Case Report

Common presentation of an uncommon anaemia in a resource-limited setting: A diagnostic challenge

Shankar Roy[1], Monika Pathania[1], Ravi Kant[1], Minakshi Dhar[1], Amisha[1], Paras Malik[1], Vyas Kumar Rathaur[2]

[1]Department of Medicine, AIIMS, Rishikesh, Uttarakhand, [2]Professor, KD Medical College Hospital and Research Institute, Mathura, Uttar Pradesh, India

Abstract

A 38-year-old female in the reproductive age group presented with anaemia in a resource-poor setting. The patient was given multiple transfusions during the course of her treatment. After a proper work-up she was diagnosed with Coomb's negative autoimmune haemolytic anaemia (AIHA). She was later treated with steroid and she showed significant improvement. Early diagnosis in her case at the primary care level with other causes of anaemia in mind could have prevented unnecessary transfusions and morbidity. Proper history and approach to anaemia is the key in a resource-poor setting.

Keywords: Autoimmune haemolytic anaemia, blood transfusion, Coomb's negative, haemolysis

Introduction

The most common nutritional deficiency disorder in the world is anaemia. As per the National family health survey -3 (NFHS), 55% of women in India are anaemic, and iron deficiency is the most common cause for it.[1]

Autoimmune haemolytic anaemia (AIHA) is a rare type of anaemia with an incidence of 0.8 to 3% per 100,000/year.[2] The diagnosis of AIHA is done by direct antiglobulin test (DAT) and indirect antiglobulin test (IAT). These tests were discovered back in 1945 by Coombs, Mourant, and Race.[3] But, gradually, the cases of Coomb's negative AIHA cases were getting reported. Among reported cases of AIHA in the Western data, 5 to 10% were Coomb's negative.[4] Although proper Indian data are lacking, here we are reporting one of those rare cases of AIHA with negative Coomb's test along with a history of multiple transfusion in district-level hospitals. In a country like India, it is a common practice in the primary level of care to transfuse blood and then to put on long nutrition supplements as a therapeutic measure for anaemia. The same happened to our patient also. Hence, an intelligent suspicion, followed by proper referral or accurate diagnostic work-up can prevent the use of unnecessary blood products and related complications. Here lies the importance of thorough clinical examination and picking up the important findings, especially when working in a resource-limited setup.

Case History

A 38-years-old female without prior comorbidity presented to the medicine outpatient department (OPD), with chief complaints of generalised weakness for 4 months, yellowish discolouration of the sclera for the past 1 month, and history of multiple blood transfusion in past 2 months without any improvement. There was no history of any drug exposure (e.g. penicillin or cephalosporin groups); pregnancy loss; family history or

Address for correspondence: Dr. Vyas Kumar Rathaur, Head of Department, Department of Medicine, AIIMS, Rishikesh, Uttarakhand, India.
E-mail: vyasrathaur@gmail.com

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evidence of infection, hematemesis, melena, haematuria, rash, joint paint and/or fever. On general examination, she was found to be obese with a body mass index (BMI) of 26.4, with pallor and icterus, without any lymphadenopathy or clubbing, koilonychia, glossitis or angular stomatitis. Her vitals were stable with splenomegaly 5 cm below the left costal margin, without any ascites. Other system examinations were found to be within normal limits. Her routine investigations [Table 1] showed severe anaemia with high mean corpuscular volume (MCV), high reticulocyte count, unconjugated hyperbilirubinemia with high lactate dehydrogenase (LDH) value along with normal vitamin B12, folate, iron and ferritin level. Peripheral blood smear, although got affected by multiple transfusions outside, showed a dimorphic anaemia picture with adequate white blood cell (WBC) and platelet count. Other anaemia work-up including DAT and IAT were found to be negative. But, her anti-nuclear anti-bodies (ANA) report was positive with a speckled pattern in 1:100 titrations. Further advanced investigations were not done due to affordability issues.

Other investigations

Viral markers (HBsAg, Anti-HCV, Anti-HIV): Negative

Urine routine and microscopy: WNL

LDH: 380 unit/L, **Vitamin B12**: 1437, **Folate**: >24**, Iron**: 85 mg/dL, **Ferritin**: 1424.6 ng/mL, **Cortisol**: 28.65 ug/dL

FT3: 2.01**, FT4**: 1.39**, TSH**: 5.06

ICT for malarial parasite: Negative

USG abdomen: Hepatosplenomegaly with hyper-dynamic portal circulation

ANA: Positive (1:100), **DCT**: Negative, **ICT**: Negative, **G-6PD:** 754

Osmotic fragility test: Negative, **Sickling test**: Negative

Peripheral smear: No hemoparasite seen, **Bone marrow aspiration:** Suggestive of haemolytic anemia with marrow showing erythroid hyperplasia with megaloblastic maturation

Differential Diagnosis

Differential diagnoses of Coomb's negative anaemia are hereditary spherocytosis (HS), paroxysmal nocturnal haemoglobinuria (PNH), haemolytic uremic syndrome (HUS), G6PD deficiency and subsequent drug exposure.

