Prognostic Significance of Thrombocytosis in Idiopathic Sideroblastic Anemia

By Ruth Rogers Streeter, Cary A. Presant, and Edward Reinhard

In order to determine the prognostic significance of thrombocytosis in idiopathic sideroblastic anemia, the clinical courses of 17 patients were reviewed. Six patients (36%) had thrombocytosis, and none developed acute leukemia. Nine patients (53%) had normal platelet counts, and one developed acute leukemia. Two patients (12%) were thrombocytopenic, and one died of acute leukemia. There was little correlation between survival and platelet count. Sixty-three additional case reports of idiopathic sideroblastic anemia were collected from the literature. Analysis of those patients and the patients in the present study documented transformation to acute leukemia in 5 of 9 (56%) thrombocytopenic patients, 4 of 54 (7.4%) thrombocytopenic patients, and of 17 patients with thrombocytosis (p < 0.05). Therefore patients with idiopathic sideroblastic anemia and thrombocytosis appear to have a decreased likelihood of leukemic transformation.

Although Dameshek believed erythroleukemia and acute myeloblastic leukemia to be inevitable outcomes for all patients with idiopathic refractory sideroblastic anemia,1,2 the literature would support a much lower incidence of transformation to leukemia. Kushner et al. noted 7 patients with acute leukemia out of 94 with sideroblastic anemia reported in the literature, an overall incidence of 7.4%.3 They concluded that idiopathic refractory sideroblastic anemia was not inevitably a preleukemic process, but that a small subset of patients with idiopathic refractory sideroblastic anemia were likely to develop leukemic transformation subsequently.

A means of identifying those patients with idiopathic refractory sideroblastic anemia who are at high or low risk of conversion to erythroleukemia or acute myeloblastic leukemia would be of prognostic value to physicians and patients. Since we have recently seen several patients with idiopathic refractory sideroblastic anemia and associated thrombocytosis, we have studied the clinical courses of patients with idiopathic sideroblastic anemia at this medical center. In reviewing our cases and those in the literature we find that an increased platelet count is less frequently associated with conversion of the disorder to acute leukemia than is a decreased or a normal platelet count.

MATERIALS AND METHODS

Twenty-three patients with sideroblastic anemia were seen by members of the Hematology-Oncology Division of Washington University School of Medicine between 1963 and 1976. Sideroblastic anemia was defined as anemia with large numbers of ringed sideroblasts in marrow aspirates. In addition, all had increased marrow iron stores, and many had megaloblastic changes in the bone marrow. Five patients were excluded due to a history of ingestion of drugs known to produce sideroblastic anemia, a simultaneous malignancy, or lack of follow-up information. One
patient was excluded due to splenectomy, which raised the platelet count. The remaining 17 patients were all refractory to treatment with vitamin $B_12$ or folic acid, or had normal blood concentrations of vitamin $B_12$ and folic acid. All patients were refractory to pyridoxine, and most to anabolic steroids.

Platelet counts were performed by the method of Brecher and Cronkite, and were reviewed. Since other factors (e.g., secondary folic acid deficiency) may sporadically lower the platelet count, the highest recorded platelet count was related to the subsequent clinical course. A platelet count of 500,000 or above was defined as thrombocytosis. Patients with thrombocytosis had elevated platelet counts on multiple occasions.

**RESULTS**

The data obtained are summarized in Table 1. The median survival of the 17 patients was 5 yr from onset of the anemia. Of the 17 patients studied, 6 (35.5%) had platelet counts above 500,000 at the initial presentation or during the course of their disease. Patients in this subgroup included 4 men and 2 women with a mean age at onset of 55 yr, compared to a mean age of the total group of 64 yr. The mean duration of disease was 8.5 yr, and 4 of 6 patients were alive at the time of analysis. None have developed leukemia, although 1 patient developed adenocarcinoma of the rectum 3 yr after diagnosis of anemia and thrombocytosis.

Of the 17 patients, 2 (11.8%) were thrombocytopenic. The mean age at onset was 69 yr. Neither is living; the survival after diagnosis of anemia was 1 yr in both instances. One patient died of acute myeloblastic leukemia 10 mo after the diagnosis of sideroblastic anemia.

The remaining 9 patients (53%) had platelet counts between 150,000 and 500,000. There were 6 women and 3 men. All have died, 2 with solid tumors and 1 of acute myeloblastic leukemia. The mean age at onset of sideroblastic anemia in this group was 70 yr, and the mean duration of illness was 5.7 yr.

