UNUSUAL HEMOLYTIC ANEMIAS

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Unusual Immune Hemolytic Anemias

- Combined cold and warm AIHA.
- AIHA with a negative direct antiglobulin (Coombs) test.
- AIHA following blood transfusion.
- AIHA in pregnancy.
- Drug-induced AIHA.
- The passenger lymphocyte syndrome.
- Sickle cell hemolytic transfusion reaction syndrome (“Hyperhemolysis Syndrome”).

AIHA DURING PREGNANCY

- AIHA is at least four times more frequent during pregnancy.
- Occasional women develop AIHA with each pregnancy with resolution of hemolysis between pregnancies.
- Women in remission from AIHA when getting pregnant may relapse in first trimester.

CLINICAL COURSE

- The severity of AIHA may increase during pregnancy, especially in third trimester.
- Severely anemic women appear to have more frequent premature deliveries and stillborn children.
- Treatment for AIHA during pregnancy should not be delayed until severe anemia develops.
- AIHA in infants caused by maternal autoantibody is unusual except when the mother has severe anemia.

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MANAGEMENT

- **Treatment for AIHA during pregnancy should not be delayed until severe anemia develops.**
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Drug-Induced Immune Hemolytic Anemia

- Most drugs that cause immune hemolytic anemia do not cause AIHA.
- Drug-dependent antibodies are demonstrable *in vitro.*
- Some drug-dependent antibodies may be detected using drug-coated RBCs (e.g., penicillins).
- Most drug-dependent antibodies are detected by incubating a solution of drug with patient's serum and observing for hemolysis, agglutination or positive IAT.

Drug-adsorption Mechanism; Penicillin-Induced Immune Hemolytic Anemia

- Occurs during administration of large doses of penicillins (and other drugs that bind tightly to the RBC membrane).
- Hemolytic anemia is generally gradual in onset.
- DAT is strongly positive due to RBC-bound IgG.
- Antibody in serum and eluate from patient's RBCs reacts with penicillin-coated RBCs.
- A high titer penicillin antibody is present in the patient's serum.

The Hapten Mechanism

- The drug combines with cellular proteins.
- The drug-cell combination becomes antigenic, that is, the drug is acting as a hapten.
- Patient need take only a small amount of the drug.
- Hemolytic anemia is often acute, severe, and associated with hemoglobinemia, hemoglobinuria and renal failure.

Immune hemolytic anemia caused by drug-dependent antibodies other than the "penicillin type"

- Patients' RBCs are often sensitized with complement only.
- The drug usually is loosely bound to the RBCs *in vitro* so it is not possible to make drug-coated RBCs for *in vitro* testing.
- Patient's serum reacts with RBCs in the presence of the drug.

DRUG-INDUCED AIHA

- First reported with methyldopa in 1966.
- Antibodies in the serum and eluate from the patient's RBCs are characteristic of those found in warm antibody AIHA.
- Drug-induced AIHAs should be differentiated from true autoimmune disease.
- They are caused by an exogenous agent and are temporary reactions that resolve upon discontinuing the drug administration.
- Therefore, they are examples of bystander immune cytolysis.

