Autoimmune Hemolytic Anemia During Pregnancy
With Hemolytic Disease in the Newborn

By Rolf Baumann and Harry Rubin

A young woman had idiopathic autoimmune hemolytic anemia occurring in the last weeks of pregnancy. The hemolytic process was quite severe in the mother but responded to steroid therapy and transfusions. The baby was born with a mild form of hemolytic disease with elevated indirect bilirubin levels, increased normoblasts and reticulocytes, and a positive direct antiglobulin test. The child did not require any exchange transfusions, and although the hemoglobin fell to a low of 9.7 g/100 ml 1 mo after delivery, it continued to rise to normal levels after that. The child is developing normally. The antibody was an IgG globulin, presumably 7S, and crossed the placenta to react with the fetal red cells. The antibody showed no specificity when tested with a panel of cells, including Rh null cells.

AUTOIMMUNE HEMOLYTIC ANEMIA has rarely been reported in pregnancy, and there are few observations of its effect on the fetus.\textsuperscript{1-5} This report presents our observations in this rare clinical event.

CASE REPORT

E.B., a 31-yr-old white female in the 37th wk of her second pregnancy, experienced rapidly progressive symptoms of severe anemia that, after 1-wk duration, required hospitalization on May 11, 1971. No blood transfusions had ever been administered. She had no symptoms of infection during her pregnancy, and the only drugs she was taking were oral iron and multivitamins containing 1 mg of folic acid.

The patient had hepatitis in 1957. In September 1969, her first pregnancy was terminated after 16 wk by a spontaneous abortion. In February 1970, she suffered from a nonspecific chorioretinitis of the left eye. Toxoplasma fluorescent antibody titer at that time and repeated in May 1970 was less than 1:16. The patient’s father had a single episode of acute hemolytic anemia at the age of 30 and was treated with splenectomy in 1940. He is now living and well.

On admission, the patient complained of severe weakness. She was pale but not icteric. The temperature was 99.4°F, the pulse rate was 132, and the blood pressure was 120/60. There was a grade one over six systolic murmur at the apex. The liver was palpable 4 cm below the costal margin, and the spleen tip was felt. The size of the uterus corresponded to 36–37 wk of gestation; the cervix was soft and partially effaced.

The hemoglobin was 3 g/100 ml, and the hematocrit was 6.2%. The RBC count was 300,000 with 58% reticulocytes. There were 28 normoblasts/100 white cells. Sequential hematologic data are shown in Table 1. The bone marrow showed massive normoblastic erythroid hyperplasia; the myeloid-erythroid ratio was 0.3, and the iron stores were

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Table 1. Mother's Hematologic Data

<table>
<thead>
<tr>
<th>Date</th>
<th>Hb (g/100 ml)</th>
<th>Hemocrit (%)</th>
<th>Reticulocytes (%)</th>
<th>WBC/cu mm</th>
<th>Platelets/cu mm</th>
<th>Direct Anti-globulin Titer</th>
<th>Indirect Anti-globulin Titer</th>
<th>Prednisone Dosage (mg/day)</th>
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<tr>
<td>Dec. 30, 1970</td>
<td>11.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>May 4, 1971</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20,700</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>May 11, 1971</td>
<td>3.0</td>
<td>6.2</td>
<td>58</td>
<td>28,300</td>
<td>288,000</td>
<td>1:64</td>
<td>1:2</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
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<tr>
<td>May 21, 1971</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1:16</td>
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<tr>
<td>June 8, 1971</td>
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<td>-</td>
<td>-</td>
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<td>1:16</td>
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<td>25</td>
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<tr>
<td>July 9, 1971</td>
<td>11.7</td>
<td>34</td>
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<tr>
<td>August 6, 1971</td>
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<td>-</td>
<td>-</td>
<td>1:4</td>
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<td>10</td>
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<tr>
<td>Oct. 1, 1971</td>
<td>11.9</td>
<td>-</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
<td>1:4</td>
<td>Negative</td>
<td>10</td>
</tr>
</tbody>
</table>

