Delayed Hemolytic Transfusion Reactions

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ABSTRACT

Delayed hemolytic transfusion reactions continue to occur in spite of the use of all of the currently available techniques of antibody detection. Both low titers of the antibodies and dosage effects appear to contribute to the failure of detection. A rapid anamnestic response can occur with transfusion of the appropriate antigen. The clinical as well as the laboratory presentation of delayed hemolysis may vary from case to case and thus confuse the true nature of the reaction. The Kidd antibodies are, as a group, more frequently reported in delayed reactions than are any other antibodies.

Introduction

Eventually, nearly everyone who is involved with the transfusion of blood encounters the patient who will crossmatch as compatible by all of the currently available techniques, yet at some time following transfusion will begin to destroy the transfused red cells. This is the most insidious of all transfusion reactions, the so-called delayed hemolytic reaction. Full recognition of the inability of routine cross-matching techniques to insure the survival of transfused red cells occurred fairly late in the history of modern transfusion, although Loutit and Mollison had pointed out the unexpectedly poor survival of some transfused cells as early as 1943. Even with the introduction of routine Coombs and enzymes techniques for antibody screening, delayed hemolytic reactions continue to occur to the present day.

Antibodies Involved

Certain antibodies have developed a reputation for producing delay hemolytic reactions. The Kidd antibodies, in particular, are so frequently incriminated that they have been labelled the "treacherous Kidd antibodies." In table I are listed the antibodies most commonly reported in delayed hemolytic transfusion reactions. Although anti-E is more frequently reported, the combined frequency of anti-Jka, anti-Jkb and anti-Jka-Jkb is greater than for any other antibody system. Anti-c is also frequently noted in such reactions. The true incidence of these antibodies is impossible to determine, since most delayed hemolytic reactions are no longer considered reportable. The development of multiple antibodies in the same patient, often stated to be a rarity, occurred in 38 percent of the cases reported in table I. There is no discernible pattern of association among the antibodies developed. In one rather unique case not included in table I, anti-E, anti-c, anti-Jkb, anti-s, anti-Fyb and anti-IH all ultimately developed in the serum of a single patient. A delayed hemolytic transfusion reaction occurred, but it is not en-
TABLE I
INCIDENCE OF REPORTED ANTIBODIES IN
DELAYED TRANSFUSION REACTIONS

<table>
<thead>
<tr>
<th>Antibody</th>
<th>No.</th>
<th>%</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>10</td>
<td>23.3</td>
<td>3,4,7,9,15,16,19,32,36</td>
</tr>
<tr>
<td>Jka</td>
<td>8</td>
<td>18.6</td>
<td>5,6,9,12,20,27,34</td>
</tr>
<tr>
<td>c</td>
<td>7</td>
<td>16.3</td>
<td>3,9,15,16,20,34</td>
</tr>
<tr>
<td>Jkb</td>
<td>4</td>
<td>9.3</td>
<td>16,21,25,26</td>
</tr>
<tr>
<td>Jka-Jkb</td>
<td>2</td>
<td>4.6</td>
<td>5,26</td>
</tr>
<tr>
<td>Fy*</td>
<td>2</td>
<td>4.6</td>
<td>3</td>
</tr>
<tr>
<td>K</td>
<td>2</td>
<td>4.6</td>
<td>3</td>
</tr>
<tr>
<td>k</td>
<td>2</td>
<td>4.6</td>
<td>7,18</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>2.3</td>
<td>3</td>
</tr>
<tr>
<td>U</td>
<td>1</td>
<td>2.3</td>
<td>23</td>
</tr>
<tr>
<td>e</td>
<td>1</td>
<td>2.3</td>
<td>3</td>
</tr>
<tr>
<td>Lu*</td>
<td>1</td>
<td>2.3</td>
<td>3</td>
</tr>
<tr>
<td>Lu*</td>
<td>1</td>
<td>2.3</td>
<td>3,4</td>
</tr>
<tr>
<td>Ce</td>
<td>1</td>
<td>2.3</td>
<td>3</td>
</tr>
</tbody>
</table>

tirely certain which of these antibodies were involved. Possibly the immunologic systems of such patients tend to respond in an exaggerated fashion to antigenic stimulation.