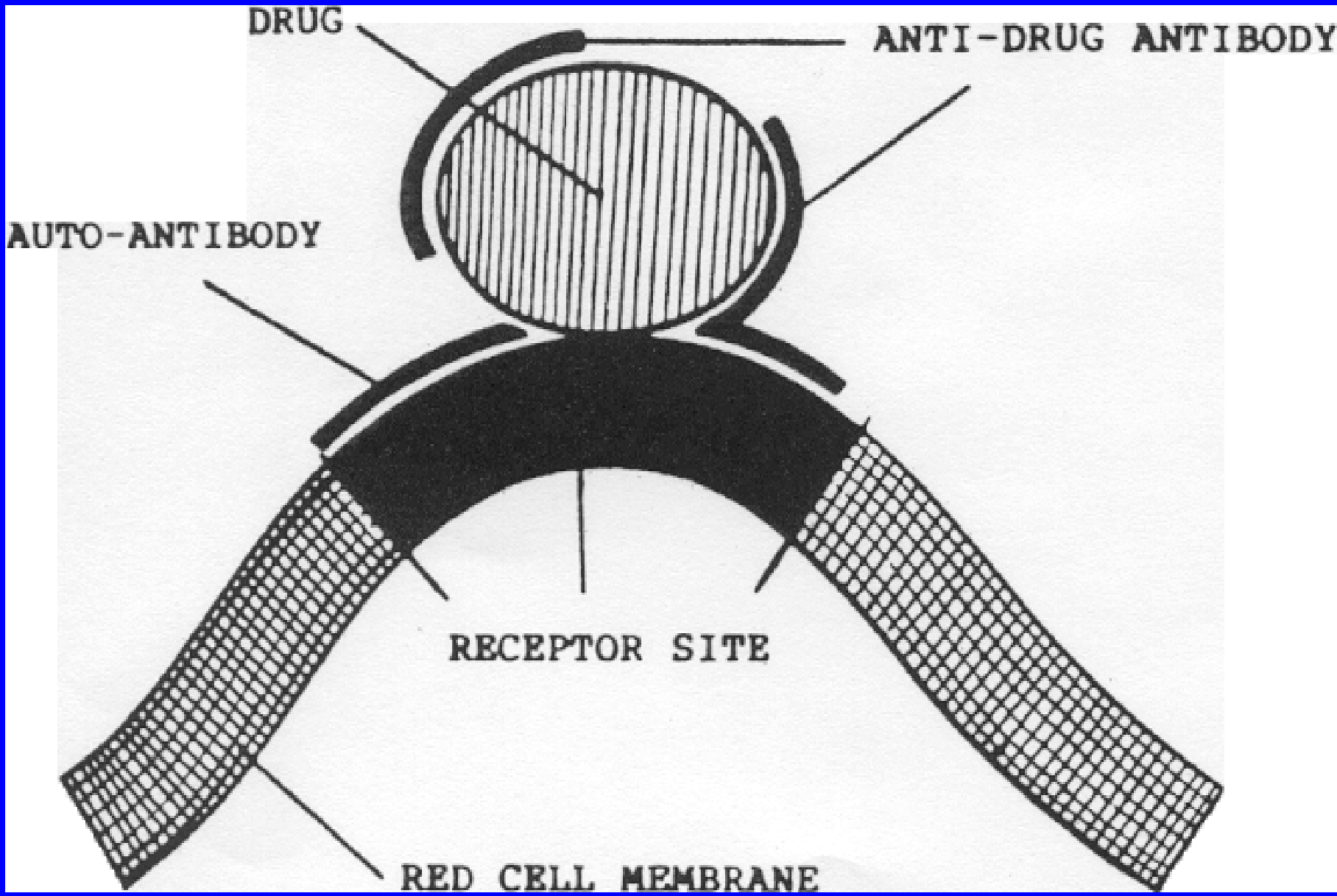
DRUG-INDUCED AIHA

Implicated Drugs

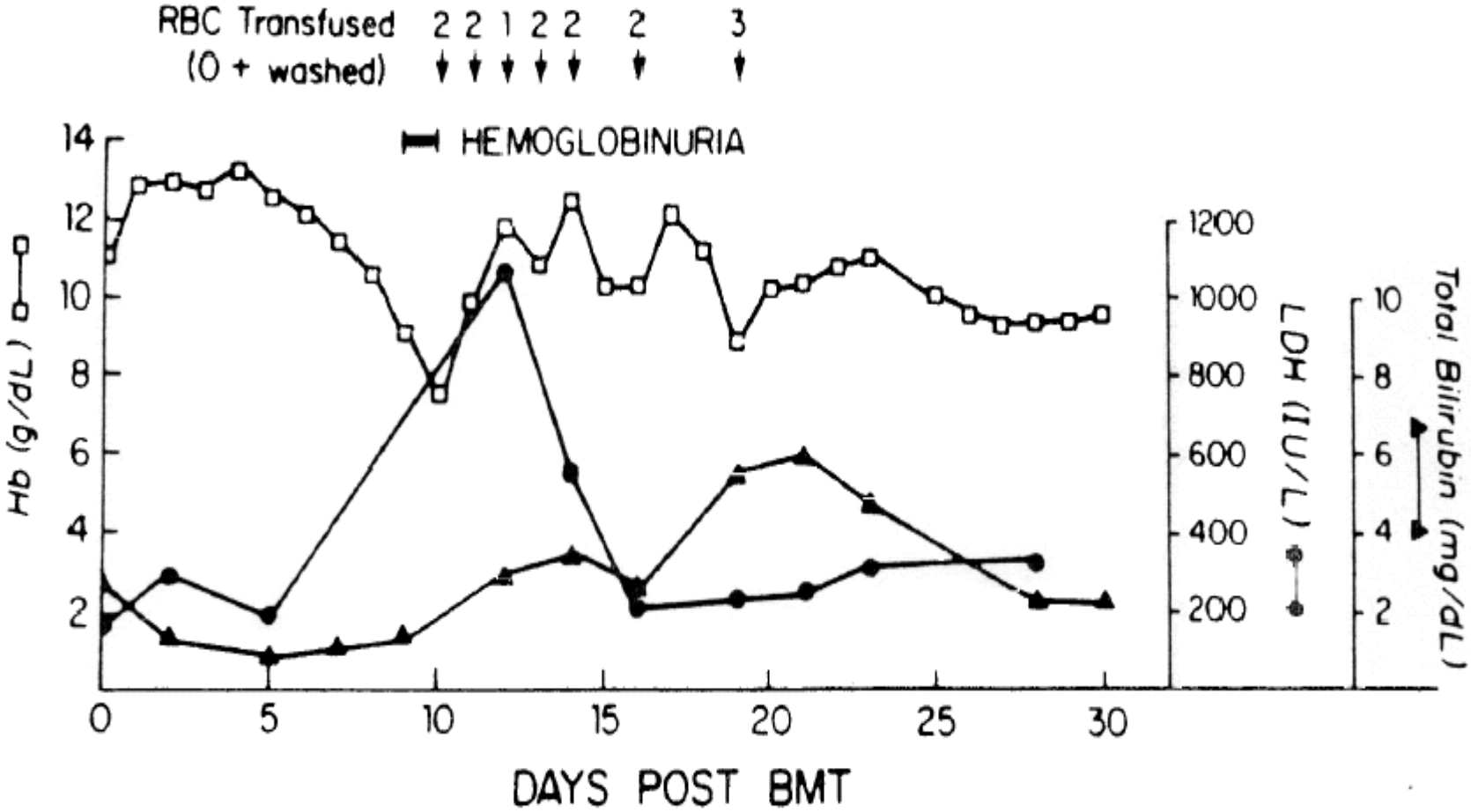
- Methyldopa
- Fludarabine (hemolysis may be acute and severe)
- Levodopa
- Procainamide
- Nonsteroidal anti-inflammatory drugs
- Chlorpromazine, diphenylhydantoin, rituximab, methysergide (??)

MECHANISM OF IMMUNE RESPONSE TO DRUGS

- Initiated by primary interaction of the drug with constituents of blood cell membrane.
- Two types of antibodies are produced – drug-dependent and drug-independent.


