Case Report

Primary Autoimmune Hemolytic Anemia Due To Warm Reactive Autoantibodies: A Rare Case Report

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Abstract:

Autoimmune hemolytic anemia (AIHA) is an acquired form of hemolytic anemia in which autoantibodies target red blood cell (RBC) membrane antigens, inducing cell rupture (lysis). It affects both pediatric and adult populations, although its presentation in childhood is relatively rare, with the annual incidence estimated to be approximately 0.8 per 100,000 individuals under 18 years old [3]. Here we report one such a rare case of autoimmune hemolytic anemia due to primary warm reactive autoantibodies in a 3 year old female child. As there was presence of hemolysis in peripheral blood smear & other investigations also, Direct coomb's test was done & it came out to be positive which was suggestive of autoimmune hemolytic anemia, as following laboratory reports are suggestive of continuous destruction of RBC & after introduction of steroids parameters of hemolysis came out to be normal suggestive of warm reactive autoantibodies type of AIHA. Clinically also patient improved & her urine colour also became normal after when prednisolone started. Patient also did not have any features of secondary causes of warm autoantibody like Systemic lupus erythematous, immunodeficiency disorders, ulcerative colitis & lymphoproliferative disorders so it was considered primary or idiopathic. W-AIHA tends to have a chronic course and is not expected to subside without treatment. It can be a fatal disease, with a mortality rate of up to 4% in children, either because of the acuity of the presentation or because of being refractory to treatment and requiring multiple lines of therapy with frequently associated toxicity. Fortunately, our patient responded to steroid therapy.

Key words: Autoimmune hemolytic anemia (AIHA), Direct Coomb's Test (DCT), Corticosteroids, Warm reactive autoantibody, Blood transfusion.

Introduction:

Autoimmune haemolytic anaemia (AIHA) is an acquired sort of haemolytic anaemia during which autoantibodies target red blood corpuscle (RBC) membrane antigens, inducing cell rupture (lysis). Hemolysis triggers compensatory RBC production by increasing erythropoietin levels; however, this response is usually insufficient to redress normal hemoglobin blood levels resulting in anemia. AIHA is characterized as "extrinsic" because the autoantibodies affect otherwise normal RBCs. . A recent systematic review assessing AIHA terminology concluded that there's significant heterogeneity within the definition and diagnostic criteria for the disease.[1] In most of the reviewed studies, AIHA was defined as hemolytic anemia with a positive direct comb's test (DCT) and concurrent exclusion of alternative diagnoses. However, there are limitations in the use of that definition since it does not include DAT-negative cases. AIHA is assessed as "warm" or "cold" supported the optimal temperature at which the antibodies present maximal reactivity and as primary or secondary counting on the presence of a recognized underlying cause, like immunodeficiency, infections, medications, or malignancy.[2]

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It affects both pediatric and adult populations, although its presentation in childhood is comparatively rare, with the annual incidence estimated to be approximately 0.8 per 100,000 individuals under 18 years old.[3] Children with AIHA can present with a variable degree of severity. The most common sort of AIHA within the pediatric population is thanks to warm-reactive autoantibodies. Warm antibody AIHA (w-AIHA) is diagnosed in additional than half autoimmune hemolytic episodes.[4–6] Cold reactive antibodies are liable for the less frequent sorts of the disease, referred to as cold agglutinin syndrome (CAS) and paroxysmal cold hemoglobinuria (PCH), defined by the immunoglobulin (Ig) isotype against the RBCs: IgM in CAS and IgG in PCH. A small subset of cases is recognized as "mixed AIHA," with laboratory work-up revealing serologic findings of both w-AIHA and CAS. Drug induced autoimmune hemolytic anemia is also a possibility but it is rare. Here we report one such a rare case of autoimmune hemolytic anemia due to primary warm reactive autoantibodies in a 3-year-old female child.

Table 1: Classification of autoimmune hemolytic anemia (AIHA)[7]

Type	Antibody Class	Temp. of maximal activity (^{0}celcius)	DCT Positivity
Warm antibody AIHA (w-AIHA)	IgG	37	IgG ± C3
Cold agglutinin syndrome (CAS)	IgM	4	C3 only
Mixed AIHA	COLD IgM & WARM IgG	4 and 37	IgG and C3
Paroxysmal cold hemoglobinuria (PCH)	IgG	4	±C3

Case report:

A 3-year-old female child came to OPD with chief complaint of fever and dark colored urine with no complaints during micturition. Fever was insidious in onset, high grade, intermittent and peaks up to 102° F and associated with mild cough and cold, parents noticed dark colored urine since last week. Her parents also complaints of decreased appetite and not gaining weight. No similar history in past. No history of any drug intake or any blood transfusion since 1 year. No history of trauma & sore throat in the past & family history does not reveal any kidney or hemolytic disorders. Birth history reveals prenatal, natal postnatal period was uneventful. She is immunized till date.

