Natural History of Idiopathic Refractory Sideroblastic Anemia

By Mario Cazzola, Giovanni Barosi, Paolo G. Gobbi, Rosangela Invernizzi, Alberto Riccardi, and Edoardo Ascari

We analyzed the natural history of idiopathic refractory sideroblastic anemia (IRSA) in 37 patients studied between 1969 and 1986. Although erythroid abnormalities were prominent in all, 12 patients also showed involvement of the granulocytic and/or megakaryocytic cell lines, and nonrandom chromosomal aberrations were observed in five of 23 patients studied for such defects. Measurements of erythroid marrow function showed in most cases erythroid expansion with ineffective erythropoiesis. In seven patients, however, the erythroid activity was found to be inappropriately low for the degree of anemia. Transfusion dependence occurred in 26 of 37 cases. Iron overload was a common feature at presentation but produced clinical manifestations of hemochromatosis only in those patients who subsequently had a regular need for blood transfusions. Five patients progressed to bone marrow failure, and another five patients (two of whom had monosomy 7) evolved into acute nonlymphocytic leukemia (ANLL). The median survival was 72 months, with a high transfusion requirement, multilineage defects, and inappropriately low erythroid proliferation being associated with a poor prognosis. The most common causes of death were complications of iron overload and evolution into ANLL. We conclude that (a) the natural history of IRSA is characterized by an initial phase of erythroid hyperplasia and ineffective erythropoiesis, which is usually stable for many years but in a subset of patients may be followed by a phase of marrow failure with or without the later emergence of leukemic blasts; (b) peripheral blood counts, measurement of erythroid marrow function, and chromosomal analysis are useful for identifying subjects at risk of evolution into marrow failure or ANLL; and (c) IRSA patients with no need for blood transfusions are very likely to be long survivors, whereas those who become transfusion dependent are at risk of death from the complications of secondary hemochromatosis.

IDIOPATHIC REFRATORY sideroblastic anemia (IRSA) is a disorder of unknown etiology that occurs predominantly in older adults. Diagnostic features are ineffective erythropoiesis and ring sideroblasts, ie, erythroblasts with perinuclear iron granules representing iron-encrusted mitochondria. IRSA has recently been included in the group of myelodysplastic syndromes or preleukemic states, although in most instances it appears to be a condition involving only the erythroid line. The nature of IRSA has been a controversial subject. Some 20 years ago Dame-Shek" suggested that there is a spectrum of abnormal erythropoiesis that shades from acute nonlymphocytic leukemia (ANLL) with erythroid abnormalities to IRSA, a condition thought to be an early stage of erythroleukemia. In most subsequent studies, IRSA was found to be a benign disease with a median survival greater than 60 months and a low propensity for evolution into ANLL. In other studies, however, its clinical course appeared to be severe, with median survival not significantly different from those of other myelodysplastic syndromes such as refractory anemia with excess of blasts (RAEB) and chronic myelomonocytic leukemia.

Some of these discrepancies are likely due to the small numbers of patients studied and the different criteria used in defining IRSA. In the past 18 years we have had the opportunity of studying 37 patients with IRSA in a single institution. We felt that there was enough controversy in the literature to merit a detailed analysis of these cases to obtain deeper insight into the natural history of this condition.

MATERIALS AND METHODS

This report discusses 37 patients with IRSA studied by us at the Department of Internal Medicine, University of Pavia, Italy, between 1969 and 1984. Clinical follow-up was continued until June 1986, and none of the survivors were followed for less than 18 months.

Patient population. At the initial evaluation all patients admitted to our department with refractory anemia were subjected to bone marrow aspiration, and slides were prepared with Prussian blue stain preparations. The iron stains were interpreted according to the criteria of Hillman and Finch. An abnormal, ferritin-type sideroblast was defined as a normoblast with ten or more perinuclear iron granules encircling at least one third of the circumference of the nucleus. All in most instances it appears to be a condition involving only the erythroid line. The nature of IRSA has been a controversial subject. Some 20 years ago Dame-Shek* suggested that there is a spectrum of abnormal erythropoiesis that shades from acute nonlymphocytic leukemia (ANLL) with erythroid abnormalities to IRSA, a condition thought to be an early stage of erythroleukemia. In most subsequent studies, IRSA was found to be a benign disease with a median survival greater than 60 months and a low propensity for evolution into ANLL. In other studies, however, its clinical course appeared to be severe, with median survival not significantly different from those of other myelodysplastic syndromes such as refractory anemia with excess of blasts (RAEB) and chronic myelomonocytic leukemia.

