

**Jaundice and Rash 24 Days after Cardiac Surgery**  
**Case study by Jim Perkins, M.D. and Gerald Hoeltge, M.D. (©2009)**  
**ANSWERS**

1. What transfusion reaction is present in this case? What clinical features allow you to make that diagnosis? How would you classify this reaction within the various classification systems used for transfusion reactions?

*This patient demonstrates the classic clinical picture of transfusion-associated graft-versus-host disease (TA-GVHD). He presents in delayed fashion with multisystemic disease, most prominently involving the skin and liver. Also prominent were cytopenias.*

*TA-GVHD is an immune-mediated, delayed reaction. The immunity is on the “minor side” meaning that it is due to donor immunity, a feature which it shares with most cases of TRALI, some hemolytic reactions, particularly those due to transfusion of group O single-donor platelets into group A individuals, and rare allergic transfusion reactions. Many febrile reactions might also be classified in this way, namely those which are due to receipt of cytokines generated in the donor unit. If immune reactions are classified according to the cell type involved, TA-GVHD is due to receipt of donor leukocytes.*

2. This type of transfusion reaction was originally described in patients who were immunosuppressed. Do you think that this patient was immunosuppressed? What is the pathogenesis of the reaction in this case? Which donor do you think was responsible for this reaction? Why?

*This patient had no obvious cause of immunosuppression at the time of his operation. Instead, he appears to have a good “one way HLA match” with donor #3 at the HLA-A, -B, -Cw, -DRB, and -DQB loci. A one way match exists when the donor is homozygous for an HLA haplotype shared by the recipient. This means that the recipient’s immune system see the donor’s lymphocytes largely as “self”, but the donor’s lymphocytes will respond to those of the recipient as foreign. For example, at the HLA-A locus the recipient would see the donor’s A1 antigen as self, but the recipient’s A24 antigen would be foreign to the donor’s lymphocytes. Note that the same analysis holds in this case for the B, Cw, DRB1, and DQB1. At the DPB1 locus, one of the donor’s antigens is identical to one of the recipient’s and the other is very similar. Overall then the recipient, in spite of having a normal immune system, presumably tolerated engraftment of donor lymphocytes. However, the engrafted donor lymphocytes were able to mount an immune attack on the recipient’s tissues.*

3. Why did the patient have a hypoplastic marrow? How does this reaction differ from the more common presentation of this problem in bone marrow transplant recipients? How does this explain his most prominent cause of death?

*In the case of TA-GVHD the recipient’s hematopoietic progenitor cells are subject to the same immune attack by the donor’s engrafted lymphocytes as are the rest of the recipient’s tissues. Therefore, pancytopenia is a hallmark of this reaction, and death due to overwhelming infection, as occurred in this case, is typical. In contrast when GVHD complicates bone marrow transplantation, the hematopoietic progenitor cells are of donor origin and are the one tissue seen as self by the engrafted lymphocytes. Thus although cytopenias may be observed after bone marrow transplantation due to poor graft function, they are not an essential part of the GVHD pathogenesis.*

4. How might this reaction have been prevented? What patients should receive this form of prophylaxis? What type of donation would increase the likelihood of this reaction?

*In order to engraft, donor lymphocytes must be present in sufficient number and must be viable. Donor lymphocytes can be rendered non-viable by irradiation at doses that do not otherwise destroy the function of the donor's red cells or platelets. TA-GVHD has occurred after receipt of leukocyte reduced, cellular components, but the rate of this reaction has declined in the United Kingdom since the introduction of universal leukocyte reduction. Finally, TA-GVHD due to RBC transfusion appears to be more common in situations in which relatively fresh units are chosen.*

*Patients with cellular immunodeficiency are at risk for TA-GVHD including those with severe combined immunodeficiency and a variety of hematopoietic malignancies including acute and chronic leukemias, Hodgkin's disease, and other lymphomas. TA-GVHD has been described in children being treated for rhabdomyosarcomas and neuroblastoma, and after intrauterine transfusion and exchange transfusion for hemolytic disease of the newborn. Of interest, it has not been described in transfused AIDS patients.*

*Directed donation by blood relatives increases the incidence of a one-way match, and the first case of TA-GVHD identified in a non-immunosuppressed individual occurred after transfusion of a fresh unit of whole blood to the father of the donor (Thaler, NEJM, 1989).*