DRUG
ANTI-DRUG ANTIBODY
AUTO-ANTIBODY
RECEPTOR SITE
RED CELL MEMBRANE

PASSENGER LYMPHOCYTE SYNDROME



THE PASSENGER LYMPHOCYTE SYNDROME

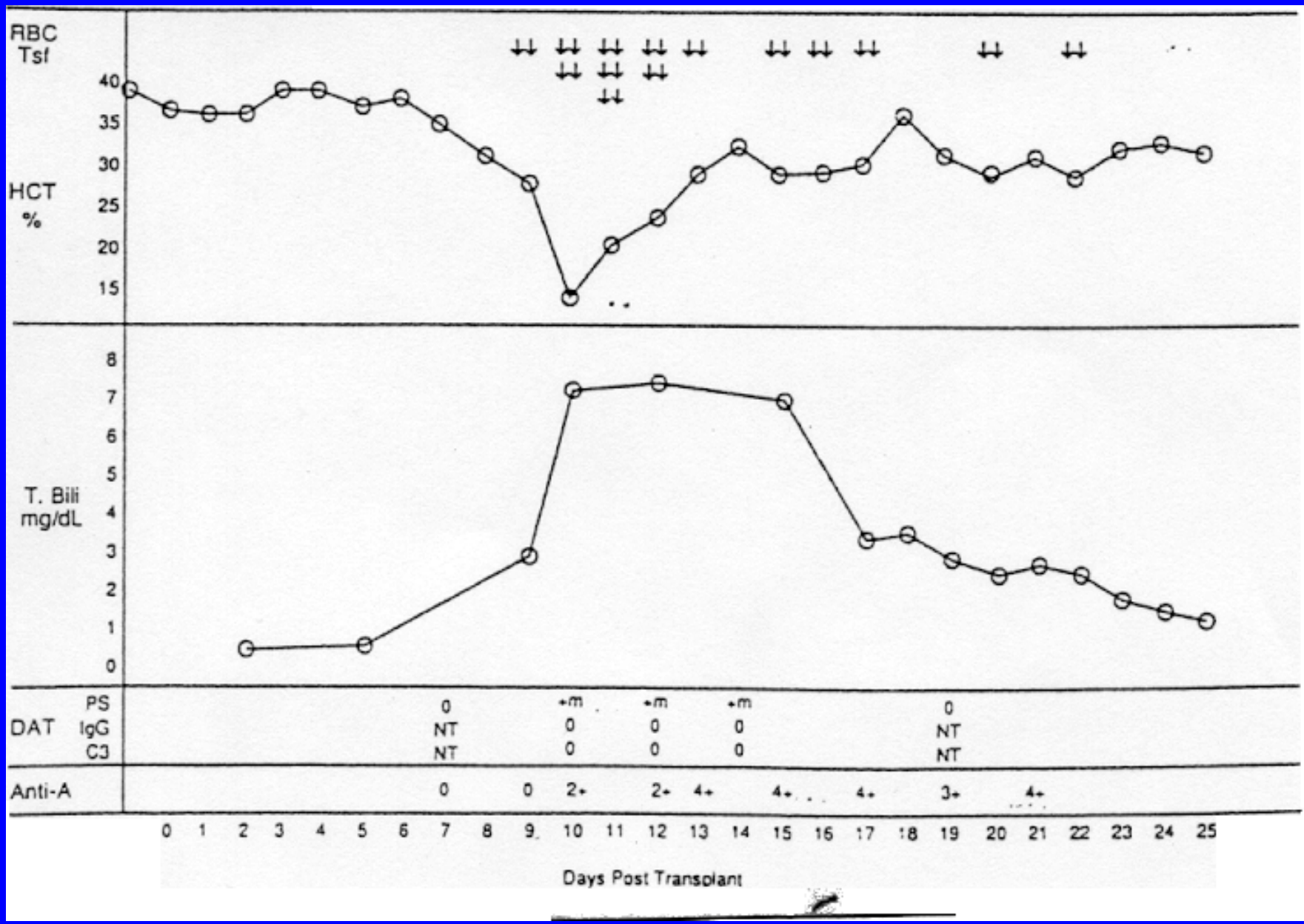
- Acute onset of hemolysis about 1-2 weeks after transplantation.
- Hemolysis may be brisk with rapid decrease in hemoglobin.
- Hemoglobinemia and hemoglobinuria may be present.
- Minor blood group incompatibility, usually within the ABO blood group.

THE PASSENGER LYMPHOCYTE SYNDROME

- The DAT (Coombs' test) is positive, usually with anti-C3.
- The serum and RBC eluate contain anti-A and/or anti-B.
- The development of positive DAT, the finding of anti-A and/or anti-B in the serum and onset of hemolysis do not occur until about 1-2 weeks after transplant.