Some of these discrepancies are likely due to the small numbers of patients studied and the different criteria used in defining IRSA.¹ In the past 18 years we have had the opportunity of studying 37 patients with IRSA in a single institution. We felt that there was enough controversy in the literature to merit a detailed analysis of these cases to obtain deeper insight into the natural history of this condition.

MATERIALS AND METHODS

This report discusses 37 patients with IRSA studied by us at the Department of Internal Medicine, University of Pavia, Italy, between 1969 and 1984. Clinical follow-up was continued until June 1986, and none of the survivors were followed for less than 18 months.

Patient population. At the initial evaluation all patients admitted to our department with refractory anemia were subjected to bone marrow aspiration, and slides were prepared with Prussian blue stain

From the Department of Internal Medicine and Medical Therapy, University of Pavia School of Medicine, Italy. Submitted February 13, 1987; accepted September 17, 1987. Supported by grants from the Italian National Research Council, Special Project "Oncology," Contract Nos. 86.00352.44 and 86.00549.44, and by the Italian Association for Cancer Research. Address reprint requests to Mario Cazzola, MD, Clinica Medica II, Policlinico S. Matteo, 27100 Pavia, Italy.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

© 1988 by Grune & Stratton, Inc.

From www.bloodjournal.org by guest on October 21, 2017. For personal use only.
Hematologic studies. Routine hematologic examinations were performed according to standard methods. The criteria of Juneja et al were used to grade the severity of dyserythropoiesis, dysgranulopoiesis, and dysthrombopoiesis. Leukocyte alkaline phosphatase scores were determined on peripheral blood leukocytes in 15 cases. Body iron status was evaluated by measuring plasma iron, total iron-binding capacity (all cases), and serum ferritin (19 cases) and by grading liver iron (15 cases).

Follow-up and treatment. After diagnosis, each patient was followed until death or for a median period of 39 months (range, 18 to 170 months). Thirty-two patients received a course of pyridoxine, 300 mg/d administered orally for a period of at least 3 months. Twenty-six patients also had a therapeutic trial of androgens for at least 6 months. Two different preparations were used: testosterone enanthate, 250 to 500 mg intramuscularly once weekly, and oxymetholone, 150 mg/d orally. In deciding whether to administer red cell transfusions, the main goal was to maintain the lowest hemoglobin level tolerated by the individual patient.

Chromosome analysis. Chromosomal analyses were performed on bone marrow aspirates and peripheral blood from 23 of 37 subjects with QFQ-and GTG-banding techniques. Most of them were done in Dr Marco Fraccaro’s laboratory at the University of Pavia School of Medicine. A few analyses were performed in other laboratories in Italy.

Ferrokinetic measurement of erythroid marrow function. Plasma iron turnover (PIT) was measured by standard methods and calculated by using the following formula:

\[ \text{PIT (mg/dL whole blood [wb]/d)} = \frac{\text{Pl (\mu g/dL)} \times 100 - \text{Hct} \times 0.9}{T_{1/2} \text{ (min)} \times 100} \]

where Pl is plasma iron and \( T_{1/2} \) is the plasma radioiron half-disappearance time.

Additional calculations were made to convert the PIT to the iron uptake by the erythron (erythron iron turnover [EIT]), which represents a measure of total erythropoietic activity. The following formula was used:

\[ \text{EIT (mg/dL Wb/d)} = \frac{\text{PIT (mg/dL wb/d)} - \left[ \frac{(\text{Pl (\mu g/dL)}}{100 - \text{Hct} \times 0.9)} \times 0.0035 \right]}{100} \]

In a study of 53 normal subjects taken as a normal reference group, EIT was found to be 0.50 ± 0.12 mg/dL whole blood/d. The relative rate of erythropoiesis was derived from the patient’s EIT divided by the mean normal EIT (0.50 mg/dL whole blood/d).

