Hemolytic Transfusion Reaction Due to Anti-Le\textsuperscript{a}

By G. ALBIN MATSON, JOHN COE AND JANE SWANSON

THE INSTANCES in which hemolytic transfusion reactions have been caused by the Lewis groups are apparently not numerous. Only five cases have been reported (Krieger and Simmons, 1949,\textsuperscript{1} DeVries and Smitskamp, 1951,\textsuperscript{2} Brendemoen and Aas, 1952,\textsuperscript{3} VonLauer et al., 1954,\textsuperscript{4} and Mollison and Cutbush, 1955.\textsuperscript{5} Pickles also is reported to have had a case of transfusion reaction which was attributed to anti-Le\textsuperscript{a}.

REPORT OF CASE

The hemolytic transfusion reaction reported here was in a 55 year old white female patient, Mrs. N, who entered the Minneapolis General Hospital on October 16, 1953 for treatment of osteomyelitis of the femur. In May 1952 she was involved in an automobile accident, sustaining a fracture of her right mid femur and wrist. The femur was fixed with a nail but subsequently became infected so that the nail had to be removed in July 1953. She was placed in a hip spica and transferred to the Minneapolis General Hospital in October 1953 for further treatment. Detailed information concerning her physical status and the results of laboratory investigations prior to her admission to Minneapolis General Hospital were not available. However, the patient remembered receiving a single transfusion at the time the femur was nailed in 1952 and two subsequent transfusions at the time the nail was removed in July 1953. She experienced no reaction with any of these transfusions.

The patient remembered no previous illnesses or hospitalizations since childhood. Before the age of 10 the patient sustained many fractures of a wide variety of bones reported to be due to osteogenesis imperfecta. She stated the fractures became so common during this period that her father learned to set the bones himself and she did not even go to a doctor. Her mother also had many fractures as a child, and the patient’s daughter has osteogenesis imperfecta. After the age of 10 she sustained no fractures until that resulting in her present admission. She received no transfusions prior to 1952.

On October 27 internal fixation and bone graft of the old fracture site was attempted. During this procedure the patient, who was shown to be Group O Rh positive Rh\textsubscript{1} (CD\textsubscript{e}), received without incident six bottles of O Rh positive compatible blood. Following this operation, the patient again developed a wound infection from which Staphylococcus aureus, coagulase positive, was cultured. She was given antibiotics which decreased the evidence of infection, and on December 10, 1953 an attempt was made to close the wound by debridement and secondary closure. This was a failure and the wound had to be reopened.

At this time she received one additional bottle of Group O Rh positive compatible blood without reaction. The wound continued to contain hemolytic Staphylococcus aureus on culture although the patient did not have an elevation of temperature and the leukocyte count remained between 5,000 and 6,000 with a normal differential. However, her hemoglobin gradually fell to 10.1 Gm. per cent, and a transfusion was ordered for supportive therapy. A crossmatch using fresh Group O Rh positive blood from the bank was set up by the high protein method only, and the technician noted no agglutination. When this transfusion was started on January 13, 1954, the patient complained almost immediately of pain in the arm. The interne, realizing the blood was flowing very rapidly and that it was cold, cut down the rate of flow but permitted the transfusion to continue until 200 cc. had been given, at which time it was obvious that a true transfusion reaction was occurring.

From the Minneapolis War Memorial Blood Bank and Minneapolis General Hospital.

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The patient experienced pain in the back, her temperature went to 103.6 F., there was flushing, nausea, vomiting and the pulse was elevated to 110. Plasma obtained at this time revealed a hemoglobin of 490 mg. per cent by the method of Flink and Watson, and urine obtained during the three hour period following the transfusion was a port wine color giving a 4+ qualitative test for hemoglobin. Six hours after the transfusion the urine was again clear. The qualitative test for hemoglobin was negative. The patient was free of symptoms, and the next day there was only 0.73 mg. per cent of bilirubin in her serum. Urinary output remained good throughout the episode. The donor blood was retyped and again found to be Group O Rh positive, but saline and Coombs crossmatches demonstrated definite incompatibility with the patient's serum. Subsequently, the patient has received without incident one bottle of Group O Rh positive blood compatible by crossmatching.