THE PASSENGER LYMPHOCYTE SYNDROME

- Antibody is produced by proliferating lymphocytes that are contained in the donor marrow (passenger lymphocytes).
- Hemolysis of patient's incompatible RBCs occurs and is caused by anti-A or anti-B.
- The hemolysis resolves when the patient's incompatible RBCs are hemolyzed and replaced by transfused Group O RBCs.


RBC
Tsf
HCT
%
40
35
30
25
20
15
T. Bili
mg/dL
8
7
6
5
4
3
2
1
0
DAT
PS
IgG
C3
0
NT
NT
+m
0
0
+m
0
0
+m
0
0
0
NT
NT
Anti-A
0
0
2+
2+
4+
4+
4+
3+
4+
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Days Post Transplant

Transfusion Requirements of Washed Group O RBCs

Patient's RBC Vol. Day +5	Vol. of Grp. O RBCs Transfused Day +5 to +20
2039 ml	4680 ml
1592 ml	4680 ml
1635 ml	4680 ml

MASSIVE HEMOLYSIS AFTER MINOR ABO INCOMPATIBLE BMT

- Hemolysis of transfused washed Group O RBCs was occurring.
- About 1.5 liters of Group O RBCs were hemolyzed during the 15 day period during which hemolysis occurred.
- Hemolysis was caused by anti-A or anti-B.

ADSORPTION OF A AND B SUBSTANCE ONTO GROUP O RBCs

- Renton PH, Hancock JA. Uptake of A and B antigens by transfused group O erythrocytes. Vox Sang 1962;7:33
- Crookston MC, Tilley CA. A and B and Lewis antigens in plasma. Proceedings of the 5th International Convocation on Immunologics. Basel: Karger 1977:246-256.

TYPING IRREGULARITIES AFTER MINOR ABO INCOMPATIBLE BMT

- A year or more after transplantation, weak agglutination occurs when testing with anti-A,B. (Branch and Petz, unpublished observations.)
- Arndt et al (Transfusion 1999;39 43S-44S) used flow cytometry to demonstrate that group O cells absorbed A and B substance.

Passenger Lymphocyte Syndrome Summary

- Minor blood group incompatibility is present, almost always in ABO system, e.g., Donor Group O, patient Group A or B.
- Lymphocytes infused with the donor marrow stem cells proliferate and produce anti-A and/or anti-B beginning about 1 week after transplantation.
- The patient's incompatible RBCs are hemolyzed.
- In unusual cases, transfused group O RBCs are also hemolyzed requiring numerous transfusions.

BYSTANDER IMMUNE CYTOLYSIS

BYSTANDER IMMUNE CYTOLYSIS MAY BE DEFINED AS IMMUNE DESTRUCTION OF CELLS BY ANTIBODY DIRECTED AGAINST AN ANTIGEN THAT IS NOT AN UNMODIFIED INTRINSIC COMPONENT OF THE CELL MEMBRANE.

SICKLE CELL ANEMIA

- 24-year-old woman.
- History of prior transfusions.
- Hematocrit = 18%
- Transfused to hematocrit of 36.8%.
- Severe delayed hemolytic transfusion reaction began 2 days later.
- Hematocrit reached a nadir of 7.4%.

