Variability of the Erythropoietic Response in Autoimmune Hemolytic Anemia: Analysis of 109 Cases

By Jane L. Liesveld, Jacob M. Rowe, and Marshall A. Lichtman

One hundred-nine cases of autoimmune hemolysis were reviewed to determine the frequency of reticulocytopenia, the state of the erythroid marrow in reticulocytopenic cases, and the course of reticulocyte production indices with time and glucocorticoid treatment. The mean hematocrit at presentation was 24 mL/dL, but 30% of cases had an initial hematocrit <20 mL/dL. Median reticulocyte percentage at diagnosis was 9%, and median reticulocyte production index was 2.8 times basal. Twenty percent of cases had an initial reticulocyte count <4%, and 37% had an initial reticulocyte production index <2.0 times basal. These reticulocytopenic patients were nearly evenly distributed between warm and cold antibody-mediated cases and between primary and secondary cases. Fifty-four percent of reticulocytopenic cases had a bone marrow examination during hospitalization. Three-fourths of these marrows showed erythroid hyperplasia, and erythroid hypoplasia was seen in only one case. Eighty-eight cases had serial reticulocyte measurements, and in only 15% of patients did the reticulocyte production index remain <2.0 times basal. Thus, in most cases, the initially low reticulocyte production index may represent a lag in marrow responsiveness to hemolytic stress. In cases with persistent reticulocytopenia, ineffective erythropoiesis is suggested by the frequency of marrow erythroid hyperplasia. In the cases that were initially reticulocytopenic and demonstrated an increase in reticulocyte production index, the magnitude of this increase was significantly greater in glucocorticoid-treated patients than in those not so treated, indicating that a glucocorticoid sensitive component exists in the marrow erythropoietic response to hemolysis. Awareness of the frequency of an initial reticulocytopenia in cases of autoimmune hemolysis may be important in initial diagnosis and treatment.

MATERIALS AND METHODS

The medical records of 109 consecutive cases of autoimmune hemolysis at two University of Rochester hospitals (Strong Memorial Hospital and St Mary's Hospital) from 1965 to 1985 were reviewed. Charts were located by means of a computerized numerical diagnosis coding system. Criteria for inclusion as a case of autoimmune hemolysis were (a) a positive direct Coombs' test with anemia or clinical evidence for hemolysis or (b) a clinical diagnosis of autoimmune hemolytic anemia with elevated cold agglutinin titers in cases in which complete serologic test results were not available in the record (three cases). One case with a clinical diagnosis of Coombs' negative autoimmune hemolytic anemia was also included.

Age at diagnosis, year of presentation, sex, race, Coombs' test results, and hematocrit at presentation were recorded for all 109 patients. Initial reticulocyte counts were available in 108 cases. Other information recorded when available included the second, highest, lowest, and last reticulocyte counts during the hospital admission (88 patients), lowest and last hematocrit, first WBC count and WBC differential count, first platelet count, first mean corpuscular volume (MCV), first serum lactic dehydrogenase (LDH), and first total and direct bilirubin measurements. The description of the marrow aspirate and biopsy was recorded when available. Historical information obtained included associated illnesses, treatment administered, and number of transfusions. Cases were classified according to the following hemolysis subtypes: primary warm antibody, primary cold antibody, secondary warm antibody, secondary cold antibody, and drug-induced antibody.

Adjustments of the reticulocyte count for hematocrit (corrected reticulocyte count) and for determination of reticulocyte production index (RPI) were made. Tests of statistical significance between group means or frequencies were done with Student's t test or chi-square test, respectively. The microcoombs' test was performed using the antiglobulin consumption technique. Serum LDH and bilirubin were determined using standard laboratory procedures. Indirect bilirubin was calculated as the difference between total and direct bilirubin measurements. Group data are expressed as the mean ± 1 SD unless otherwise specified.

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RESULTS

Patient Characteristics and Type of Hemolytic Antibody

One hundred-four of the the 109 cases in this study were diagnosed while they were inpatients. Patients ranged in age from 4 months to 91 years. Seventy-one of the cases (65%) were female, and 38 were male (35%). Ninety-five percent of the patients were white and 5% were black.