Statistical analyses. Details for each patient were put into a computer and analyzed as follows. Statistical analyses were performed with the statistical package MacSS (Statsoft, Tulsa, OK) run on a Macintosh 512k (Apple Computer, Inc, Cupertino, CA) personal computer. This package includes basic statistical analyses and advanced multivariate statistics. A number of biologic and clinical parameters were scrutinized to recognize those exhibiting a prognostic value for survival. These included: age; sex; hemoglobin concentration; WBC, neutrophil, and monocyte counts; platelet count; plasma iron; transferrin saturation; bilirubin concentration; EIT; ring sideroblast percentage; and transfusion requirement. Parameters with a continuous distribution were assayed both as binary variables by using different working levels and as continuous variables. The effect of each variable was first analyzed individually by estimating survival from the date of diagnosis by the Kaplan-Meier method and differences between survival curves by the log rank test. The scoring system of Mufti et al (Bournemouth score) was also evaluated for its capability of predicting disease outcome. A score of 1 is assigned for each of the following presenting features: (a) hemoglobin <10 g/dL, (b) neutrophils <2.5 x 10^9/L, (c) platelets <100 x 10^9/L, and (d) bone marrow blasts >5%. Bournemouth scores may range from 0 to 4. The final method of analysis was an exponential survival model. This method assumes that the survival time for each patient has a simple exponential distribution in which the scale parameter, ie, the average time to failure, depends on one or more concomitant variates. Preliminary investigations based on hazard plotting demonstrated that the exponential model was adequate to describe the survival of the patient population. A step-upward procedure was adopted in assessing the prognostic value of different parameters for length of survival. Each factor was first examined individually, and the one most strongly related to length of survival was selected. Next, the remaining parameters were added in turn to the first, and the one that most improved the prediction of survival or \( \Delta \) log likelihood was selected and added to the analysis. More variables were added until none of them could significantly improve the \( \Delta \) log likelihood (\( P > .05 \)).

RESULTS

Clinical and hematologic characteristics. The 37 patients ranged in age from 28 to 80 years (median value, 64) (Fig 1). Hematologic parameters are reported in Table 1. Anemia was macrocytic in 84% and hypochromic in 46% of cases. The reticulocyte index was generally decreased, which reflected a red cell output inappropriately low for the degree of anemia. Leukocyte and/or platelet counts were abnormal in ten of the 37 patients.

Body iron status at presentation. Plasma iron and transferrin saturation were simultaneously increased in 21 of 37 subjects, which suggested increased iron stores at their initial evaluation before any blood transfusion (Table 1). In accordance with this, 19 of 19 patients had elevated serum ferritin values, and 14 of 15 had increased stainable iron on liver biopsy specimens at clinical onset.

LAP score and bone marrow morphology. Values of leukocyte alkaline phosphatase (LAP) were abnormally low in five of 15 patients in whom the test was performed. Bone marrow examination showed increased cellularity and erythroid hyperplasia with dyserythropoiesis in 95% of cases;
by definition ring sideroblasts were present in all patients. Marked dysgranulopoiesis was observed in three of 37 subjects and marked dysthrombopoiesis in two of 37 subjects. Overall, 12 of 37 patients showed at least one quantitative (leukopenia, monocytois, thrombocytopenia, excess of blasts) or qualitative abnormality (low LAP score, marked dysgranulopoiesis, or dysthrombopoiesis) indicating involvement of the granulocytic and/or megakaryocytic cell lines.

Chromosomal abnormalities. Nonrandom abnormalities were found in five of 23 cases: three patients had trisomy 8, and two had monosomy 7 (see later) as sole abnormalities. The three individuals with trisomy 8 had isolated anemia without any evidence of other cell line involvement.