THE SICKLE CELL HEMOLYTIC TRANSFUSION REACTION SYNDROME

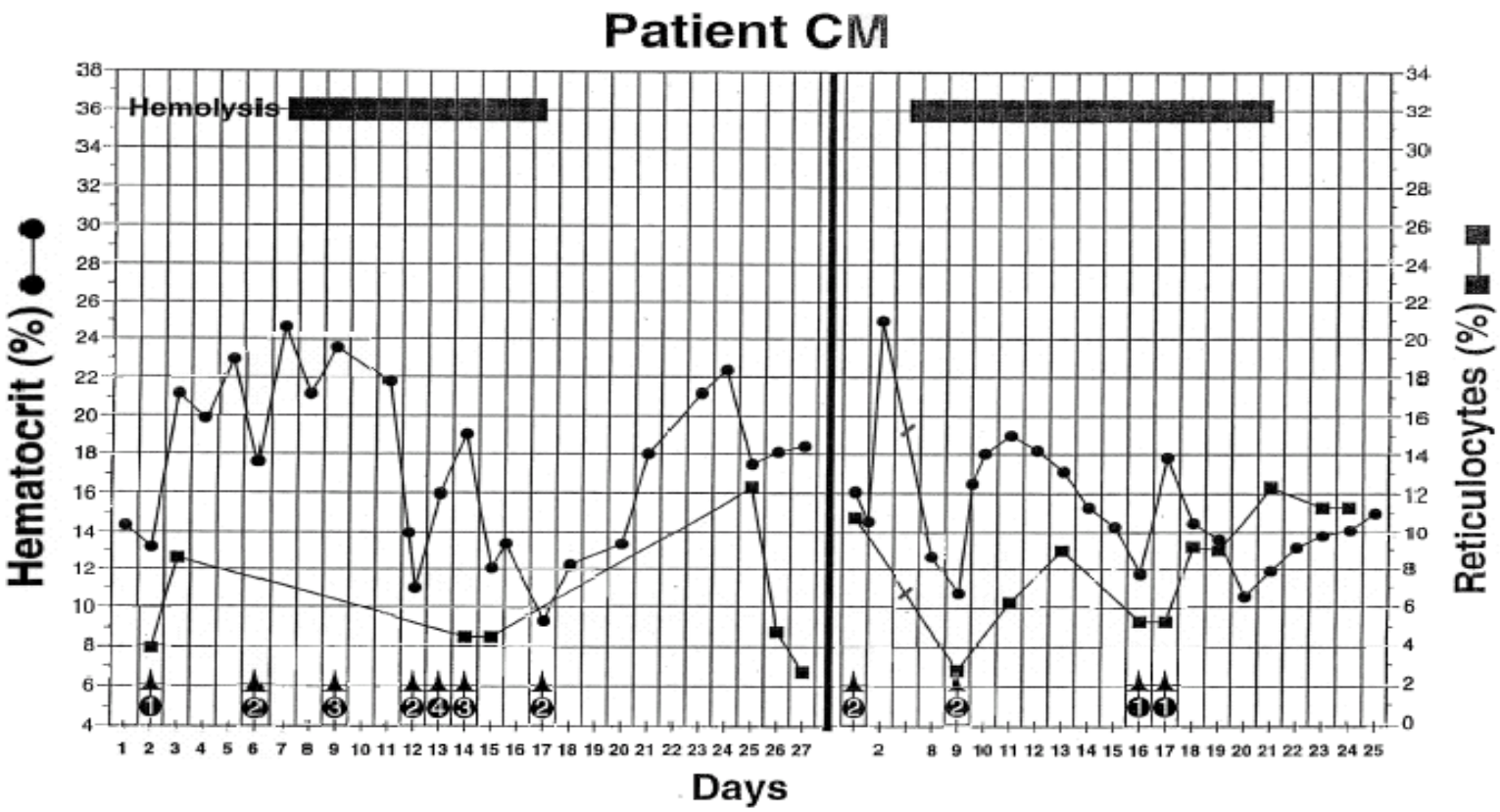
- MANIFESTATIONS OF AN ACUTE OR DELAYED HEMOLYTIC TRANSFUSION REACTION (HTR).
- DEVELOPMENT OF MORE SEVERE ANEMIA FOLLOWING TRANSFUSION THAN WAS PRESENT PREVIOUSLY, SUGGESTING HEMOLYSIS OF AUTOLOGOUS RBCs.
- MARKED RETICULOCYTOPENIA COMPARED TO PATIENT'S USUAL RETICULOCYTE LEVEL.