Categories of hemolysis. Table 1 summarizes the frequency of hemolysis types identified by serologic and clinical studies. Nine of the drug-induced cases were associated with α-methyldopa26 and one with procainamide.27 Three cases were not classifiable into one of these categories: One case had mixed features (warm and cold antibodies) and one case was direct Coombs’ negative; in one case, the direct Coombs’ test was positive but the γ and complement Coombs’ reagent results were lost from the record. Four cases in this series had positive microcoombs’ tests; ie, >40 molecules IgG per cell, when the direct Coombs’ test was negative.

Presenting Hematocrits and Reticulocyte Counts

Hematocrit. At the time of diagnosis, the median hematocrit of patients was 24 mL/dL; range 9 to 56 mL/dL. The patient with the initial hematocrit of 56 mL/dL had severe chronic obstructive lung disease and cor pulmonale with higher baseline hematocrits. Figure 1 shows the cumulative frequency curve of presenting hematocrits.

Reticulocyte counts. The median reticulocyte percentage of patients at their presentation was 9% (range 0.4% to 92%). The mean reticulocyte count corrected to a hematocrit of 45 mL/dL (corrected reticulocyte count) was 7.4 ± 7.3 (median 5, range 0.1 to 45). The mean RPI was 3.8 ± 3.5 times basal (median 2.8, range 0.06 to 19 times basal). Figure 2 shows the cumulative frequency curve of the initial reticulocyte measurements. Reticulocyte counts were available in 108 of 109 patients. In the remaining case, the blood smear showed marked polychromatophilia, but this patient was excluded from analyses involving reticulocyte quantification. In the 88 cases in which serial reticulocyte counts were available, the first reticulocyte count was strongly correlated with the second reticulocyte count (r = .87, P < .0001). In 80% of cases with serial reticulocyte values available, the second reticulocyte count was obtained within 3 days of the first count.

By linear regression analysis, the reticulocyte percentage was significantly inversely correlated with the presenting hematocrit (r = −.35, P < .001), although the correlation was weak. The corrected reticulocyte percentage and RPI did not correlate significantly with presenting hematocrit. Table 1 shows the mean presenting hematocrits and reticulocyte values based on the type of hemolysis. Although primary cold antibody-mediated hemolysis cases had a higher mean hematocrit and lower reticulocyte production index, the sample size was too small to reach conclusions regarding the significance of these differences.

Initial WBC and Platelet Counts

WBC counts were obtained in 108 patients. The mean WBC was 10,602 ± 6,571 cells/μL, with a median of 9,000 cells/μL. The range was 1,500 to 137,000 cells/μL. Three WBC values ≥30,000 cells/μL were excluded when the mean was calculated. Each of these three values occurred in a case of chronic lymphocytic leukemia. Median WBC counts were normal in both primary and secondary cases of warm hemolysis but were elevated in the primary and secondary cold antibody groups; 11,250 and 12,900 cells/μL, respectively.

Thirteen percent of cases had a decreased total WBC (<4,500 cells/μL), and ~40% of all patients had an elevated total WBC (>11,000 cells/μL). All 14 cases with leukopenia at diagnosis had warm antibody-mediated hemolysis and were equally divided between primary and secondary types. Mean hematocrit in the leukopenic group was 25 ± 8.6 mL/dL (median 23 mL/dL), and mean RPI was 2.9 ± 2.0 times basal (median 2.5). Six of the 14 cases with leukopenia