Treatment

The patient was started on steroid (prednisolone 1 mg/kg/day) therapy after ruling out any infection. Her haemoglobin concentration significantly improved from 2.9 to 4.1 g/dL, and in the next 5 days, it further improved up to

Table 1: Laboratory work-up of the patient

Investigation	Date 11/09/18	Date 15/09/18	Date 16/09/18	Date 22/09/18	Date 25/09/18
Haemoglobin (g/dl)	2.9		Steroid	4.1	5.3
RBC count (million/mm^3)	0.83		Started	1.23	1.74
TLC (per mm^3)	4300			5100	10580
DLC (%) N/L/M/E/B	73/20/5/0.7/0.5			65/30/3.9/0.1/0.3	69/26/2.7/0.1/0.6
Platelet count (lakh/mm^3)	1.44			90000	1.27
Haematocrit (%)	9.5			15.6	22.7
PT (sec)	10.1	11.7			
INR	1	1.02			
ESR (mm/hour)					
Bilirubin (Total) (mg/dL)	5.23				
Bilirubin (Direct) (mg/dL)	1.41				
SGPT	21				
SGOT	22				
ALP	87				
GGT	30				
S. protein (g/dL)	6.2				
S. albumin (g/dL)	3.6				
S. globulin (g/dL)	2.6				
Blood urea (mg/dL)	27				
S. creatinine (mg/dL)	1.05				
S. Na+ (mmol/L)	132				
S. K+ (mmol/L)	4.2				
S. uric acid (mg/dL)	15.2				
S. calcium (mg/dL)	8.7				

RBC=Red blood cell, TLC=Total leukocyte count, DLC=Differential leukocyte count, PT=Prothrombin time, INR=International normalised ratio, ESR=Erythrocyte sedimentation rate, SGPT=Serum glutamic pyruvic transaminase, SGOT=Serum glutamic oxaloacetic transaminase, ALP=Alkaline phosphatase, GGT=Gamma-glutamyl transferase, S. = Serum

5.3 g/dL. Thus, a diagnosis of Coomb's negative AIHA was retrospectively confirmed. Oral proton pump inhibitor (PPI) and calcium vitamin D3 supplements were added to minimise the side effects of the steroid.

Outcome and follow-up

Over the course of hospital stay, the patient improved and was discharged with the advice to follow-up for tapering the steroid and to start immune modulators (azathioprine, cyclosporine, etc.)

Discussion

Haemolytic anaemia can be inherited or acquired. One of the most common causes of acquired haemolytic anaemia is the immunologic destruction of red blood cells (RBCs). In general, the clinical features are severe anaemia, jaundice, splenomegaly, haemoglobinuria, reticulocytosis and raised LDH.

The classification of AIHA is as follows:[5]

1. Warm autoimmune haemolytic anaemia (wAIHA)
2. Cold autoimmune haemolytic anaemia
   a. Cold agglutinin disease (CAD)
   b. Paroxysmal cold haemoglobinuria (PCH)
3. Mixed autoimmune haemolytic anaemia

The most common form (>80%) of AIHA is due to IgG antibodies that react with its antigen at the core body temperature, i.e. 'warm agglutinins'.[6] The AIHA is diagnosed by a positive DAT or IAT, also called the Coomb's test. The patient's RBC is washed with saline, then anti-human globulin (AHG) is added, following which RBC suspensions are centrifuged and examined for agglutination. In the gel micro-column method, the red cells are filtered through a gelatinous matrix mixed with AHG reagents and then the non-agglutinated RBCs pass through the column.[7]

AIHA with negative DAT is uncommon and warrants further etiological work-up. In our case, most of these came negative. The proposed mechanism for Coomb's negative test is that IgM and, particularly, IgA antibodies (if present) may be undetected by the polyclonal anti-human-globulin serum. Therefore, a special DAT using anti-IgA or anti-IgM antibodies may be required in such cases.[8] However, due to financial constraints, these tests could not be done in our case.

Differential diagnoses of Coomb's negative anaemia are HS, PNH, HUS, G6PD deficiency and subsequent drug exposure. HS was ruled out by the absence of family history, osmotic fragility test and peripheral smear examination. PNH was ruled out by a normal platelet and WBC count with normal urine and no evidence of thrombosis. HUS was ruled out as there was no history of preceding diarrhoea-like symptoms and without typical peripheral smear and normal kidney function tests. The absence of insulting drug history and a normal G6PD level on laboratory investigation has compelled us to exclude the diagnosis of G6PD deficiency.

The AIHA treatment is mainly to prevent the immune destruction of the RBCs. Steroids are the first line of treatment, with prednisolone 1 mg/kg body weight. Once the haemoglobin is settled and reticulocytosis is resolved, steroids can be tapered off over several weeks. The response to steroid therapy may take a few days to 3 weeks. The second line of therapy includes splenectomy and anti-CD20 monoclonal antibody (mAbs) rituximab. If splenectomy is not appropriate for any cause, immune modulators can be started, such as azathioprine, cyclosporine, mycophenolate or cyclophosphamide.[9]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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