A correlation between platelet count and survival was attempted. Linear regression analysis revealed only a weak association between the two ($r = 0.57$). Patients with higher platelet counts tended to live longer, but the onset of anemia was at a mean age of 55 yr versus 70 yr in other patients. Since the correlation was weak, it is likely that other factors are more important in determining survival. The causes of death listed in Table 1 support that conclusion.

Two patients (11.8%) developed acute leukemia. Brief case histories of these patients are presented below:

Patient 7 was a 61-yr old white man referred in July 1970 for evaluation of chronic anemia. His hematocrit was 29%, and the platelet count was 435,000 cells/cu mm. A bone marrow aspirate and biopsy showed large numbers of ringed sideroblasts, but less than 5% myeloblasts. Serum $B_12$ and folic acid contents were normal. Pyridoxine and anabolic steroids were given without therapeutic effect. In July 1973 he developed increased weakness. The hematocrit had decreased to 15%, the white blood cell count was 3600 cells/cu mm, and the platelet count was 85,000 cells/cu mm. A repeat bone marrow aspirate showed increased numbers of myeloblasts. In September 1973 his platelet count decreased further to 4000 cells/cu mm. A third bone marrow at this time showed progressive accumulation of myeloblasts. The patient received blood transfusions as his only therapy, and died 12 mo later of acute myocardial infarction.
### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Onset (yr)</th>
<th>Sex</th>
<th>Highest Platelet Count (cells/cu mm)</th>
<th>Survival Years</th>
<th>Transition to Leukemia</th>
<th>Other Malignancies</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>1,550,000</td>
<td>3+</td>
<td>—</td>
<td>Living; adenocarcinoma of rectum 3 yr after diagnosis of anemia</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>M</td>
<td>1,515,000</td>
<td>8</td>
<td>—</td>
<td>—</td>
<td>Dead; hemosiderosis, thromboembolism</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>M</td>
<td>1,461,500</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>Dead; pleural effusion, uremia</td>
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<tr>
<td>4</td>
<td>50</td>
<td>F</td>
<td>1,060,000</td>
<td>16+</td>
<td>—</td>
<td>—</td>
<td>Living, increasing transfusion requirements</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>F</td>
<td>845,000</td>
<td>10+</td>
<td>—</td>
<td>—</td>
<td>Living, stable course</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>M</td>
<td>610,000</td>
<td>2+</td>
<td>—</td>
<td>—</td>
<td>Living, stable course</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>M</td>
<td>435,000</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>Leukemia, 3 yr after diagnosis of anemia</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>F</td>
<td>400,000</td>
<td>17</td>
<td>—</td>
<td>—</td>
<td>Dead; metastatic adenocarcinoma of breast</td>
</tr>
<tr>
<td>9</td>
<td>78</td>
<td>M</td>
<td>370,000</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>Dead; arteriosclerotic heart disease</td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>F</td>
<td>370,000</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>Dead; no autopsy, organic brain syndrome</td>
</tr>
<tr>
<td>11</td>
<td>60</td>
<td>F</td>
<td>365,600</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>Dead; congestive heart failure, no autopsy</td>
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<tr>
<td>12</td>
<td>76</td>
<td>F</td>
<td>320,000</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>Dead; malignant melanoma of vulva ½ yr after diagnosis of anemia</td>
</tr>
<tr>
<td>13</td>
<td>78</td>
<td>M</td>
<td>318,000</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>Dead; pneumonia</td>
</tr>
<tr>
<td>14</td>
<td>78</td>
<td>F</td>
<td>225,000</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>Dead; no autopsy</td>
</tr>
<tr>
<td>15</td>
<td>69</td>
<td>F</td>
<td>195,000</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>Dead; congestive heart failure</td>
</tr>
<tr>
<td>16</td>
<td>64</td>
<td>F</td>
<td>98,000</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>Dead; hepatitis</td>
</tr>
<tr>
<td>17</td>
<td>74</td>
<td>M</td>
<td>69,000</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>Leukemia 6 mo after diagnosis of anemia</td>
</tr>
</tbody>
</table>

Patient 17 was a white 74-yr-old man seen in November 1968 for evaluation of refractory anemia. His hematocrit was 25%, the white blood cell count was 4900 cells/cu mm, and the platelet count was 63,000 cells/cu mm. A bone marrow aspirate showed large numbers of ringed sideroblasts but only 2% myeloblasts. Pyridoxine was given without response. In May 1969 his hematocrit was 28%, white blood cell count 5600 cells/cu mm, and platelet count 40,000 cells/
cu mm. A bone marrow aspirate showed a left shift in the myeloid series with 25%, myeloblasts. There was erythroid hyperplasia with multinucleated erythroid precursors. No therapy was given. Two months later he developed pneumonia, and after a complicated hospitalization he died in September 1969.

