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### RESEARCH ARTICLE

#### DELAYED HEMOLYTIC TRANSFUSION REACTIONS (DHTR) AND HYPERHEMOLYSIS SYNDROME IN CHILDREN WITH SICKLE CELL DISEASE (SCD) : A CASE REPORT: JUBAIL, KINGDOM OF SAUDI ARABIA

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#### Abstract

Delayed hemolytic transfusion reactions (DHTRs) occur in patients who have received transfusions in the past. These patients may have very low antibody titers that are undetectable on pretransfusion testing, so that seemingly compatible units of red blood cells (RBCs) are transfused. DHTRs are a potentially life-threatening complication of sickle-cell disease (SCD) treatment. In SCD, DHTRs appear to be an immune process that develop because of differences in erythrocyte antigens between blood donors and patients .

**Aim:** DHTR is one of serious complication of blood transfusion that happens due to alloimmunized which is lead to hyperhaemolysis syndrome , DHTR can be managed by steroid and Intravenous immunoglobulin ( IVIG ) and prevented by accurate records with extended matching for certain population.

**Methodology:** The consent of the patient and his family was obtained to publish and highlight his health condition in detail and to follow up with the case to match the research results and work on it under the framework of case reporting.

**Conclusion:** DHTR can be managed by steroid and Intravenous immunoglobulin ( IVIG ) with good outcomes, DHTR can be prevented by means of accurate records, extended matching for certain population with high risk of developing alloantibodies such as individuals with SCD and B-thalassemia with proper handling of administration of blood product and proper notation in the patient medical records and blood bank records as well as the use of medical card for patient to known RBC alloantibodies.

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#### Introduction:-

Delayed hemolytic transfusion reactions (DHTRs) occur in patients who have received transfusions in the past. These patients may have very low antibody titers that are undetectable on pretransfusion testing, so that seemingly compatible units of red blood cells (RBCs) are transfused. DHTRs are a potentially life-threatening complication of

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sickle-cell disease (SCD) treatment. In SCD, DHTRs appear to be an immune process that develop because of differences in erythrocyte antigens between blood donors and patients .(1)

Blood transfusion can lead to serious complications such as red blood cells( RBCs )alloimmunization, iron overload, delayed hemolytic transfusion reaction and infection.(2,3) blood transfusion is a one of the decisive managements in case of acute and chronic complications in SCD.

Delayed hemolytic transfusion reaction occurs within weeks after receiving PRBCs and characterized by musculoskeletal pain, anemia, jaundice, change in urine color and laboratory finding such as increase in level of lactate dehydrogenase (LDH) and immune-hematological analysis (4)

4.2% of all causes of death in SCD are due to DHTR which is frequently misdiagnosed as a case of vaso-occlusive crisis (5)

DHTR can be preventable by using a fully, phenotype matched RBCs for Rh, kell, duffy, kidd, lewis, MNSs, P, Lu and other antigens . A careful medical history including history of previous blood transfusion and physical examination are very crucial. (6)

Treatment is mainly by supportive management. High dose of steroid is used for immune system modulation as a first line of management in severe DHTR with or without IVIG to suppress macrophage activity, with no evidence-based study support to use one over the other (7)

This report will highlight a case of 9 years old boy that's a known case of SCD presented as a case of vaso-occlusive crisis then discovered to have DHTR.

### **Ethical Consideration**

The ethical approval for this case was obtained from research committee at Royal Commission Hospital, Jubail/ kingdom of Saudi Arabia.

### **Case Presentation**

A 9 years old boy known case of sickle cell disease presented to ER in Royal Commission Hospital, Jubail in the kingdom of Saudi Arabia complaining of right lower limb pain and dark urine for 3 days and yellowish discoloration over his face and sclera for one day duration.

This patient has been on Hydroxyurea 25mg/kg , Folic acid 1 mg orally twice per week and regular follow up in the paediatric haematology clinic in our hospital with history of multiple vaso-occlusive crisis and blood transfusion that improved dramatically after initiation of hydroxyurea therapy with no previous history of irregular antibodies against RBCs.

Patient had a history of tonsillectomy 4 weeks before the presentation , in Dr. Sulaiman Al Habib hospital Khobar where he received one unit of PRBCs before the procedure; our efforts to obtain the full phenotyping of the transfused unit at the mentioned hospital were unsuccessful

We admitted him as a case of acute hemolytic anemia on top of chronic hemolytic anemia and vaso-occlusive crisis to be treated by IV fluid, analgesia, and blood transfusion

Upon the admission, the initial investigations showed that there was a significant drop in his haemoglobin to 5.60 g/dL, his low steady state haemoglobin was between 7-8 g/dL, as a result of this clinical condition, 2 units of packed red blood cells (PRBCs) were requested .

patient received 2 unit of PRBC one unit was fully phenotype matched ( E, K, Fy<sup>a</sup>, Fy<sup>b</sup>, Le<sup>a</sup>, Lu<sup>a</sup> negative ) and the second one was fully phenotype matched except Lu<sup>a</sup> positive.

Patient received blood transfusion under cardiopulmonary monitoring without any complications but he continued to complain about the pain and was shifted to PICU for morphine infusion as per protocol.

On the second day of hospitalization and after receiving the PRBCs, his haemoglobin dropped from 7.40 g/dl to 6.80 g/dl and he received another one unit of phenotypically matched packed red blood cells (PRBCs) .

After the second unit of blood transfusion his hemoglobin rose to 9.10g/dl and the patient was vitally and clinically stable and his pain subsided

On day 11 of hospitalization, the patient was still having mild jaundice, dark red urine, with ongoing hemolysis evidenced by investigation and positive direct COOMBS test ( IgG positive , C3d Positive ) and Haemoglobin had dropped to 5.2g/dL. The patient was transfused with PRBC that were fully phenotype matching including Lu<sup>a</sup> that was omitted in the second transfused unit. After the last unit transfusion, Hemoglobin rose to 6.3g/dL.