**SEROLOGIC EXAMINATION**

**Tests on Cells**

A post-transfusion sample of red cells of the patient taken the day of the reaction was found to belong to Group O Rh positive Rr (CDe/cde). The cells gave weak reactions to anti-E and anti-S sera which produced small clumps but left many cells unagglutinated, suggesting the presence of two kinds of blood. After the addition of a potent anti-E serum (free from anti-D) to the mixture, the supernatant ce cells failed to react with anti-E or anti-S serum. The patient is not a twin, thus ruling out the possibility of the existence of a blood group chimera as reported by Dunsford et al. The possibility appeared, therefore, that cells from one or more of the October or December compatible transfusions received by the patient prior to the reaction had survived well and that these cells possessed the rh*(E) and S antigens. All the cells in the mixture were agglutinated with anti-D serum, showing that both patient and donor possess this antigen. After the mixture was treated with anti-C serum, a comparatively small number of cells were left unagglutinated, showing that the donor lacks the C factor. From this it was determined that Mrs. X's cells were O CDe/cde ss whereas the surviving transfused cells were O cDE/cde S.

More complete blood grouping formulae of Mrs. X's cells, the “reaction” donor’s red cells (#801), a compatible blood (#7396) subsequently given with no reaction, and two additional bloods (#6215, #6225) which were found to be incompatible by cross-matching, are shown in table 1.

**Tests on Serum**

From the formulae given in table 1 it was suspected that the antibody in the patient's serum responsible for her hemolytic transfusion reaction was anti-Le^e_. Hemolysis and agglutination were observed in both saline and albumin media when crossmatches were repeated with cells of Donor #801 and the patient's pre-transfusion sample of serum. The indirect anti-globulin crossmatch was also positive. An additional 20 bloods were tested with her serum, 15 of which

<table>
<thead>
<tr>
<th>Mrs. X</th>
<th>0</th>
<th>MaNs</th>
<th>P+</th>
<th>Rh (CDe/cde)</th>
<th>Le (a-b-)</th>
<th>Fy (a+)</th>
<th>K-</th>
<th>Lu (a-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#801 (Reaction)</td>
<td>0</td>
<td>MNS</td>
<td>P+</td>
<td>Rh (CDe/cde)</td>
<td>Le (a-b-)</td>
<td>Fy (a+)</td>
<td>K-</td>
<td>Lu (a-)</td>
</tr>
<tr>
<td>#7396 (Compatible)</td>
<td>0</td>
<td>MS</td>
<td>P-</td>
<td>Rh (CDe/CDe)</td>
<td>Le (a+b+)</td>
<td>Fy (a-)</td>
<td>K+</td>
<td>Lu (a-)</td>
</tr>
<tr>
<td>#6215 (Incompatible)</td>
<td>0</td>
<td>NaNs</td>
<td>P+</td>
<td>Rh (CDe/cDe)</td>
<td>Le (a-b-)</td>
<td>Fy (a-)</td>
<td>K-</td>
<td>Lu (a-)</td>
</tr>
<tr>
<td>#6225 (Incompatible)</td>
<td>0</td>
<td>MaNs</td>
<td>P-</td>
<td>Rh (cDE/cDe)</td>
<td>Le (a+b-)</td>
<td>Fy (a+)</td>
<td>K-</td>
<td>Lu (a-)</td>
</tr>
</tbody>
</table>

**Table 1.—Blood groups of cells studied**
HEMOLYTIC TRANSFUSION REACTION DUE TO ANTI-LEa

Table 2.—The Reaction of N’s Serum with Red Cells of Different Lewis Groups

<table>
<thead>
<tr>
<th>Red Cells</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le (a – b +)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Le (a – b -)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Le (a + b -)</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

“Exact” probability for 0 8 0 = 1 in 1287

were compatible. All these 15 lacked the Lea antigen. Her fresh serum produced hemolysis and agglutination in both saline and albumin with three incompatible bloods tested and agglutination without hemolysis in two others. These all contained the Lea antigen. When N’s serum was inactivated at 56 C. for fifteen minutes, its agglutinating power was not impaired but its hemolytic activity was greatly reduced. We concluded from these tests that anti-Lea was present, which we found to be most strongly active at 25 C. A small amount of anti-Leb also showed up at 12 C. When red blood cells of known Lewis groups were tested with N’s serum, the results were as summarized in table 2.