Table 1. First Hematocrit and Reticulocyte Count According to Type of Hemolysis

<table>
<thead>
<tr>
<th>Hemolysis Type</th>
<th>Frequency of Cases (%)</th>
<th>Hematocrit (mL/dL)</th>
<th>Reticulocyte Count (%)</th>
<th>Reticulocyte Production Index (× Basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary warm antibody</td>
<td>47</td>
<td>51</td>
<td>25 ± 8.6(23)</td>
<td>18 ± 20(10)</td>
</tr>
<tr>
<td>Secondary warm antibody</td>
<td>22</td>
<td>24</td>
<td>25 ± 9.4(24)</td>
<td>14 ± 12(9)</td>
</tr>
<tr>
<td>Primary cold antibody</td>
<td>7</td>
<td>8</td>
<td>32 ± 11.30(30)</td>
<td>9.6 ± 11.4</td>
</tr>
<tr>
<td>Secondary cold antibody</td>
<td>12</td>
<td>13</td>
<td>26 ± 7.4(26)</td>
<td>11 ± 7.1(8)</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>9</td>
<td>10</td>
<td>28 ± 6.2(29)</td>
<td>13 ± 10(10)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>3</td>
<td>3</td>
<td>22</td>
<td>3.6</td>
</tr>
<tr>
<td>All cases</td>
<td>100</td>
<td>109</td>
<td>26 ± 8.8(24)</td>
<td>15 ± 16(9)</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD. Median values are shown in parentheses. Medians and SD are not shown for the three unclassified cases.
also had platelet counts <120,000/μL, and one other case developed thrombocytopenia later. Seven of the 14 had a palpable spleen, and one had splenic enlargement by radionuclide scan. None of the cases with leukemia had received myelosuppressive drugs, and none had marrow infiltrative disease.

Of the patients with leukocytosis at presentation, approximately one-third had cold antibody-mediated hemolysis. Forty percent of these cases had initial reticulocyte production indices ≤ 2.0 times basal, but none had thrombocytopenia. Mean hematocrit in this group was 23 ± 9.2 mL/dL. Figure 3A shows the cumulative frequency of the neutrophil count; Fig 3B shows the cumulative frequency of the lymphocyte count.

Initial platelet counts were available in 85 patients. An additional 19 patients had normal platelet estimates. Mean initial platelet counts did not differ significantly between subjects with warm antibody-induced or cold antibody-induced hemolysis. Figure 4 shows the cumulative frequency of initial platelet counts. Each of the 13 cases with thrombocytopenia at presentation was warm antibody-mediated, and these were divided approximately equally between primary and secondary types. Six of these cases had been given a clinical diagnosis of idiopathic thrombocytopenic purpura. One patient had chronic lymphocytic leukemia, and one had lymphoma with marrow involvement. Mean hematocrit in patients with thrombocytopenia was 30 ± 7.6 mL/dL (median 32), and mean RPI was 2.6 ± 1.5 times basal (median 2). In the 16 cases with thrombocytosis, 13 were warm antibody-mediated cases, two were secondary cold antibody-mediated cases in young adults, and one was a mixed warm- and cold-mediated case—also in a pediatric patient. Twelve of these 16 cases with thrombocytosis had a total WBC >11,000 cells/μL. Mean hematocrit in those cases with thrombocytosis was 21.3 ± 6.4 mL/dL (median 21), and mean RPI was 3.9 ± 4.6 times basal (median 2.4).

**Effect of Glucocorticoid Treatment on Reticulocyte Count**

Serial reticulocyte counts were available in 88 cases. Glucocorticoids were used in 65 of these 88 cases (Table 2). Thirty-nine of these 65 cases had an increase in RPI while on steroids; in the other 26, the production index either remained stable or decreased. As summarized in Table 2, those who demonstrated an increase in reticulocyte production index while on steroids had lower mean initial hematocrits and RPIs than did those without such reticulocyte response. The magnitude of the increase in RPI in response
to steroids (3.5 to 7.2 times basal) was significant as measured by the paired \(t\) test \(P < .01\). Seventy-five percent of cases reached their maximum RPI by 6 days after the initiation of glucocorticoid treatment, which represented the tenth day of hospitalization.

Fourteen of the 23 patients not treated with glucocorticoids also had an increase in their RPI. This mean increase (1.5 to 3.8 times basal) was also statistically significant \(P < .01\). Seventy-five percent of untreated cases attained their maximum increase in RPI by 10 days of hospitalization.

