Hypotension is another nonspecific finding of moderate/severe transfusion reactions that broadens the differential diagnosis.[25] Profound hypotension occurring soon after the start of the transfusion may be the result of an immediate hemolytic transfusion reaction from ABO incompatibility, septic shock caused by the infusion of components contaminated with bacteria, the patient's underlying disease, or a coincidental clinical event that is unrelated to the transfusion (eg, cardiogenic shock secondary to myocardial infarction). In many of these cases, the presence (or absence) of fever can be helpful. Fever would be expected to accompany hemolytic transfusion reactions and bacterial contamination/sepsis but not allergic reactions. Hypotension with cutaneous manifestations in the absence of fever would be suggestive of an ATR. Less commonly, acute hemolytic reactions can have cutaneous manifestations secondary to complement activation and release of anaphylatoxins. In these cases, the clerical check and laboratory evaluation for hemolysis may be helpful in making the diagnosis.

Finally, the rapid development of symptoms after the initiation of transfusion is a major clue to the diagnosis of an allergic reaction, as few other types of reactions present as quickly. Immediate hemolytic transfusion reactions from ABO incompatibility, or septic shock from transfusion of blood contaminated with bacteria, are characterized by the rapid onset of fever and chills. The absence of fever and the presence of cutaneous manifestations distinguish the immediate ATRs from the immediate reactions caused by hemolysis or sepsis.[25]

Pathophysiology

Efforts by immunologists to understand the pathophysiology of ATRs have been ongoing since the practice of blood transfusion started. Classically, an interaction between an allergen contained in the blood component and an IgE antibody preformed by the patient is assumed to be the primary mechanism of ATRs.[26] The allergen is an exogenous antigen, usually a protein in the plasma of the transfused blood component, to which the recipient was previously sensitized. The IgE antibody, residing on the surface of mast cells and basophils in the tissues and circulation of the recipient, may be activated by the binding of an allergen contained in the transfused component, causing the release of various mediators, including histamine, leukotrienes, chemokines. The pathophysiology of this reaction is described in immunology textbooks as a type I hypersensitivity reaction and explains all signs and symptoms of

anaphylactic transfusion reactions. Transfusion reactions following this pathophysiologic mechanism vary in severity from mild urticaria to bronchospasm and shock. A summary of possible mechanisms of anaphylactic and severe anaphylactoid reactions is presented in Table 3-3. But these mechanisms cannot explain the pruritic and urticarial symptoms observed most commonly in 90% of mild to moderate ATRs. Thus, IgE-independent mechanisms should also be considered as responsible for symptoms of ATRs and are reviewed below as well.

Table 3-3. Possible Mechanisms of Anaphylactic and Anaphylactoid Transfusion Reactions

1. Preexisting class-specific IgA antibodies in patients with IgA deficiency.
2. Preexisting subclass or allotype-specific IgA antibodies in patients with normal serum IgA levels.
3. Preexisting antibodies to polymorphic forms of other serum proteins (IgG, albumin, haptoglobin, alpha-1 antitrypsin, transferrin, C3, C4, etc) that the patient is lacking.
4. Preexisting HLA antibodies (postulated).
5. Transfusion of allergens to which a patient is presensitized, such as drugs (penicillin or aspirin), chemicals (formaldehyde, ethylene oxide, trimellitic anhydride plasticizer, methylene blue), etc.
6. Passive transfer of IgE antibodies (to drugs, foods, etc) in transfusion recipients.
7. Coincidental anaphylactic or anaphylactoid reaction to drugs (eg, aspirin, anesthetic agents, muscle relaxants, etc), foods, or other substances to which the patient is exposed before or during the transfusion.
8. Coincidental anaphylactic or anaphylactoid reaction in an atopic patient.
9. Mast cell activation induced by increased levels of C3a and C5a anaphylatoxins or by abnormal IgE oligomers in the transfused blood component.
10. Transfusion of components containing high histamine levels (postulated).

Allergen-Dependent Pathways

Plasma Allergens

Allergens that are associated with ATRs are proteins contained in the blood donor plasma against which the recipient develops an antibody. The allergens most commonly recognized as responsible for the severe type of allergic reactions are IgA and haptoglobin, for which recipients may have a deficiency and develop an antibody. Interestingly, not all patients with deficient IgA or haptoglobin levels develop a transfusion reaction. More importantly, those recipients who do have allergic reactions and present with a deficiency of either protein usually have demonstrable anti-IgA and/or anti-haptoglobin. On the other hand, there are patients with normal serum levels of IgA and presence of specific IgA antibodies who have a history of severe ATRs.[3] In any case, measurements of IgA levels as well as IgA antibodies are recommended in patients presenting with anaphylactic-type ATRs.

IgA and IgA Antibodies

IgA is the primary type of immunoglobulin in secretions (milk, saliva, tears, and respiratory and intestinal secretions). Isolated IgA deficiency (extremely low serum IgA with normal levels of other immunoglobulin classes) is the most common primary immunodeficiency. The pattern of inheritance is variable, with different cases being autosomal dominant or recessive. The defect is a block in the differentiation of surface-IgA-expressing B cells to IgA-secreting plasma cells. The α heavy chain genes and the expression of membrane-associated IgA are normal. The disorder can also be acquired as a result of toxoplasmosis, measles, rubella, or other viral infection, or exposure to drugs, alcohol, benzene, etc. About 1 in 700 individuals of European ancestry (in contrast to 1 in 18,500 Japanese natives) has extremely low serum IgA.[27-30]

From the perspective of an allergy/immunology practice, a person with serum IgA <5 mg/dL can be considered IgA "deficient" and thus potentially at risk for respiratory tract allergy and a variety of autoimmune disorders [especially systemic lupus erythematosus (SLE) and rheumatoid arthritis], as well as recurrent sinopulmonary infections and diarrhea leading to permanent airway and intestinal damage. However, the large majority of IgA-deficient people are completely asymptomatic.[27-31]