

California Association
for
Medical Laboratory Technology

Distance Learning Program

A Problematic Blood Transfusion

Author:

David S. Hewitt, M.D.
Medical Director, Clinical Laboratory
Kaweah Delta District Hospital
Visalia, CA 93291

Course 056-928
1.0 CE/Contact Hour
Level: Intermediate

**CAMLT is approved by the California Department of Health Services as a CA CLS
Accrediting Agency (#0021)
and this course is approved by ASCLS for the P.A.C.E.® Program (#519)**

**1895 Mowry Ave, Suite 112
Fremont, CA 94538-1700**

**Phone: 510-792-4441
FAX: 510-792-3045**

Notification of Distance Learning Deadline

December 31 at 11:59 PM is the deadline for submission of distance Learning materials for CE credit for the calendar year. This deadline means that must have submitted your materials and passed the test questions. Individuals who wait until December 31 to submit their answer sheet, and fail the test, will have no further recourse. CE units cannot be awarded. Don't risk losing your license! Allow yourself enough time to retake the test should you fail on your first attempt.

A Problematic Blood Transfusion

Case Presentation

A 35-year old Cambodian male was hospitalized late one evening with weakness, fatigue, jaundice, and splenomegaly. The patient's admission laboratory results were as follows:

<u>Test</u>	<u>Patient result</u>	<u>Reference range</u>
WBC:	7.5 x 10 ³ / μ L	4.0-11.0 x 10 ³ / μ L
RBC:	3.5 x 10 ⁶ / μ L	4.60-6.20 x 10 ⁶ / μ L
Hemoglobin:	6.7 g/dL	14.0-18.0 g/dL
Hematocrit:	19.4 %	40.0-54.0 %
MCV:	55 fL	80.0-100.0 fL
MCH:	19.1 pg	24.0-31.0 pg
MCHC:	34.5 g/dl	32.0-36.0 g/dl
RDW:	17	11.5 – 14.5
Plt:	125 x1000/ μ L	130-400 x1000/ μ L
Na ⁺	134 mmol/L	135-145 mmol/L
K ⁺	4.4 mmol/L	3.6-5.0 mmol/L
Cl ⁻	102 mmol/L	101-111 mmol/L
CO ₂	26 mmol/L	21- 31 mmol/L
Glucose	107 mg/dL	70-110 mg/dL
Bilirubin	2.5 mg/dl	< 1.2 mg/dl
Blood pressure	113/70 mm/Hg	

Red cell morphology: marked anisocytosis, microcytosis, schistocytes, basophilic stippling and target cells

The patient had been referred for hospital admission by his family physician. Patient history revealed that his initial presentation for his ongoing disease was at age two with symptoms of chronic fatigue and small size. He was subsequently diagnosed with beta thalassemia major and had been on increasingly frequent transfusions since that time.

His admitting physician ordered a type and crossmatch for two units of packed red blood cells for transfusion. During the screening process, all three screening cells were positive, and the antibody workup revealed positive reactions to all panel cells. The auto control cells were also positive and no compatible units were found, not even by using a pre-warmed technique. The direct antiglobulin test (DAT) was positive: polyspecific IgG 3+, monospecific IgG 3+, and C3d negative. Further testing at a blood bank reference facility identified patient alloantibodies to E, c, Fy^b, Jk^a, S and K with both warm and cold-reacting autoantibodies.

Although the antibody picture was fairly grim, in light of the patient's hemoglobin and hematocrit values, the physician opted to transfuse using an "*in-vivo*" crossmatch technique. The units subsequently chosen for this procedure were negative for E, c, Fy^b, Jk^a, S and K. The patient experienced a febrile reaction to the first unit, but he tolerated the second unit well. The hospital stay was uneventful and the patient was discharged on the morning of the third day.

Course Objectives

At the end of this course the participant will be able to:

1. Identify the thalassemia disease characteristics.
2. Describe the benefits of transfusion therapy for thalassemia major.
3. Describe the complications of multiple transfusion therapy
4. Discuss the “*in-vivo*” compatibility test.