In order to demonstrate more clearly that the offending antibody in N’s serum was anti-Lea and to rule out the presence of some additional rare antibody which might also have been responsible for the transfusion reaction, it appeared to be desirable to add to N’s serum equal parts of ABO non-secretor saliva which contained Lea but not Leb substance. The serum so treated should not agglutinate or sensitize the reaction donor’s cells unless some other antibody were also present. These tests with controls were done in saline and by the indirect antiglobulin method. The results are shown in table 3.

The results shown in table 3 would seem to establish that it was the anti-Lea in N’s serum which had caused her hemolytic transfusion reaction, for when her

Table 3.—Agglutination Tests Using N’s Serum Treated with ABO Non-Secretor Saliva (Containing Lea Substance)

<table>
<thead>
<tr>
<th>Cells Tested</th>
<th>Results of Tests*</th>
<th>Treatment of Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline Tests</td>
<td>Coombs</td>
</tr>
<tr>
<td></td>
<td>25 C. 37 C.</td>
<td></td>
</tr>
<tr>
<td>N’s serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>801 Le (a + b -)</td>
<td>- - -</td>
<td>Equal parts N’s serum and non-secretor saliva allowed to stand at room temperature for 1 hour. 2 drops serum-saliva mixture + 2 drops 2% cells suspended in saline.</td>
</tr>
<tr>
<td>6215 Le (a + b -)</td>
<td>- - -</td>
<td></td>
</tr>
<tr>
<td>6225 Le (a + b -)</td>
<td>- - -</td>
<td></td>
</tr>
<tr>
<td>7396 Le (a - b +)</td>
<td>- - -</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le (a + b -) cells</td>
<td>hem. hem.</td>
<td>Same as above except saline was added instead of saliva</td>
</tr>
<tr>
<td>801</td>
<td>4+ 4+ 4+</td>
<td></td>
</tr>
<tr>
<td>7396</td>
<td>- - -</td>
<td></td>
</tr>
</tbody>
</table>

* All tests incubated for 30 minutes
serum was neutralized with ABO non-secretor saliva (which contains Le* substance), no other antibody remained to react with the reaction donor's cells.

Titration tests were done to determine the strength of the anti-Le* in N's serum (table 4).

The serum showed a titer of 16 when tested against 2 per cent suspension of papain-treated red blood cells and incubated at 37 C. for 30 minutes. The first tube in this test showed some hemolysis.

The anti-globulin augmentation test done by Sturgeon's technique gave a titer of 8. The Lewis groups of N's two living children were found to be Le (a-) suggesting that the anti-Le* found in her serum and which was responsible for the hemolytic transfusion reaction apparently resulted from the multiple transfusions she had received.

Although the hemolytic transfusion reaction described above was undoubtedly due to anti-Le*, it does not necessarily follow that anti-Le* invariably causes transfusion reactions. Actually, the majority of instances of anti-Le* do not cause reactions. As naturally occurring antibodies, they have low titers which do not as a rule react at 37 C. Lewis antibodies do, however, become potentially important in transfusions following an antigenic stimulus of a previous transfusion or pregnancy.

**Summary**

A case is reported in which a transfusion of whole blood of group Le (a+b−) produced a severe hemolytic transfusion reaction in a patient of group Le (a−b−). The anti-Le* in the patient's serum had apparently been stimulated by previous transfusions. No other antibody was demonstrable by us in this case.

**Summario in Interlingua**

Es reportate un caso in que le transfusion de sanguine integre del gruppo Le (a+b−) produceva un sever reaction hemolytic in un patiente del gruppo Le (a−b−). Le anti-Le* in le sero del patiente habeva apparentemente essite stimulat per previe transfusiones. Nulle altere anticorpore esseva demonstrabile in iste caso.

**References**

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5. Pickles, Margaret M.: Unpublished data.
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