Erythroid marrow activity, transfusion dependence, and iron overload. Erythroid marrow activity, as estimated by EIT, ranged from normal to as high as 13.1 times basal (Fig 2). Anemia was found to be hypoproliferative (erythroid activity, less than three times basal) in seven of 37 patients. A regular need for transfusion at presentation or later was found in 26 of 37 patients: the remaining 11 individuals never needed RBC transfusions during the follow-up. As shown in Table 2, the nontransfused patients differed from the transfused ones in having higher values for hemoglobin, neutrophil count, and EIT at presentation. Within the group of

### Table 1. Hematologic Characteristics of the 37 Patients With URSA

<table>
<thead>
<tr>
<th></th>
<th>Geometric Mean (Range)</th>
<th>Normal Reference Range</th>
<th>No. of Patients With Values That Were Decreased</th>
<th>Normal</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>7.5 (4.0-11.9)</td>
<td>F, 12-16; M, 14-18</td>
<td>37/37</td>
<td>6/37</td>
<td>31/37</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>103 (86-125)</td>
<td>83-97</td>
<td>17/37</td>
<td>20/37</td>
<td></td>
</tr>
<tr>
<td>MCHC (g/dL)</td>
<td>31.7 (26.1-34.7)</td>
<td>32-36</td>
<td>33/37</td>
<td>3/37</td>
<td>1/37</td>
</tr>
<tr>
<td>Reticulocyte index (%)</td>
<td>0.4 (0.1-1.4)</td>
<td>0.7-1.3</td>
<td>8/37</td>
<td>28/37</td>
<td>1/37</td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td>5.1 (2.1-11.8)</td>
<td>4.0-10.0</td>
<td>4/37</td>
<td>33/37</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count (10^9/L)</td>
<td>2.6 (0.4-5.6)</td>
<td>1.5-7.5</td>
<td>36/37</td>
<td>1/37</td>
<td></td>
</tr>
<tr>
<td>Monocyte count (10^9/L)</td>
<td>0.2* (0-5.9)</td>
<td>0-1.0</td>
<td>5/15</td>
<td>10/15</td>
<td></td>
</tr>
<tr>
<td>LAP score</td>
<td>49 (8-164)</td>
<td>40-140</td>
<td>6/37</td>
<td>30/37</td>
<td>1/37</td>
</tr>
<tr>
<td>Platelet count (10^9/L)</td>
<td>206 (20-790)</td>
<td>150-450</td>
<td>8/37</td>
<td>24/37</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.0 (0.40-2.21)</td>
<td>0.3-1.0</td>
<td>1/37</td>
<td>15/37</td>
<td>21/37</td>
</tr>
<tr>
<td>Plasma iron (µg/dL)</td>
<td>162 (58-223)</td>
<td>65-100</td>
<td>5/15</td>
<td>32/37</td>
<td></td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>63 (19-93)</td>
<td>16-50</td>
<td>19/19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum ferritin (µg/L)</td>
<td>684 (390-1,550)</td>
<td>F, 15-170; M, 20-300</td>
<td>37/37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ring sideroblasts (%)</td>
<td>63 (24-91)</td>
<td>≤10</td>
<td>37/37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration.

*Median.

### Table 2. Comparison of IRSA Patients Without and With Regular Need for Transfusion at Presentation or Later

<table>
<thead>
<tr>
<th></th>
<th>No Need for Transfusion (n = 11), Geometric Mean (Range)</th>
<th>Regular Need for Transfusion (n = 26), Geometric Mean (Range)</th>
<th>Student’s t Test, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64* (46-80)</td>
<td>61* (28-78)</td>
<td>NS</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>9.0 (7.1-11.9)</td>
<td>6.9 (4.0-11.6)</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td>5.9 (3.6-8.7)</td>
<td>4.8 (2.1-11.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Neutrophil count (10^9/L)</td>
<td>3.3 (1.1-5.8)</td>
<td>2.4 (1.4-5.3)</td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>Platelet count (10^9/L)</td>
<td>240 (119-790)</td>
<td>186 (20-425)</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma iron (µg/dL)</td>
<td>167 (125-222)</td>
<td>159 (58-223)</td>
<td>NS</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>63 (46-93)</td>
<td>63 (19-93)</td>
<td>NS</td>
</tr>
<tr>
<td>EIT (mg/dL whole blood/d)</td>
<td>3.64 (2.29-6.56)</td>
<td>2.05 (0.41-5.41)</td>
<td>P &lt; .01</td>
</tr>
</tbody>
</table>

NS = not significant (P > 0.05).

