHD* showed he was negative for the RHD inactivating pseudogene and had none of 18 of the most common partial D genotypes. The discrepancy between his positive e genotype and negative phenotype for e is likely due to an altered *RHCE* gene, though complete sequencing could not be performed.

Following 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 ten-day course of prednisone (2 mg/kg/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 & B, parainfluenza 1-3, and RSV, 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 ANA), immunodeficiency (normal serum immunoglobulins), or malignancy, making this a primary AIHA.

Samples from the patient exhibited a weakly positive DAT for 2-3 months following his initial presentation. Subsequently, the DAT became negative, and he had complete resolution of his hemolysis one 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 the antibody-mediated erythrophagocytosis by splenic macrophages. Cold AIHA is caused by IgM antibodies 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. Bi-phasic 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 under the age of four, likely due to their association with common childhood infections such as viral respiratory infections and *Mycoplasma pneumoniae*[9]. In most case series, warm AIHA constitutes the about 60% of cases[10] in pediatric patients. 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 due to warm antibodies, 64% versus 26% due to cold antibody and 10% 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% 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% (38/64) had primary AIHA[10], similar to a series of 26 children in India showed that 65% 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 under 2 years and older than 12 year of age 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 should not play a role in the development of auto anti-D antibodies. The D antigen is the most immunogenic antigen in the setting of the development of alloantibodies following 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 pan-reactive Rh antibodies, but having only anti-D antibodies is rare in AIHA[15].

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

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Table 1

Selected abnormal laboratory values in this patient consistent with a brisk hemolytic process and end-organ ischemia due to 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 mmHg	40-50 mmHg
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%

Laboratory Test	Patient's Results	Normal Range
Factor VIII	363%	58-132%
Fibrinogen	276 mg/dL	202-404 mg/dL
D-Dimer	1390 ng/mL	>255 ng/mL