On examination, poorly nourished, average built, weight 10kg, height 84cm, head circumference 48cm, mid arm circumference 14cm, patient is severely stunted and severely underweight. Only one fever spike was present, otherwise patient had normal temperature throughout admission period. Pallor and mild icterus was there. Lymphadenopathy absent. Extremities were warm. Patient was haemodynamically stable. Head to toe examination was normal. On abdominal examination mild hepatoslenomegaly was there. Other systems were normal.

Patient was admitted in our hospital and routine investigations were sent. Blood investigations showed moderate anemia with leucocytosis & normal platelets but raised reticulocyte, ESR & lactate dehydrogenase count. There was also evidence of raised serum bilirubin (direct & indirect) and SGOT. Renal function test, CRP, ASO titer & electrolytes were normal. Blood culture also came out to be normal. Urine routine and microscopy-Normal, No evidence of red blood cell or hemoglobin, moderate urobilinogen was present in urine. Other causes of Anemia and Fever ruled out by laboratory investigation. Chest X-ray was normal, abdominal ultrasonography was suggestive of mild hepatosplenomegaly. Hb electrophoresis & sickling test was normal. As there was presence of hemolysis in peripheral blood smear & other investigations also, Direct coomb's test was done & it came out to be positive which was suggestive of autoimmune hemolytic anemia, as following lab reports are suggestive of continuous destruction of RBC & after introduction of steroids parameters of hemolysis came out to be normal suggestive of warm reactive autoantibodies type of AIHA.

Clinically also patient improved & her urine colour also became normal after when prednisolone started. Patient also did not have any features of secondary causes of warm autoantibody like Systemic lupus erythematous, immunodeficiency disorders, ulcerative colitis & lymphoproliferative disorders so it was considered primary or idiopathic.

Patient was treated symptomatically with antipyretics, IV antibiotics, fluid administration & PCV transfusion. Tablet folic acid also started in prophylactic dose. As patient was having normal temperature, extremities were warm, we started Tablet Prednisolone at 2 mg/kg/day. On day 5 again Hemoglobin dropped even after 2 PCV transfusion & parameters of hemolysis were raised so Prednisolone dose increased up to 4 mg/kg/day. Patient responded to this treatment & there was serial decrease in hemolytic parameters & increase in hemoglobin.

Patient then counseled about relapse & regular follow up & then discharged on day 12 with tapering dose of steroids. Patient came to follow up after a week & then DCT was positive but no signs or laboratory findings suggestive of hemolysis so steroids continued. After 4 weeks of steroid therapy DCT became negative. But steroids tapered slowly over 6 months.

Table 2: Serial Laboratory Findings

	Day 1	Day 3	Day 5	Day 7	Day 9
Hb	5.8	7.6	5.3	8.1	10.9
TLC	14.3	20.7	17.8	14.2	9564
Platelet	335	269	239	259	312
Reticulocyte count	20	16	24	12	2
LDH	3654	3898	3568	1950	958
Total bilirubin	8.6	7.0	6.4	5.0	1.1
Direct bilirubin	3.8	2.2	2.3	1.9	0.2
Indirect bilirubin	4.8	4.8	4.1	3.1	0.9
SGOT	76.8	72.6	61.9	45	28
SGPT	39.6	25.4	26	20	21
ESR	42				
Urobilinogen	Moderately raised				Absent
DCT	Positive				
Intervention Done	prednisolone started at 2 mg/kg/day & PCV transfusion	prednisolone at same dose & second PCV transfusion	prednisolone started at 4 mg/kg/day & third PCV transfusion	prednisolone at same dose & fourth PCV transfusion	

Discussion:

An acute presentation of autoimmune hemolytic anemia is frequently a life-threatening, fast-progressive disease and requires prompt diagnosis, initiation of treatment, and close monitoring. Therefore, the first question to be answered on presentation of a patient with evidence of hemolytic anemia, is if this is an immune-mediated hemolytic anemia by ruling out other potential causes. To resolve this question, based on an algorithmic approach for the evaluation of hemolytic anemia, the DAT historically known as direct Coombs is the first test to be ordered, along with complete blood count (CBC), reticulocyte count, LDH, Sr. Bilirubin, and blood smear preparation for review.[7]

In DCT, a polyspecific anti-IgG and anti-C3 reagent, is added to the patient's washed RBCs in suspension, resulting in cell agglutination when positive.[8] As DCT in our setting is both IgG & complement specific, we were not able to differentiate between Warm antibody AIHA (w-AIHA) & cold agglutinin syndrome. So response to steroids was taken into account. Patient responded to steroids so considered as Warm antibody AIHA.