**Analysis of Features in Cases Presenting With Low RPI**

Figure 5 depicts the cumulative percentage graph of the initial RPI. Forty (37%) of the 108 cases with reticulocyte counts initially had an RPI of \(\leq\)2.0 times basal. About 30% of those with primary warm antibody-mediated disease, 30% with secondary warm antibody-mediated disease, 50% with primary cold antibody-mediated disease, 50% with secondary cold antibody-mediated disease, and 30% with drug-induced disease had an initial RPI \(\leq\) 2.0 times basal. The higher percentage found in cases of cold antibody-mediated disease compared with warm antibody-mediated hemolysis was not significantly different by chi-square test. A higher proportion of the group with an RPI \(\leq\) 2.0 was transfused (53% \(\times\) 38%), and a lower proportion received steroids (65% \(\times\) 87%), although these differences were not statistically significant by chi-square test. Mean hematocrit, platelet count, WBC, and serum LDH did not differ significantly between the two groups. The mean indirect bilirubin was significantly higher (3.3 \(\pm\) 2.1 \(\pm\) 1 mg/dL) in those with production indices \(\leq\) 2 times basal, perhaps a reflection of both hemolysis and ineffective erythropoiesis.

As noted previously and in Table 2, 53 of 88 cases with serial reticulocyte values had an increase in RPI during hospitalization; in the other 35 cases, the index remained stable or decreased. As shown in Fig 6, 13 (15%) of the 88 cases had a maximum RPI that was \(\leq\) 2.0 times basal, indicating persistent reticulocytopenia during hospitalization. Fifty-four percent of the 13 cases with persistently low reticulocyte values received steroids.

In 33 of 40 cases with initial RPI \(\leq\) 2.0, serial reticulocyte values were available. Twenty-five of the 33 or 76% had increases in RPI (1.2 to 4.1 times basal) \(P < .01\). In 15 of these patients who received glucocorticoids, this increase was more substantial (3.9 \(\pm\) 3.6 times basal \(\times\) 2.3 \(\pm\) 2.0) than in those ten not receiving steroids \(P < .01\). Seventy-five

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**Table 2. Effect of Glucocorticoid Treatment on RPI**

<table>
<thead>
<tr>
<th>Glucocorticoids</th>
<th>Effect on Reticulocyte Production Index</th>
<th>No. of Cases</th>
<th>Hct on Day of Initial RPI</th>
<th>Initial Reticulocyte Production Index</th>
<th>Highest Reticulocyte Production Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administered</td>
<td>Increase</td>
<td>39</td>
<td>22 ± 5.7</td>
<td>3.5 ± 2.9</td>
<td>7.2 ± 4.3</td>
</tr>
<tr>
<td></td>
<td>No increase</td>
<td>26</td>
<td>26 ± 8.1</td>
<td>6.1 ± 5.2</td>
<td>7.2 ± 5.2</td>
</tr>
<tr>
<td>None</td>
<td>Increase</td>
<td>14</td>
<td>23 ± 7.2</td>
<td>1.5 ± 0.3</td>
<td>3.8 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>No increase</td>
<td>9</td>
<td>30 ± 6.6</td>
<td>4.1 ± 5.6</td>
<td>7.2 ± 5.2</td>
</tr>
</tbody>
</table>

RPI, reticulocyte production index; Hct, hematocrit.

Total cases = 88 with serial reticulocyte measurement available; data presented as mean ± SD.

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**Fig 5.** Cumulative percentage of 108 cases with a given reticulocyte production index (RPI) at presentation. Production index was calculated based on initial reticulocyte percentage and hematocrit values on the same day as described in the Materials and Methods section. Thirty-seven percent of cases had an initial production index \(\leq\)2.0 times basal.

**Fig 6.** Comparison of cumulative percentage of the initial and peak reticulocyte production indices in the 88 patients in whom serial reticulocyte values were obtained. Although 37% of patients had a reticulocyte index \(\leq\)2.0 times basal initially, only 15% did not reach a reticulocyte index \(>\)2.0 during serial observations.
percent of those receiving steroids had their highest RPI within 8 days of starting the hormone, which represented the twelfth hospital day. In the eight cases with an initial RPI ≤ 2.0 without a measured increase in reticulocyte production, 50% had received steroids.

