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Case Report

Rh_{null}: a rare blood group phenotype

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Abstract

Rh_{null} phenotype is a rare blood group characterized by the lack of expression of all Rh antigens (D, C, c, E and e) on the red cells. The phenotype is further classified into the regulator and amorph type based on underlying genetic defect. The clinical significance of its recognition is that such patients suffer from Rh_{null} syndrome associated with osmotically fragile red cells called stomatocytes with subsequent chronic haemolytic anaemia of varying degree. Another importance is that such subjects readily form alloantibodies on exposure to Rh antigens.

We report herein rare Rh_{null} phenotype in a young pregnant female which was detected as a part of routine antenatal work-up for red cell antibody screening and identification.

Introduction

The Rh blood group system consists of at least 45 independent antigens and was first described in 1939. It is one of the most polymorphic and immunogenic systems and, next to ABO, is the most clinically significant blood group in transfusion medicine.[1]

Rh_{null} phenotype (also referred to as Rh_{null} syndrome or Rh_{null} disease) is a rare blood group with a reported frequency of approximately 1 in 6 million individuals.[1] The characteristic hallmark of Rh_{null} phenotype is the lack of all Rh antigens on the RBCs. In addition to lacking Rh antigens, Rh_{null} cells also lack LW and Fy5, and have a reduced expression of Ss, U, and Duclos antigens.[2] In Rh_{null} subjects the commonest antibody formed in response to transfusion or pregnancy reacts with all cells except Rh_{null} cells.[3]

The Rh_{null} is produced by at least two different genetic mechanisms. The 'amorph' type is the result of molecular change in RHCE gene with a deleted RHD gene, whereas the more common 'regulator' type is associated with the defect in RHAG gene. Both genotypes result in the same clinical syndrome characterised by chronic haemolysis of varying severity, with stomatocytosis, spherocytosis, increased osmotic fragility, altered phospholipids asymmetry, altered cell volume, defective cation fluxes, and elevated Na+/K+ ATPase activity.[1]

In this report, we describe the rare Rh_{null} phenotype in a young female who was referred to our laboratory for routine antenatal red cell antibody screening and identification. To the best of our knowledge this is the first case report of Rh_{null} syndrome from Pakistan.

Case Report

A 22-year-old pregnant female previously typed as blood group A, Rh (D) negative with positive red cell antibody screen was referred to AKUH clinical laboratory for identification of antibody. Her past history was significant for long-standing anaemia of mild to moderate severity of unknown etiology that did not respond to therapeutic trials with iron or other vitamin supplementations. Her obstetrical history revealed that she was second gravida. Her only previous baby was a healthy two year old male child. There was no history of abortion, miscarriage or any foetal loss. She had no history of previous blood transfusion. Her family history revealed that her parents had a consanguineous marriage and she had four siblings, all were alive and well with no history of chronic anaemia or any suspected blood disorder.

Her ABO and D blood types as well as red cell antibody test were repeated. The test was performed on the gel cards. It was observed that serum agglutinated uniformly all four tested panel red cells, giving 4 + reactions at room temperature, at 37ºC and at the antiglobulin phase. The direct antiglobulin and auto-control tests were negative. No red cell antibody was identified at this stage. This prompted technologists to perform more detailed serological workup including typing for various red cell antigens. Phenotypes were determined by haemagglutination in gel cards (DiaMed AG, Morat, Switzerland) with monoclonal antibodies specific for Rh (D, C, c, E, and e) antigens. These tests were confirmed in duplicate and also rechecked by manual tube testing. Based on serological studies, the patient's red cells were typed as blood group A, Rh null (D -, C- , E-, c-, e-), Cw-, K+, Kp^a, Kp^{b+}, Js^{b+}, Fy^{a+}, Fy^{b+}, Jk^{b-}, Le^{a-}, Le^{b-}, P^{1+}, M+, N-, and S-. Further blood samples were requested for haematological studies which showed Hb: 10.8 gm/dl, Hct: 32.6%, MCV: 100 fl, MCH 25.9 pg: and MCHC 35.2 g/dl. The platelets and differential white cell count were within normal limits. The reticulocyte count was 9% and the osmotic fragility of red cells was increased, with mean corpuscular fragility (MCF) of 0.70 gm/dl after 24 hours

incubation at 37°C (Normal range: 0.465 - 0.59 gm/dl). Haemoglobin electrophoresis revealed normal HbA and HbA2 with no elevation of HbF. Examination of the peripheral smear showed numerous spherocytes, some stomatocytes and polychromasia. These serologic and haematological investigations enabled one to diagnose Rh null phenotype in the patient. It was assumed that patient had developed anti Rh antibodies presumably anti-Rh 29 which is the most common antibody detected in similar settings. However, because of lack of sophisticated facilities, further diagnostic serological or molecular work up was not possible.

Discussion

Rh-deficiency syndrome results from the lack (Rh_{null}), or severe reduction (Rhmod), of Rh blood group antigens. This condition was first described in 1961 by Vos[4] and his colleagues when a sample of blood completely failed to react with various Rh antiseras. Three years later, the term "Rh_{null}" was described by R. Ceppellini.[5] To date there are at least 43 persons belonging to 14 families with Rh_{null} phenotype who have been reported in the literature. A few Rh_{null} individuals were recognized because of the presence of Rh antibodies in their sera while others were detected with routine Rh phenotyping of the red cells. Interestingly three cases were identified when the patients were investigated for haemolytic anaemia and abnormal red cell morphology.[3]

The disorder arises when individuals inherit, in an autosomal recessive manner, either a suppressor gene unrelated to the RH locus (regulator type) or a silent allele at the locus itself (amorph type). Rh_{null} cells lack not only Rh polypeptides (D and CE) but are also deficient in the Rh-associated glycoprotein (RhAG), glycophorin B, CD47 and LW glycoprotein.[6]

Immunized Rh_{null} people in response to transfusion or pregnancy have produced antibodies varying in specificity from apparently straightforward anti-e or anti-C to several examples that reacted with all red cells tested except those from other Rh_{null} people. This antibody, considered to be "anti-total Rh," has been given the numerical designation anti-Rh29.3 In this report, the patient probably got immunized during pregnancy or child birth and the antibody present in patients sera reacted with all cells tested and therefore was labeled as anti-total Rh (Anti-Rh29).

The clinical, haematological, and biological abnormalities associated with this rare disorder indicate that it affects the membrane integrity of red blood cells and evident in this report with spherocytic haemolytic anaemia, stomatocytosis and increased osmotic fragility of red cells. Further genetic testing for the underlying mutation for characterization of regular or amorph type and extended family studies were not performed in this case because of the non availability of relevant samples.

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