Case Discussion

Many diseases are concentrated in certain ethnic or geographic groups. Sickle cell anemia occurs predominantly in blacks, and gastric carcinoma is strikingly more common in Chinese in their own country than in other populations (including Chinese that have moved to the United States). The *thalassemias* are a heterogeneous group of hemoglobinopathies found predominantly in persons of Mediterranean, Asian, and African ancestry. (Indeed, the name *thalassemia* comes from the Greek *thalassa*, the [Mediterranean] sea.) These diseases are characterized by mutations in (or deletions of) the hemoglobin genes that produce one of the major constituent hemoglobin chains, resulting in the characteristic RBC abnormalities. These include microcytic anemia, anisocytosis and poikilocytosis, often with basophilic stippling and target cells. Target cells are produced by the volume-surface area mismatch resulting from the decrease in hemoglobin content.

The thalassemias are grouped according to which hemoglobin chain is missing— α -thalassemia lacks or has abnormal hemoglobin α -globin chains, and β -thalassemia lacks or has abnormal β -globin chains. Severity of disease corresponds to the degree of genetic penetration for the abnormality (abnormal chain or absent chain). Thalassemia may be combined with another hemoglobinopathy, including hemoglobin C or hemoglobin S.

[more information on thalassemia is included in Distance Learning course #922, “Hematology Case Study: a hypochromic, microcytic anemia.”]

Treatment

Patients with α -thalassemia major face chronic anemia and may require life-long transfusion support. The most common treatment for major forms of α -thalassemia is red blood cell transfusions. These transfusions are necessary to provide the patient with a temporary supply of healthy red blood cells with normal hemoglobin capable of carrying the oxygen that the patient’s body needs. While thalassemia patients formerly were given infrequent transfusions, clinical research has led to using a program of more frequent regular blood cell transfusions that has greatly improved the patient’s quality of life. Today, most patients with a major form of thalassemia receive red blood cell transfusions every two to three weeks, amounting to as much as 52 pints of blood a year.

Benefits of transfusion therapy

Hypertransfusion is probably the most beneficial method of treating thalassemia major short of bone marrow transplantation. Transfusions should be given in sufficient frequency and amount so as to produce a hemoglobin level of at least 9.3 g/dL. This level not only provides adequate oxygen carrying capacity but also partly suppresses the patient's erythropoietin production. This decreased stimulus to RBC production results in less bone marrow hyperplasia. Thus one of the complications of thalassemia major—skeletal changes of skull, facial bones, long bones and hand bones—is ameliorated. If untreated, this hyperplasia results in facial abnormalities, spontaneous fractures, leg ulcers, dental and orthodontic problems and tumor masses causing compression in various organs.

Transfusion therapy also prevents or decreases splenomegaly and the need for splenectomy.

Complications of transfusion therapy

Aside from the expense and inconvenience, frequent transfusion can carry significant morbidity in the form of increased risk of infectious disease (including hepatitis and HIV), hemochromatosis (chronic iron overload with tissue deposition of iron) with its attendant problems (*v.i.*), immediate transfusion reactions (e.g., febrile or urticarial reactions), and development of alloantibodies that may complicate crossmatching for subsequent transfusions. In addition, such patients may also develop non-specific antibodies that further cloud the issue. Patients with primary hematologic disorders not infrequently develop autoantibodies that produce a strong reaction in the auto control cells.

Hemochromatosis

Since each unit of blood contains about 250 mg of iron, a hypertransfusion regimen adds an average of four times the normal total body iron each year. This causes deposition of iron in organs, usually resulting in multiple organ damage. Some consequences are delayed or partial puberty, cirrhosis of the liver, and diabetes. Iron deposits in the heart are the most serious, causing heart failure and death in the teens or twenties if the patient goes untreated.

