Hyperhaemolysis Syndrome in Thalassaemia Major

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Hyperhaemolysis

Hyperhaemolysis is used to describe the phenomenon whereby the post-transfusion Hb is lower than the pre-transfusion level. This suggests that there is destruction of the patient’s own cells as well as those which have been transfused.
3yr old male with thal intermedia (phenotype) and a diagnosis of homozygous δβ thalassaemia. He has 2 siblings who are not affected.

First admitted on 15/7/11 with an URTI for past 10 days requiring oral antibiotics. Hb 62g/dL. Transfused 1 unit and discharged.
Lab results

Group O pos, R1r, Fy(a+b-), Jk(a-b+), K-, CMV neg.
No antibodies were detected on 1st admission.

Weak non-specific reactions were noted in August.

October: A panagglutinating antibody was detected.

November: Panagglutinating antibody still present.
DAT positive IgG and C3d. Eluate showed no specificity.
Admitted 10/8/11 with a viral illness and discharged on 1/12/11. For a bone marrow transplant from his mother.

Both bone marrow and stem cells were transplanted. It was thought that the addition of stem cells would increase the number of mesenchymal cells which would give a better outcome.
Progress

MelR received 51 phenotyped CMV negative units in 71 days.

Haemolysis was refractory to steroids, IvIg, mycophenylate and splenectomy.
2\textsuperscript{nd} Transplant

Transplanted in January 2012 with a cord blood donor. This cured his thalassaemia but the haemolysis continued.

He had 9 admissions in total. Final admission was 11/04/12 for fever and diarrhoea.
MelR died 29/4 from multi-organ failure.

Products received: 112 units RBC
- 34 platelet transfusions
- 3 units of FFP
- 6 vials CMV IgG
- 78g Intragram
- 18 x 100ml Albumex 20
- 2.6L Albumex 5
Innocent Bystander Haemolysis

No one proven mechanism. Dameshek described “innocent bystander” phenomenon in 1965. Caused by complement activation by antigen-antibody reactions remote from the putative RBCs.

1970: It was shown that lysis could be associated with the membrane attack complex C5b-9.
Hyperhaemolysis in Sickle Cell Disease

Mechanism unclear.
May be due to bystander lysis, suppressed haemopoiesis or both. Autoantibodies may also play a role.
It has also been suggested that there may be a functional defect in CD59. Also found in some thalassaemia patients.
Hyperhaemolysis in Sickle Cell Disease

Can occur associated with a classic DHTR but often occurs in the absence of any demonstrable RBC alloantibodies.

85% of SCD patients have platelet antibodies after >50 transfusions. About 50% of the antibodies have HLA specificity.

These antibodies may be responsible for activating complement causing haemolysis.
Sickle and Thalassaemia patients

Suggested that there may be a functional deficit of CD59 and this may affect the cytolytic C5b-9 making the red cells more susceptible to lysis.

Red cells may be destroyed by antibody-dependent cell mediated cytotoxicity with levels of antibody below serological detection threshold.
Other suggested mechanisms

Win et al (2008) suggested that interactions of activated macrophages with intracellular adhesion molecule-4 (ICAM-4) on red cells may be responsible.
Transfused RBCs

ICAM-4

Activated macrophages

HbSS

Sickle reticulocytes

either via

ICAM-4

Sickle reticulocytes

or

α4β1

VCAM-1

CD11c/CD18
ICAM-4

- ICAM-4 gene encodes the LW antigen and is restricted to red cells.
- ICAM-4 is absent in LW(a-b-) and Rh\textsubscript{null} cells yet they function normally.
- ICAMs are ligands for integrins.
- ICAM-4 is increased on sickle cells. Antibodies to ICAM-4 partially inhibit adhesion of sickle red cells to activated endothelium.
- Interactions between ICAM-4 and integrins on vessel wall endothelium may be involved in the microvascular occlusions in sickle cell disease.
- ICAM-4 may be involved in the binding of RBCs to macrophages in the spleen as part of the removal of senescent red cells.
References