Of the 55 cases with initial RPI > 2 and serial reticulocyte values, 28 (51%) had further increases in reticulocyte values during hospitalization. This increase was significant (4.6 vs 8.1 times basal) as measured by paired t-test, and all but one of these 28 patients were treated with steroids. Seventy-five percent of these patients had attained their highest RPI by the tenth hospital day, and in 75% this occurred within 5 days of starting steroid treatment. Twenty-two of the 27 cases with initial RPI > 2 who had no rise in RPI had received steroids.

A marrow aspirate or biopsy was performed in 21 of the 40 patients with RPI ≤ 2.0 (Table 3). Sixteen (76%) of these cases had erythroid hyperplasia. Only one patient had erythroid hypoplasia. Three patients had marrow involvement with lymphoma or leukemia.

Thirty-six of 68 cases diagnosed with an RPI > 2 had a marrow examination. Thirty-three (92%) had erythroid hyperplasia. In the other three cases, erythroid activity was not reported. One of these three cases showed marrow infiltration of small lymphocytes compatible with chronic lymphocytic leukemia, and another showed infiltration with breast carcinoma cells.

### DISCUSSION

This series of cases of autoimmune hemolytic anemia shares many characteristics with prior reported series, including a ~70% incidence of warm antibody-mediated cases—excluding drug-induced cases, an age range extending from months to the tenth decade, and a case ratio of female to male of ~2:1. The spectrum of associated malignant and immunologic diseases is also similar to that found in prior series.

Although a wide range of both initial hematocrits and reticulocyte counts occurs in patients with autoimmune hemolysis, >50% of cases are diagnosed with hematocrit levels <25 mL/dL. The wide range of reticulocyte values at diagnosis and the weak inverse correlation of initial reticulocyte percentage to hematocrit confirm that the range and severity of anemia reflect several interacting variables, including the rate of hemolysis, the degree of marrow response to the hemolytic anemia, and the duration of the anemia.

The presentation of a significant proportion of patients with reticulocyte counts that do not suggest a marrow response to hemolysis could lead to misdiagnosis of a hypoproliferative anemia or a missed diagnosis of immune hemolytic anemia if a Coombs' test is not obtained. Reticulocytopenia may contribute to the decision to transfuse or to withhold glucocorticoids more frequently in individual cases, a tendency that was noted in this series.

The subsequent increase in reticulocyte index in most patients who initially had reticulocytopenia is compatible with a more lengthy time dependency in their marrow response to hemolysis. The increase in reticulocyte index during hospitalization occurred as frequently in patients treated with glucocorticoids as in those not so treated. Pirofsky found that reticulocytosis usually occurred in patients with initially low reticulocyte counts with steroid therapy; however, no nontreated comparison group was reported in that series. In our study, glucocorticoid treatment did not seem to shorten the time to peak reticulocyte count in treated patients as compared with untreated patients. The difference in the peak reticulocytosis in glucocorticoid-treated patients as compared with untreated patients may indicate that the marrow response has a steroid-sensitive component as well. Glucocorticoid-treated patients had a peak reticulocyte index during serial study nearly twice that of untreated patients. A firm conclusion, however, cannot be drawn because this was not a prospective randomized study, and there may have been unidentified differences in the glucocorticoid-treated and untreated groups.

It is difficult to ascertain the prevalence of reticulocytopenia in autoimmune hemolysis from prior reports because patients in those studies were selected for type of hemolysis (warm v cold or primary v secondary), and reticulocyte production indices were not provided and reticulocyte values were not compared with hematocrit in individual cases. Allgood and Chaplin found that five of 47 idiopathic warm antibody-mediated cases had reticulocyte values <5%. In their review, Crosby and Rappaport showed that 15 of 31 idiopathic cases were reticulocytopenic, as were 12 of 23 secondary cases. This series was based on case files from the Armed Forces Institute of Pathology, and the authors believed that the series selected for severe cases. Pirofsky reported that 49% of reticulocyte counts were <2% in a group of 195 warm antibody-mediated cases. Pirofsky's series included cases with positive antiglobulin tests without documentation of hemolysis as well as cases of autoimmune hemolysis, and it contained a high proportion of secondary cases (82%). Twenty-six percent of idiopathic cases and ~50% of secondary cases had reticulocyte counts <2%. In secondary cases, low counts were not related to chemotherapy or marrow infiltration.