4 U packed cell transfusion

Table 2. Baby's Hematologic Data

<table>
<thead>
<tr>
<th>Date</th>
<th>Hb (g/100 ml)</th>
<th>Hemocrit (%)</th>
<th>Reticulocytes (%)</th>
<th>Normoblasts/100 WBC</th>
<th>WBC/cu mm</th>
<th>Platelets/cu mm</th>
<th>Direct Antiglobulin Titer</th>
</tr>
</thead>
<tbody>
<tr>
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<td>18.6</td>
<td>54</td>
<td>28</td>
<td>28</td>
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<td>57.5</td>
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<td>46</td>
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<td>-</td>
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<tr>
<td>June 14, 1971</td>
<td>12.0</td>
<td>34</td>
<td>1.3</td>
<td>0</td>
<td>9,100</td>
<td>-</td>
<td>Negative</td>
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<td>28</td>
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<td>Negative</td>
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<tr>
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<td>11.5</td>
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<td>2.5</td>
<td>0</td>
<td>11,800</td>
<td>Adequate</td>
<td>Negative</td>
</tr>
<tr>
<td>March 29, 1972</td>
<td>12.0</td>
<td>38</td>
<td>1.1</td>
<td>0</td>
<td>9,000</td>
<td>Adequate</td>
<td>Negative</td>
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<tr>
<td>April 5, 1972</td>
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<td>37</td>
<td>0.7</td>
<td>0</td>
<td>9,000</td>
<td>210,000</td>
<td>-</td>
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adequate. The total bilirubin was 2.8 mg/100 ml; the LDH was 850 mU/ml, and SGOT was 220 mU/ml.

Blood type was A Rh positive. The direct antiglobulin test with a specific anti-IgG antiserum was strongly positive; it was weakly positive with an anticomplement antiserum. All subsequent antiglobulin tests were of the anti-IgG type and were negative for complement coating the red cells. The indirect antiglobulin test was weakly positive. The patient's serum agglutinated trypanized red cells up to a dilution of 1 to 8; this reaction was nonspecific and occurred with all panel erythrocytes. An eluate from the patient's red cells reacted with all panel erythrocytes and also with Rh null cells in the indirect antiglobulin test. No cold or warm agglutinins were present. Haptoglobin concentration was 9 mg/100 ml. The serum iron was 330 μg/ml, with total iron-binding capacity 365 μg/ml. The serum B12 was 836 pg/ml, and the folate was 40 ng/ml. Normal values were obtained for electrolytes, blood sugar, blood urea nitrogen, creatinine, and alkaline phosphatase. Serum protein and hemoglobin electrophoreses were normal. Negative results were obtained on two LE cell preparations; there were no antinuclear antibodies, and the sugar water hemolysis test and tests for Donath-Landsteiner and heterophile antibody were all negative.

The patient was treated with 100 mg of prednisone daily and was transfused with 4 U of packed red cells. On May 14, 1971, spontaneous labor began, and the patient delivered a female infant. No further transfusions were necessary. With gradually improving hemoglobin, the steroids were gradually reduced. On June 8, 1971, the antibodies in the patient's serum were no longer detectable. As of October 1, 1971, the mother's hemoglobin is 11.9 g/100 ml, while on 10 mg of prednisone daily, and she is asymptomatic. Her reticulocyte count is normal, but her direct antiglobulin test remains weakly positive. A toxoplasma fluorescent antibody titer was less than 1:16, and a complement fixation test for cytomegalovirus showed a titer of 1:16 in March 1972.