As the body has no means of getting rid of the excess iron, treatment with iron chelation therapy must be done in order to lessen these complications. At present this may involve an infusion pump with subcutaneous infusion of Desferal (deferoxamine mesylate) for up to twelve hours at a time, five to seven times a week. The chelated iron is eliminated in the urine. Additional occasional intravenous infusion may be required. The treatment may be onerous to the patient, so compliance can be a problem. Work is being done to develop an oral chelating agent, but side-effects have so far prevented FDA approval.

Antibody formation

In patients with multiple antibodies and strong positive auto control, finding compatible units may prove impossible. As is the case with most forms of autoimmunity, the cause of autoantibody formation is largely unknown. In such cases, transfusion should be avoided if possible.

Procedures

The major crossmatch consists of testing the patient's serum against the donor's red blood cells. The crossmatch is expected to detect ABO incompatibility and clinically significant antibodies. If the antibody screen, taken through the antiglobulin phase, shows no clinically significant antibodies and there is no previous record of such antibodies, the antiglobulin phase of the crossmatch can be omitted and only testing methods that detect ABO incompatibility are required (AABB Standards, 2000). This last step may be satisfied by performing a computer verification when the computer has been appropriately validated to prevent the release of ABO-incompatible blood components (AABB Standards, 2000). If, at any time, a clinically significant antibody is found, the antiglobulin phase of the crossmatch is required.

Autoantibodies may create many problems in serologic testing. The *in vivo* compatibility test may be attempted under special conditions when patients require blood in the presence of an incompatible crossmatch, and elucidation of the nature of the incompatibility has not been achieved or compatible blood cannot be provided.

The presence of an antibody in a patient's serum does not necessarily indicate that transfusion of incompatible blood will result in shortened survival of the incompatible transfused red cells. Further, in some patients, it is preferable to transfuse to obtain temporary benefit even though one is quite certain that the RBC will not survive normally. One means of predicting the possible outcome of a transfusion when it is impossible to provide crossmatch-compatible or antigen-negative blood is to perform an "*in vivo* compatibility test."

The most sensitive method of *in vivo* compatibility testing is to follow the survival of a small volume of radiolabeled test red cells. Another method (used in this case) is to infuse over a period of 20-30 minutes an aliquot of 40-50 ml red cell from the unit to be transfused. The patient is observed for symptoms of a hemolytic transfusion reaction and a blood sample is obtained after infusion of the "test dose" to look for hemolysis. The intravascular lysis of as little as 5 ml of red cells will raise the plasma hemoglobin concentration of an adult by about 50 mg/100ml, an amount easily visible to the naked eye. Lack of hemoglobinemia suggests that immediate catastrophic hemolysis will not occur with infusion of the entire unit of blood. If visual hemolysis is seen, another sample of heparinized blood is atraumatically drawn. If visual hemolysis is still present, a pathologist is notified, and a stat plasma hemoglobin is performed. If the plasma hemoglobin is 25 mg% or less, the remainder of the unit may be infused. If the plasma hemoglobin is greater than 25 mg%, a pathologist is called and a transfusion reaction procedure is initiated.

If a second unit is given, a second heparinized specimen is obtained 30 minutes after completion of the first unit.

For long-term follow-up, a hemoglobin, hematocrit and bilirubin should be obtained at 6 hours, 12 hours, 24 hours and then three or four additional times in the next week.

Transfusion service considerations:

Hospital transfusion services face many challenges, not the least of which is a dearth of useful clinical information. It is often up to the transfusion service personnel to ferret out information concerning the patient's admitting diagnosis, current status, concurrent laboratory results, and previous transfusion history. If the information is difficult to find, it is that much more important that it be discovered. The (usually) slight delay in service caused by digging up the correct information and obtaining the appropriate consultation (with the primary physician, pathologist, nurses, etc.) will be more than offset by the prevention of problems. The right information is always better, and the safety of blood transfusion must not be compromised by obfuscation, intentional or otherwise.