Several mechanisms for reticulocytopenia in autoimmune

### Table 3. Marrow Erythroid Cellularity in Patients With Higher and Lower Reticulocyte Counts

<table>
<thead>
<tr>
<th>Reticulocyte Index</th>
<th>No. of Patients</th>
<th>Erythroid Hyperplasia</th>
<th>Erythroid Hypoplasia</th>
<th>Infiltrative Marrow Disease</th>
<th>Erythropoiesis Not Described</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.0</td>
<td>21</td>
<td>16 (76%)</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>36</td>
<td>33 (92%)</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Fifty-seven of 108 patients with reticulocyte counts had a marrow examination. Of the 40 patients with a reticulocyte index ≤2, 21 (53%) had a marrow examination. Of the 68 other patients who had a reticulocyte index >2, 36 (53%) had a marrow examination. The patient with erythroid hypoplasia had systemic lupus erythematosus.
hemolytic disease have been proposed. Some series have contained rare or infrequent cases with marrow aplasia, marrow infiltration, or megaloblastic changes.\textsuperscript{2,4} In a case of autoimmune hemolytic disease and marrow erythroid hypoplasia, an autoantibody distinct from the autoantibody against mature RBCs that was inhibitory to marrow erythroid colony-forming units (CFU-E) was demonstrated.\textsuperscript{20} Some reports have described cases with marrow aplasia and prolonged reticulocytopenia,\textsuperscript{4,6,7,16,20} others described episodic RBC aplasia,\textsuperscript{15} and still others described transient marrow aplasia with reticulocytopenia, especially in childhood, possibly related to viral infections.\textsuperscript{10,11,22} Circumstances providing a clear-cut explanation for the poor erythroid response (ie, erythroid aplasia, tumor replacement of marrow, folate deficiency, or infection) are rare.

Marrow erythroid hyperplasia in reticulocytopenic cases of autoimmune hemolysis is also well described,\textsuperscript{2,5,13,17-19,21} and these cases comprise a far larger proportion of reticulocytopenic cases, as shown by our series. Cases of autoimmune hemolytic anemia, reticulocytopenia, erythroid cells in the marrow, but with inhibition of marrow erythroid colonies by patient plasma in vitro,\textsuperscript{19} and cases with retention of radioactive iron in the marrow and not in circulating RBCs\textsuperscript{29} suggest that ineffective erythropoiesis can occur. The active erythroid marrow in the reticulocytopenic cases in our report is compatible with ineffective erythropoiesis.

The wide variability in initial WBC and platelet counts that occurs in autoimmune hemolytic anemia is also suggestive of a wide range of marrow output response to the anemia and the “stress” state. Most cases of leukocytosis could not be explained by an underlying disease. The frequent coupling of leukocytosis and thrombocytosis in individual cases suggests a trilineage marrow production increase, even though in some of these cases, an appropriate reticulocyte response was not mounted. (Theoretically, this finding could be compatible with competition among lineages for stem cell differentiation commitments.) The percentage of cases diagnosed with leukocytosis tended to be greater in patients with cold antibody-mediated hemolysis. Cases of leukopenia or thrombocytopenia occurred only in warm antibody-mediated cases, and underlying disease or splenomegaly did not usually account for these depressions of cell counts. The frequent coupling of leukopenia and thrombocytopenia is compatible with multiple lineage immune destruction in these cases, as first suggested by Evans and Duane in cases with prominent thrombocytopenia.\textsuperscript{20}

This series confirms and quantifies the wide range in the severity of anemia and in the marrow hematopoietic response to hemolysis in cases of autoimmune RBC destruction at the time of diagnosis. The significant proportion of cases diagnosed with reticulocytopenia has pathogenetic implications. Awareness of this occurrence is important to enhance prompt and accurate diagnosis and proper therapy.

Acknowledgment

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References

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