Clinical parameters are those at presentation. Student’s t test for unpaired data were performed on original data after logarithmic transformation. *Median.
transfused subjects, the following clinical manifestations were recorded as complications during the follow-up: impaired oral glucose tolerance test response (14/26), diabetes (6/26), abnormal liver function (18/26), and cardiac failure (8/26). Two patients in whom congestive heart failure was present before the diagnosis of IRSA had increasingly severe cardiac failure in the follow-up and died 8 and 12 months after diagnosis. Overall, 22 of 26 patients had at least one of the aforementioned manifestation in their clinical course. Multiple regression analysis showed that these complications correlated with the number of units of blood transfused and the value for transferrin saturation at presentation (P < .02). Because these complications developed in individuals with laboratory evidence of iron overload, they were attributed to secondary hemochromatosis.

Response to treatment. Only six of 32 (19%) patients responded to vitamin B6 treatment with an increase in hemoglobin concentration greater than 2 g/dL. The mean pretreatment hemoglobin value was 8.0 ± 0.7 g/dL, and the mean peak value of 10.5 ± 0.6 g/dL under treatment was achieved in 1.5 to 3 months. In no case did erythrocyte values return to normal; erythroid morphological abnormalities (including ring sideroblasts) persisted, and all six subjects became unresponsive to treatment in the following 1 to 18 months (median, 6). A response to androgens was observed in two of 30 patients studied (7%), but the observed responses were temporary.

Clinical evolution. Twenty-four percent of patients had a stable course during the study, whereas worsening of anemia and an increased transfusion requirement were observed in 48%. Five patients progressed to bone marrow failure, and another five evolved into ANLL. All these ten individuals were transfusion dependent. Bone marrow failure was characterized by increasingly severe pancytopenia associated with decreasing bone marrow cellularity: bone marrow examination showed a progressive decrease in the number of red cell precursors and megakaryocytes with a relative increase in myeloid precursors.

Evolution into ANLL took place in 8 months to 4.5 years from presentation and was progressive in all five patients with steps of RAEB and RAEB in transformation. Only two of these subjects had excess of blasts in the bone marrow at clinical onset: two of the remaining three patients had a bicytopenia, one with monosomy 7. Two ANLL patients died of sepsis and one of cerebral hemorrhage before any chemotherapy. The remaining two patients had short, partial remissions with combination chemotherapy.

As shown in Table 3, values on presentation for EIT, hemoglobin content, neutrophil count, platelet count, plasma iron, and transferrin saturation were lower in patients who progressed to bone marrow failure or ANLL than in the remaining ones. The degree of erythroid proliferation appeared to correlate specifically with this unfavorable clinical outcome of the disease. In particular, all of the seven patients with EIT values less than three times basal (relative marrow failure) did show such an evolution (Fig 2).

Survival, prognostic factors, and causes of death. Figure 3A illustrates the survival of the 37 IRSA patients. Survival from diagnosis ranged from 8 to 170 months, with a median value of 72 months; 20% of patients died within 24 months of diagnosis. For comparison, the median survival of 32 patients with RAEB studied between 1971 and 1984 in our department was 17 months, ie, significantly shorter. Of 15 deaths, seven took place within 24 months of diagnosis. Heart failure was the cause of death in seven subjects, all of whom had clinical and biochemical evidence of secondary hemochromatosis: the median time from diag-

<table>
<thead>
<tr>
<th>Table 3. Comparison of IRSA Patients Without and With Progression to Bone Marrow Failure or ANLL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Progression (n = 27)</strong></td>
</tr>
<tr>
<td><strong>Geometric Mean (Range)</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
</tr>
<tr>
<td>WBC (10³/L)</td>
</tr>
<tr>
<td>Neutrophil count (10⁶/L)</td>
</tr>
<tr>
<td>Platelet count (10⁹/L)</td>
</tr>
<tr>
<td>Plasma iron (µg/dL)</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
</tr>
<tr>
<td>EIT (mg/dL whole blood/dL)</td>
</tr>
</tbody>
</table>

NS = not significant (P > .05). Clinical parameters are those at presentation. Student's t test for unpaired data were performed on original data after logarithmic transformation. *Median.
nosis to death was 24 months (range, 8 to 60). Five individuals died because of evolution into ANLL (median survival, 18 months; range, 8 to 54). The remaining three subjects died of sepsis, cerebral hemorrhage, and hepatic cirrhosis, respectively.