Mechanisms of Reactions

The most commonly stated explanation of the phenomenon of delayed hemolysis is that some antigenic stimulus in the past has produced primary sensitization. Over the intervening years the titer of the antibody may drop to the point where routine crossmatching and antibody screening techniques no longer detect its presence. It has been shown that the titer of an antibody can rapidly decrease to a level where it becomes undetectable.\textsuperscript{16,25} When blood containing the appropriate antigens is transfused a rapid anamnestic response occurs with a significant rise in titer. In all of the cases listed in table I, either previous transfusions or pregnancy had occurred. Of interest is the fact the 69 percent of the cases listed in table I occurred in women. Pregnancy alone can be the initial and only stimulating event.\textsuperscript{5,6,23,26,30}

One possible explanation for the failure to detect some antigens in crossmatch procedures might be due to the gradual loss of these antigens from the red cells stored in clotted pilot tubes.\textsuperscript{15,24,38} Kell, c, and F\textsubscript{1} antigens appear especially labile. The combination of reduced antigenicity along with a low titer of antibody might well conspire to mask the antibodies presence. As noted, anti-c occurs relatively frequently in reported cases of delayed hemolytic reactions. Dosage effects seem to have been responsible for failure to detect antibodies in some cases.\textsuperscript{53,56}

The usual mode of red cell destruction is through the reticulo-endothelial system, primarily in the spleen.\textsuperscript{7} Hematuria was noted in 48 percent of the cases in table I and frank renal failure in 10 percent.\textsuperscript{12,19,23}

There are reports of a few instances where increased destruction of transfused "compatible" blood cannot be related to the presence of a detectable antibody before, during or following the hemolytic episode.\textsuperscript{1,10,11,14,17,31,35} Even the use of enzyme techniques and Coombs testing yield negative results. There is some indication that the spleen may be involved in such reactions.\textsuperscript{14,35} In one study 35 percent of immunized recipients demonstrated accelerated red cell destruction by \textsuperscript{51}Cr studies, but in only 9 percent could an actual antibody be identified.\textsuperscript{2}

Clinical and Laboratory Presentation

The clinician often does not associate the development of hemolysis with the previous transfusions particularly when the delay between transfusion and hemolysis is several days to weeks. In fact, patients are often investigated for a "hemolytic anemia" and have a hematology consultation for persistent refractory anemia.\textsuperscript{5} Often, at this point, more blood is requested and the nature of the problem becomes evident.

The development of a positive direct Coombs test is helpful, but is by no means a universal finding. Only 28 percent of the cases in table I were noted to have a positive direct Coombs test at the peak of the
reaction. In fact, the more severe the hemolysis the more likely it seems that the Coombs test will be negative during the reaction.\textsuperscript{12,22} Accelerated destruction of the antibody coated cells must rapidly remove them from the circulation. In such cases, plasma-free hemoglobin elevations indicate the hemolytic nature of the reaction. Elevations in total bilirubin levels, primarily due to increased indirect reacting bilirubin, can be expected. Interpretation of rising bilirubin levels in the presence of preexisting liver disease may be a problem in some patients. The ratio of indirect to total bilirubin has been recommended as an index to evaluate the contribution of both hemolysis and liver disease to bilirubin elevations.\textsuperscript{20} A ratio of greater than 0.4 was found to correlate well with hemolysis. Decreased haptoglobin levels were somewhat less useful.\textsuperscript{20}

During the early phases of the reaction, it may not be possible to detect the presence of the responsible antibody in the serum even in the face of rapid hemolysis.\textsuperscript{12} If detected, the titer may be too low to allow accurate identification.\textsuperscript{16} When a positive direct Coombs test coexists along with an identifiable serum antibody, the antibody responsible for the positive Coombs test may not necessarily be the same as the circulating antibody. Elution of the antibody from the Coombs positive cells is necessary to establish its identity.

Differential centrifugation techniques for the separation of the transfused cells from the patient’s own cells are useful so that the patient’s cells can be typed.\textsuperscript{28} The previously transfused units should also be typed for the antigen responsible for the reaction. This gives some idea of the number of red cells which potentially will be destroyed.

**Summary**

Delayed hemolytic transfusion reactions will unfortunately continue to occur. Factors contributing to the failure to detect antibodies on crossmatching are (1) absent or low antibody titer and (2) dosage effects or a combination of the two. It is possible that loss of antigens from stored pilot tubes could contribute to failure although no cases have definitely been linked to this possibility. Initially, neither the clinical nor the laboratory presentation may be entirely clear cut although as the reaction develops the antibody usually reveals itself. In very rare instances, no antibody may be detected at any stage.

**References**