It is estimated that DCT is negative in up to 11% of all w-AIHA cases with clinical characteristics of autoimmune hemolysis, termed "DCT negative w-AIHA".[9,10] Awareness of the limitations of the (conventional) DCT assay performed in most laboratories and blood banks is needed, to pursue further evaluation in cases that appear compatible with immune-mediated hemolytic anemia despite DCT being negative. Enhanced DCT assays, often called super-Coombs, are available in reference laboratories and significantly increase the true-positive detection rate.[11]

The warm-reactive antibodies causing AIHA bind to the RBC membrane antigens at 37°C and are typically IgG; IgA and monomeric IgM are detected in rare cases.[12] The autoantibodies are polyclonal and poly-specific, i.e., they react with multiple RBC antigens rather than a specific one and are usually directed against high incidence antigens.

Hemolysis is especially extravascular, as RBCs coated with warm-reactive antibodies are phagocytosed by splenic macrophages carrying Fcg receptors. When the antibodies on the RBC membrane have high concentration or high affinity for complement, they trigger the activation cascade up to C3b and therefore the C3b-opsonised erythrocytes are phagocytosed by the liver macrophages carrying C3-receptors. Rarely, the complement activation may proceed to the formation of membrane attack complex (C5b9), resulting in intravascular hemolysis.[13]

A significant percentage of w-AIHA in children is primary or idiopathic; during a nationwide French cohort study of 265 children, that percentage approached 40%.[4] Underlying disorders resulting in secondary w-AIHA most ordinarily include immunodeficiencies like common variable immunodeficiency (CVID) and ALPS or other ALPS-like syndromes, autoimmune diseases like systemic LE (SLE) and juvenile idiopathic arthritis, and infections, mostly viral.[4] Less frequent causes include malignancies, previous transfusions or transplantation, especially when treated with tacrolimus for post-transplant immunosuppression [14], and medications such as cephalosporins and piperacillin.[15]

Clinical presentation of w-AIHA involves non-specific signs and symptoms of jaundice, dark urine, fatigue, splenomegaly and possibly hepatomegaly, and, in chronically persistent cases, cholelithiasis and cholecystitis.[16] In children with secondary w-AIHA, clinical manifestations of the underlying disorder could also be present, as well.

The initial laboratory tests for w-AIHA aim to evaluate the presence of hemolysis and degree of anemia and include CBC with differential, reticulocyte count, peripheral blood smear review, DAT, type and screen, and serum markers like total and unconjugated bilirubin, LDH, and haptoglobin. In most patients with hemolysis, low hemoglobin levels, elevated reticulocyte count,elevated LDH and unconjugated bilirubin are common findings.[7]

Urine hemoglobin and hemosiderin evaluation may be used to differentiate intravascular (positive result) versus extravascular hemolysis.[7]

In our case urine Haemoglobin & RBCs was absent but presence of urobilinogen was there which was suggestive of haemolysis.

W-AIHA tends to possess a chronic course and isn't expected to subside without treatment. It can be a fatal disease, with a mortality rate of up to 4% in children, either because of the acuity of the presentation or because of being refractory to treatment and requiring multiple lines of therapy with frequently associated toxicity.[14] First-line therapy starts with glucocorticoids, typically given as prednisone or prednisolone orally, although intravenous methylprednisolone may be initially needed depending on the clinical status of the patient. The dose we use is 2 to six mg/kg/day of prednisone or prednisone-equivalent, divided every 8–12 h; some have reported using because the initial dose up to 30 mg/kg/day of iv methylprednisolone.[18] The initial goals are decreasing hemolysis, stabilizing hemoglobin levels, and increasing safety and tolerability of packed RBC transfusion, if needed. The steroid response rate is high, up to 80%, and is usually apparent within 24 to 72 h after initiation. After normalization of hemoglobin, the steroids should be tapered slowly over approximately 6 months, since quick tapering or abrupt discontinuation have been associated with disease relapse.[10]

Transfusion is usually indicated for symptomatic or fast-progressing anemia, which may be life-threatening, especially in cases of associated reticulocytopenia, and will not be withheld simply because of fear of theoretical complications.[18,19] Close communication between the treating hematologist and blood bank services will aim to determine if alloantiodies may be present, based on the history of previous transfusions or pregnancy. Prompt initiation of steroid treatment on presentation and shut monitoring during transfusion is suggested to attenuate the danger of transfusion reactions.

If patient is not responding well to steroids then IVIG can be considered at 1 gm/kg/day for 2 days. In refractory cases, when Hgb has not been stabilized over 100 g/L within 3–4 weeks post initiation of treatment, or when there's difficulty in weaning the kid off steroids requiring a prednisone dose higher than 1 mg/kg/day to maintain remission[17, 18], second-line options include rituximab (anti-CD20 antibody), splenectomy, and immunosuppressive agents.

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