The simple scoring system of Mufti et al. proved to be a useful prognostic indicator (Fig 3B). For the patients scoring 0 to 1, 50% survival was not reached at 170 months; for those scoring 2 to 4, the median survival was 33 months, the difference being significant (P < .0001). Causes of death in the 0 to 1 score group were heart failure (three patients), cerebral hemorrhage (one patient) and ANLL (one patient). Causes of death in the 2 to 4 score group were heart failure (four patients), ANLL (four patients), sepsis (one patient), and hepatic cirrhosis (one patient). Within the 2 to 4 score group, six individuals had extended survival (>3 years); they had hemoglobin values <10 g/dL (6/6), neutrophil counts from 1.1 to 2.3 × 10^9/L (5/6), and excess of blast in the bone marrow (2/6). One of these subjects died of sepsis as a complication of progressive neutropenia; transfusion dependence was the major problem in the other five subjects.

Table 4 shows the estimation of exponential survival probabilities as a function of clinical and biochemical variables. High transfusion requirement was the most important predictor. Peripheral cytopenia, low erythroid proliferation, and iron overload at presentation were further independent prognostic factors. The addition of EIT, plasma iron, and transferrin saturation to transfusion requirement significantly improved the Δ log likelihood. Low erythroid proliferation and evidence of iron overload at presentation increased the hazard and significantly reduced the survival. The adjunctive effect of other variables was not statistically significant.

**Patients with ring sideroblasts and excess of blast in the bone marrow.** Five individuals had 7% to 18% blasts within the nonerythroid cells in the bone marrow; their ring sideroblast count at presentation ranged from 24% to 80% (median value, 50%). Two evolved rapidly into RAEB in transformation and ANLL and survived 8 and 11 months, respectively. The remaining three had longer survival times. A 63-year-old woman had 6% to 8% marrow blasts at clinical onset, no chromosomal aberration, and isolated anemia (hemoglobin, 10.2 g/dL): she has survived 170+ months, had a stable clinical course with no need for transfusion during the first 140 months, and her condition evolved into bone marrow failure in the last 30 months. A 71-year-old woman had a similar clinical picture and has survived 117+ months without any need for blood transfusion. Finally, a 70-year-old female had pancytopenia with 45% ring sideroblasts and about 10% blasts within the nonerythroid cells in her bone marrow; she has survived more than 65 months. Over the last 12 months, she developed a high transfusion requirement (4 units every 4 weeks) and increasingly severe granulocytopenia and thrombocytopenia. The last bone marrow examination showed decreased numbers of red cell precursors and megakaryocytes with a relative increase in the number of myeloid precursors (about 25% blasts).

Exclusion of these patients from analysis of survival did not substantially modify the results. The median survival of 32 IRSA patients having <5% marrow blasts was 72 months, ie, identical with that of whole group, and analysis of prognostic factors provided results very close to those reported in Table 4.

**IRSA with monosomy 7.** A distinct clinical picture was noted in two patients with IRSA and monosomy 7. The first one, who has been previously reported, presented with anemia, hypocellular bone marrow with relative erythroid hyperplasia, 35% ring sideroblasts, 1% marrow blasts, and monosomy 7 in all the examined marrow metaphases. He developed ANLL 20 months later. The second patient presented with peripheral pancytopenia, hypocellular bone marrow with 15% blasts and 60% ring sideroblasts, and monosomy 7 in all the examined marrow metaphases. He died of ANLL 11 months later. Both patients had a clinical course characterized by recurrent infections due to defective neutrophil chemotaxis, the appearance of myeloproliferative features, and progressive evolution into ANLL.