Patient was consider to have delay hemolytic transfusion reaction ( DHTR ) and hyperhaemolysis syndrome , treated by IV methylprednisolone (2mg/kg/day)for 8 days , IV Immunoglobulin 1 gm/kg .

The patient improved, no longer complaining of pain, with a decrease rate of hemolysis based on lab findings. The DCT also tested negative after few days of transfusing the last fully phenotyped RBC that was Lu<sup>a</sup> negative.

Upon discharge on day twenty (20), the patient was clinically stable with Haemoglobin of 7.5g/dL, on oral prednisolone with clear instruction to the mother regarding future transfusion recommendations, that the child should receive fully phenotyped RBC and a copy of the child full phenotyping was given to the mother. The mother was also given post transfusion instructions.

### **Discussion:-**

Patient with SCD need RBCs transfusion to save their life, DHTR is one of serious complication of blood transfusion that happens due to alloimmunized which leads to hyperhymolysis syndrome and DHTR

DHTR can be defined as any HTRs that occurs more than 24 hours after blood transfusion, this reaction presents within one to two weeks after receiving PRBCs with interval range from 3 to 30 days due to an anamnestic response to foreign RBC antigen which recipient was previously exposed.

Hyperhymolysis syndrome is a very rare type of DHTRs in which hemolysis of transfused RBCs is accompanied by hemolysis of the patient own RBCs, it's often happens in patients that are multi-transfused, patients with SCD are likely to develop DHTRs with hyperhymolysis syndrome and this is what happened to our patient in this case report , he developed features of DHTRs after 11 days of receiving blood transfusion and continued to have similar symptoms of vaso-occlusive crisis with significant drop in Hb and ongoing hemolysis with positive direct COOMBS test (both IgG and C3d positive)

As per current protocol in our center, we perform blood group, indirect coombs test, full phenotyping and give ABO and Rh phenotype compatible blood. When patients received blood in less than 3 months , full phenotyping will be repeated after 3months of not receiving any blood transfusion to obtain a reliable full phenotyping result.

In addition, if the patient received blood and developed HTRs, we perform antibody identification in order to provide RBC that lacks the corresponding antigen .

DHTR can be managed by steroid and Intravenous immunoglobulin ( IVIG ) with good outcomes.

Our patient received steroid and IVIG and he improved, his Hb was raised without any further blood transfusion

DHTR can be prevented by means of accurate records, extended matching for certain population with high risk of developing alloantibodies such as individuals with SCD and B-thalassemia with proper handling of administration of blood product and proper notation in the patient medical records and blood bank records as well as the use of medical card for patient to known RBC alloantibodies.

**Acknowledgment:-****Summary and recommendations:**

- 1) Perform full phenotyping on all SCD and beta thalassemia patients upon 1<sup>st</sup> request of transfusion or 3 months after previous transfusion if it was missed in the last transfusion encounter.
- 2) Issue Rh and kell phenotype compatible blood for all SCD and beta thalassemia patients.
- 3) Issue post transfusion instructions to all patients who received blood and discharged within 10 days of receiving transfusion.
- 4) Patients who developed irregular antibodies must be given a BB card reflecting these antibodies to be presented whenever blood transfusion will be received in another facility other than the facility that identified the irregular antibodies.
- 5) SCD and Thalassemia patients must also be given a card reflecting their red cell full phenotyping to be presented to the Blood Bank when transfusion will occur at a different facility that has no patient transfusion history
- 6) Post transfusion instructions must be adopted as a habit for all members in the healthcare team with clear explanations of how to recognize a possible transfusion reaction and what to do at home or when the patient needs to visit the emergency department.

**Supplementary Part****Table 1:-** ( Initial investigation upon admission )

|                            |        |
|----------------------------|--------|
| WBC                        | 40.45  |
| RBC                        | 1.87   |
| HGB                        | 5.60   |
| HCT                        | 16.80  |
| MCV                        | 89.80  |
| MCH                        | 29.90  |
| MCHC                       | 33.30  |
| PLT                        | 212.00 |
| RETICULOCYTES              | 20.32  |
| BILIRUBIN CONJUGATED SERUM | 28.00  |
| TOTAL BILIRUBIN SERUM      | 246.50 |
| CREATININE, SERUM          | 36.00  |
| ALT                        | 34.00  |
| AST                        | 150.70 |
| HbF                        | 15.2%  |
| HbA2                       | 2.4%   |
| HbS                        | 82.4%  |

| phynptyoing            |                       |   |   |   |   |      |   |                 |                 |                 |                 |                 |                 |      |   |   |   |        |                 |                 |
|------------------------|-----------------------|---|---|---|---|------|---|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|------|---|---|---|--------|-----------------|-----------------|
| antigen typing         | Rh                    |   |   |   |   | Kell |   | Duffy           |                 | kidd            |                 | Lewis           |                 | MNSs |   |   |   | P      | Luthera<br>n    |                 |
| antigen                | D                     | C | c | E | e | K    | k | Fy <sub>a</sub> | Fy <sub>b</sub> | Jk <sub>a</sub> | Jk <sub>b</sub> | Le <sub>a</sub> | Le <sub>b</sub> | M    | N | S | s | P<br>1 | Lu <sub>a</sub> | Lu <sub>b</sub> |
| patient                | +                     | + | + | - | + | -    | + | -               | -               | +               | +               | -               | +               | +    | + | + | + | +      | -               | +               |
| identified<br>antibody | Unidentified antibody |   |   |   |   |      |   |                 |                 |                 |                 |                 |                 |      |   |   |   |        |                 |                 |

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