The baby weighed 2350 g, the Apgar rating was 8 at 1 min and 10 at 5 min of life. She was alert and active; the Moro reflex was positive. The pulse rate was 120; the temperature 97.4°F. The lungs were well aerated, and the liver was palpable 1 cm below the right costal margin; the spleen was not palpable. Hematologic data are recorded in Table 2. Blood type was A Rh positive. The cord blood VDRL was negative. The total bilirubin was 4.5 mg/100 ml. The direct antiglobulin test was positive with an anti-IgG reagent. Jaundice developed within the first 24 hr. The bilirubin level peaked on the third day of life at 13.2 mg/100 ml, over 88% of which was indirect reacting. Blood urea nitrogen, blood sugar, and total protein determinations were normal. Cultures of cord, nose, throat, and rectum showed no pathogenic organisms. Immunoglobulins at birth were: IgG, 1375 mg/100 ml; IgA, 0; IgM, 31 mg/100 ml. On September 3, 1971, the values were: IgG, 325; IgA, 14.5; and IgM, 68 mg/100 ml. The IgM level was raised at birth and remained so at 11 wk of age.

On June 14, 1971, at the age of 1 mo, the antiglobulin test became negative. The hemoglobin fell to a low of 9.7 g/100 ml on June 28, 1971 and then gradually rose. The baby is developing normally. In March 1972, a toxoplasma fluorescent antibody titer was less than 1:16, and the complement fixation titer for cytomegalovirus was less than 1:8; serum immunoglobulins were within normal limits.

RESULTS AND DISCUSSION

The patient's idiopathic autoimmune hemolytic anemia occurred in the last weeks of pregnancy. The antibody in the mother was an IgG immunoglobulin of the warm type. Most of the antibody was attached to the red cells; a comparatively small amount was present in the serum. Since the antibody was an IgG globulin, presumably 7S, it crossed the placenta readily and reacted with the fetal red cells. The antibody showed no specificity for erythrocyte antigens, since it reacted with all panel cells and Rh null
cells. The severe hemolytic anemia responded well to steroids and blood transfusions.

The newborn showed a compensated hemolytic process in the first week of life, evident from elevated indirect bilirubin levels, increased normoblasts and reticulocytes, and a positive direct antiglobulin test. Since the mother’s direct antiglobulin test remains positive, her red cell antigens could not be completely phenotyped and compared with that of her daughter. Both are blood type A and D positive, so that an additional isoimmunization process seems remote.

Vedovini and Benedetti reported an autoimmune hemolytic anemia in the last month of pregnancy causing fetal erythroblastosis and anemia that was treated with steroids and blood transfusions. The mother did not receive steroids until after delivery. In de Groot’s case, the Coombs’ positive hemolysis appeared in the last trimester of pregnancy and was treated with steroids and transfusions; the newborn was healthy, without further data being reported. In two instances reported in the French literature, the antiglobulin positive hemolytic anemia occurred in the fifth month of pregnancy, resulting in death of the mother and of the premature infant in one case and in a stillbirth and maternal recovery in the other case.

Silverstein et al. reported a pregnancy in a patient with Evans’ syndrome during which the hemolysis had been well controlled with steroids and the newborn had no hematologic abnormalities.

Cases of Coombs’ negative hemolytic anemias of unknown origin in pregnancy have been reported without hemolysis in the newborn.

The association of toxoplasmosis and viral infections with hemolytic anemia has been reported in the literature. Zuelzer et al. have postulated that occult viruses may play an essential role in human autoimmune hemolytic anemia and that the autoantibodies may represent a variable secondary response to virus-related antigens. They described a number of cases in which there was an association between the onset of the “warm type” of autoimmune hemolytic anemia and cytomegalovirus infection in children. Although our patient did have an episode of chorioretinitis 1 yr prior to the present illness, there was no other clinical or serologic evidence of toxoplasmosis. The later serologic studies and the normal development without any other clinical evidence of illness would rule against toxoplasma or cytomegalovirus infection in her infant.

This disease is rare in pregnancy, and not enough data are available to establish criteria for fetal prognosis. Indications for diagnostic amniocentesis are also not clear. When hemolysis presents very late in pregnancy, as in our case, or when the hemolytic process can be well controlled with treatment, as in the few reported cases in the literature, prognosis would seem to be quite good for the fetus.

ACKNOWLEDGMENT

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REFERENCES


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