Conclusion

β-thalassemia major is best treated by hypertransfusion therapy for symptoms of the disease. Complications of this therapy may include transmission of infectious disease, hemochromatosis, antibody formation and transfusion reactions. Multiple alloantibodies and autoantibodies may preclude finding crossmatch compatible units for the patient in these cases. When transfusion is critically necessary, an "in vivo" compatibility test may be performed. If the results show no reaction and adequate red cell survival, the entire unit may be given.

References for "A Problematic Blood Transfusion"

1. Cotram RS, Kumar V, Collins T. *Pathologic Basis of Disease*, 6th ed. Philadelphia, PA: WB Saunders Co.; 1999:617-618.
2. Elghetany MT, Davey RD, Erythrocytic Disorders, In: Henry JB, ed. *Clinical Diagnosis by Laboratory Methods*, 20th ed. Philadelphia, PA: WB Saunders Co.; 2001.
3. Jandl, JH. *Blood: Textbook of Hematology*, 2nd ed. Boston, MA: Little, Brown & Co.; 1996:323-348
4. Shulman I, Petz LD. Red cell compatibility testing; clinical significance and laboratory methods. In: Petz LD, Swisher SN, Kleinman S, et al. *Clinical Practice of Transfusion Medicine*, 3rd ed. NY: Churchill Livingstone; 1996:199-244.
5. Vengelen-Tyler V, ed. *AABB Technical Manual*, 12th ed. Library of Congress; 1996.
6. Wang WC, Kovnar EH, Tonkin IL, et al. High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease. *J Pediatrics*. 1991;118:377-382.

Questions Course #056-928 A Problematic Blood Transfusion

Select the **one** best answer for each question

1. What is this patient's most likely primary medical condition?
 - a. leukemia/lymphoma
 - b. myelodysplastic syndrome
 - c. paraneoplastic syndrome with electrolyte imbalance
 - d. microcytic anemia
2. What is the most likely cause of this patient's antibody results?
 - a. anti-Jka and anti-Kell antibodies
 - b. non-specific cold-reacting antibody
 - c. multiple antibodies secondary to multiple transfusions
 - d. artifact secondary to medication
3. If compatible units are not available, the most useful treatment strategy would be:
 - a. transfusion with a blood substitute
 - b. transfusion following an *in-vivo* crossmatch technique with "least-incompatible" units
 - c. simple volume repletion with adequate oxygenation
 - d. pain relief and comfort measures
4. Crossmatching of blood:
 - a. guarantees clinical improvement
 - b. can be complicated and extensive in patients with hematologic abnormalities
 - c. is never associated with adverse patient outcome
 - d. always results in compatible transfusion products.
5. Abnormal hemoglobin production in patient's red cells may produce which of the following features on a peripheral blood smear?
 - a. smudge/basket cells
 - b. mucin lakes
 - c. burr cells
 - d. target cells
6. Which of the following is not a sequela of hypertransfusion therapy?
 - a. iron overload
 - b. increased erythropoietin levels
 - c. hyperviscosity
 - d. hypersplenism
7. If this patient's primary condition was undiagnosed, which test would be most useful for diagnosis?
 - a. flow cytometric analysis of peripheral blood
 - b. bone marrow biopsy
 - c. Hemoglobin electrophoresis, HPLC, or gene arrangement
 - d. Peripheral blood smear

8. Chronic transfusion results in abnormal accumulation of iron in patient organs. This phenomenon is called:
 - a. a urticarial reaction
 - b. hypertransfusion
 - c. hemochromatosis
 - d. bone marrow hyperplasia

9. The more recent transfusion therapeutic approach for _ thalassemia major results in
 - a. more frequent transfusion reactions
 - b. a reduced incidence of complications due to excess erythropoietin production
 - c. reduced incidence of iron deposition
 - d. decreased patient survival

10. Continued good prognosis from an adult _ thalassemia major patient is most dependent on:
 - a. continued transfusion therapy
 - b. splenectomy
 - c. antibiotic therapy
 - d. alchemy therapy