Petz et al. Transfusion 1997;37:382-392

THE SICKLE CELL HEMOLYTIC TRANSFUSION REACTION SYNDROME

SUBSEQUENT TRANSFUSIONS MAY FURTHER EXACERBATE THE ANEMIA AND IT MAY BECOME LIFE-THREATENING OR EVEN FATAL.

Petz et al. Transfusion 1997;37:382-392


Patient CM
Hemolysis
Hematocrit (%)
Reticulocytes (%)
Days

THE SICKLE CELL HEMOLYTIC TRANSFUSION REACTION SYNDROME

- **Milner et al.: “Many of these reactions go unrecognized, being considered typical “vaso-occlusive” or “aplastic” crises of the disease.”**
- **Diamond et al.: “All of our patients were initially treated for sickle-cell pain crises before the full nature of the pathophysiologic process was recognized.”**

THE SICKLE CELL HEMOLYTIC TRANSFUSION REACTION SYNDROME

MANAGEMENT

- Withhold transfusions if possible.
- Corticosteroids are probably of benefit in minimizing hemolysis and augmenting erythropoiesis.
- IVIG has been reported to be beneficial.
- Close observation and supportive measures as indicated.

THE SICKLE CELL HEMOLYTIC TRANSFUSION REACTION SYNDROME

- RECOVERY IS MARKED BY AN INCREASED RETICULOCYTE COUNT AND GRADUAL IMPROVEMENT IN ANEMIA.
- AFTER RECOVERY, SIMILAR EVENTS MAY OR MAY NOT RECUR FOLLOWING SUBSEQUENT TRANSFUSIONS.
- EXCHANGE TRANSFUSIONS ARE PARTICULARLY LIKELY TO CAUSE THIS SYNDROME.

MECHANISMS FOR DEVELOPMENT OF MORE SEVERE ANEMIA FOLLOWING TRANSFUSION THAN WAS PRESENT PREVIOUSLY

- **SUPPRESSION OF ERYTHROPOIESIS**
- **HYPERHEMOLYSIS WHICH IMPLIES HEMOLYSIS OF AUTOLOGOUS RBCs.**

[HYPERHEMOLYSIS SHOULD BE DEFINED AS AN INCREASED RATE OF HEMOLYSIS.]

MECHANISMS BY WHICH HYPERHEMOLYSIS MAY OCCUR

- DEVELOPMENT OF AUTOANTIBODIES FOLLOWING TRANSFUSION.
- REACTIVE HEMOLYSIS

REACTIVE HEMOLYSIS

- **A FORM OF RED CELL LYSIS DIFFERENTIATED FROM CLASSICAL COMPLEMENT HEMOLYISIS BY THE OCCURRENCE IN THE AGSENC E OF ANTIBODY ON THE CELLS.**
- **A MECHANISM BY WHICH COMPLEMENT ACTIVATION AT ONE SITE CAN LYSE NORMAL CELLS AT A DISTANCE.**

MECHANISMS FOR HYPERHEMOLYSIS

REACTIVE HEMOLYSIS

Sickle cells are unusually sensitive to complement-mediated hemolysis.

Test and Woolworth 1994 Blood 83:842- 52.

SICKLE CELL HEMOLYTIC TRANSFUSION REACTION SYNDROME

SUMMARY

- MANIFESTATIONS OF AN ACUTE OR DELAYED HEMOLYTIC TRANSFUSION REACTION (HTR).
- DEVELOPMENT OF MORE SEVERE ANEMIA FOLLOWING TRANSFUSION THAN WAS PRESENT PREVIOUSLY, SUGGESTING HEMOLYSIS OF AUTOLOGOUS RBCs.
- MARKED RETICULOCYTOPENIA COMPARED TO PATIENT'S USUAL RETICULOCYTE LEVEL.

SICKLE CELL HEMOLYTIC TRANSFUSION REACTION SYNDROME

- A SIMILAR REACTION MAY OCCUR IN PATIENTS WITH THALASSEMIA WHO HAVE HEMOLYTIC TRANSFUSION REACTIONS.
- SEVEN CASES WERE REPORTED BY SIRCHIA ET AL. *Transfusion 1997;37:1098-1099.*

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