Because of the small number of patients included in this series, case reports and other small series from the literature were reviewed to determine the incidence of leukemic transformation in patients with low, normal, or high platelet counts. Only case studies of patients with primary idiopathic sideroblastic anemia were considered (Table 2). The results indicated a statistically greater likelihood of developing leukemia in the persistently thrombocytopenic patient (p < 0.05 by χ² analysis).

Since patients with thrombocytosis in the present study were younger than other patients, case reports in the literature were analyzed for age distribution. The mean age (± 1 SEM) for patients with thrombocytosis was 57.6 ± 3.8 yr, for those with thrombocytopenia, 61.4 ± 2.3 yr, and for the rest, 65.7 ± 1.7 yr. These differences were not statistically significant. Mean leukocyte counts (± 1 SEM) of cases reported in the literature were 6830 ± 1000 for patients with thrombocytosis, 5530 ± 860 for patients with normal platelet counts, and 3940 ± 750 for thrombocytopenic patients.

**DISCUSSION**

In this study, our small number of patients with idiopathic sideroblastic anemia and increased platelet counts did not show progression to acute leukemia. The survival of all the patients was weakly associated. The reason for this better prognosis was unclear. Kushner et al. have shown periodic requirements for blood transfusions to be the most unfavorable prognostic factor in sideroblastic anemia. However, all patients in the present study had moderate transfusion requirements, and there was no correlation between mean hemoglobin concentration or leukocyte count and platelet count (data not shown). The mean age of the patients with thrombocytosis was 55 yr, less than that of 70 yr in the other patients. It has been reported that more than 50% of deaths in idiopathic sideroblastic anemia are nonhematologic and are those normally ex-
pected in an elderly population. Only 4 of the 13 deaths in the present series were due to hematologic problems or complications.

It is of interest that in major reviews of thrombocytosis sideroblastic anemia has not been cited as a cause. Our finding of platelet counts in excess of 500,000 cells/cu mm in 35% of patients with sideroblastic anemia indicates an association which should be considered in the differential diagnosis of high platelet counts.

Kushner's review of patients with sideroblastic anemia who developed acute myeloblastic leukemia revealed little to distinguish them from other sideroblastic anemia patients. Wickramasinghe et al. noted large numbers of multinucleated erythropoietic cells in the bone marrow of patients with Di Guglielmo syndrome, while only occasional binucleate cells were seen in idiopathic sideroblastic anemia. In a study of the numbers of ringed sideroblasts in various hematologic and nonhematologic disorders, Bowman found 37%–77% ringed sideroblasts in the marrows of three patients with idiopathic refractory sideroblastic anemia as compared to 1%–4% in the marrows of patients with acute Di Guglielmo syndrome. However, the studies of Wickramasinghe et al. and Bowman distinguished patients with sideroblastic anemia and those who had already undergone transformation to erythroleukemia. Therefore, a prognostic value could not be assigned to multinuclearity or numbers of ringed sideroblasts.

Eastman et al. studied 15 patients with ineffective erythropoiesis, and grouped patients on the basis of hematologic and biochemical differences: one group with normal or increased platelet counts, bone marrow abnormalities limited to the erythroid series, and defective heme and globin synthesis; and a second group with pancytopenia, myeloid and megakaryocytic abnormalities, and normal hemoglobin synthesis. The first group of 12 patients showed no conversion to acute myeloblastic leukemia after a mean duration of 10.7 yr, while all three of the second group converted to acute myeloblastic leukemia. On examination of the marrow the latter group of three preleukemic patients had left shifts in the myeloid series and bizarre nuclear chromatin in the normoblasts.

All studies of sideroblastic anemia have consisted of small numbers of patients. While other studies of sideroblastic anemia have not emphasized platelet counts, a review of those case reports allowed a larger number of patients to be tabulated to determine the prognostic significance of the platelet count more accurately. The data demonstrated no progression to acute leukemia in patients with increased platelet counts. In the reviewed series, patients with thrombocytosis were again slightly younger, although the difference was not statistically significant.

It is likely, from this small series of patients and the literature review, that patients with idiopathic sideroblastic anemia and thrombocytosis have a proliferative defect that is different from that which leads to acute leukemia.

REFERENCES


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