**IRSA with dermal photosensitivity and greatly increased erythrocyte protoporphyrin.** IRSA was found in an elderly man who had a history of dermal photosensitivity. Exposure to sunlight produced severe burning, erythema, and edema of the exposed skin. On admission, his hemoglobin content was 7.6 g/dL, and the free erythrocyte protoporphyrin value was 1,055 μg/dL of whole blood. Ring sideroblasts represented 80% of all erythroblasts. Values for urinary excretion of δ-aminolevulinic acid, porphobilinogen, uroporphyrin, and coproporphyrin were normal. The combination of clinical and biochemical findings in this patient could probably be
explained by a defect in heme synthetase. Three similar cases have been already reported in detail.28-30

DISCUSSION

In a recent annotation, Jacobs31 concludes that IRSA is a myelodysplastic syndrome and represents a clonal abnormality in the hematopoietic stem cell that is characterized by a very specific phenotypic abnormality in which the characteristic mitochondrial changes are accompanied by ineffective erythropoiesis in the bone marrow and grossly ineffective erythropoiesis. The clonal nature of IRSA has been well demonstrated in a case report by Prchal et al using the genetic marker glucose-6-phosphate dehydrogenase (G-6-PD). Further support has been provided by the report of acute lymphoblastic leukemia as the terminal evolution of a case of IRSA and the finding of nonrandom chromosomal abnormalities in some patients.32-34

One third of IRSA patients in this study had evidence of involvement of other cell lines at presentation and ten of 37 later evolved into bone marrow failure or ANLL, which suggests that IRSA is not a pure erythroid disorder. Many hematologists, however, define IRSA as a refractory anemia with ring sideroblasts and no minimal dysplasia in the other cell lines. The rationale of our patient selection, however, becomes clear by examining the case of IRSA studied by Prchal et al.32 This 67-year-old black female was heterozygous for G-6-PD isozymes A and B and had a typical sideroblastic anemia with no dysplasia in the other cell lines. The G-6-PD isozyme analysis of the erythrocytes, granulocytes, macrophages, platelets, and B and T lymphocytes demonstrated the presence of only isozyme A, whereas the skin fibroblasts and salivary epithelial cells contained both isozyme A and B. Thus, not only erythroid progenitors but also myeloid and megakaryocytic progenitors were clonal and by inference abnormal. The difference was at the phenotypic level; myeloid and megakaryocytic progenitors were still capable of differentiating into morphologically and quantitatively normal leukocytes and platelets, whereas, erythroid maturation was less efficient. Presumably, a further genetic change in this woman could result in the appearance of dysgranulopoiesis and/or dysthrombopoiesis in accordance with the general model of multistep pathogenesis that has been suggested also for the myelodysplastic syndromes.35 The most controversial point in our patient selection was the inclusion of patients with excess of blasts together with ring sideroblasts (five patients). Juneja et al36 have classified such cases as RAEB, and Yoshida et al37 have shown that with respect to survival they are more comparable to RAEB than IRSA. An unanswered question, however, is whether these patients may be in a transitional state from IRSA to RAEB in accordance with the aforementioned multistep pathogenesis.38 Because our aim was to define the natural history of IRSA, we had to include these patients in our analysis. The results obtained suggest that an excess of blasts is likely to represent an unfavorable prognostic factor in IRSA patients, although similar subjects who have only anemia and no need for blood transfusions may survive several years.

There have been only occasional reports of aplasia as a complication of IRSA.4 Progression from typical ineffective erythropoiesis to eventual complete failure of red cell production has been described by Singh et al.36 This was confirmed in our study because the need for blood transfusions was associated with lower proliferative activity of the erythroid marrow (Table 2). In a few cases, there was also a failure in leukocyte and platelet production, i.e., bone marrow failure. It should be noted that an association between clonal hematopoietic proliferation and hypoplastic anemia has been reported.39 Clonal progenitors may both completely suppress the expression of normal progenitors and gradually lose their capacity to proliferate and differentiate, thus producing a switch from ineffective erythropoiesis to marrow hypoplasia.

The incidence of leukemic transformation in our study is in agreement with published observations indicating that approximately 10% of IRSA patients have subsequent leukemic evolution. Most of those who develop leukemia survive less than 4 months, although better results have been recently reported with current combination chemotherapy.40 A number of disease characteristics appeared to be helpful in predicting the outcome of IRSA and identifying high-risk patients (Table 3 and 4). The simplest prognostic marker was provided by peripheral blood findings. multilineage defects were associated with a poor prognosis, which suggests that when IRSA is phenotypically expressed also in the myeloid and megakaryocytic progeny the risk of bone marrow failure or ANLL is higher. An important practical aspect is that the scoring system of Mufti et al39 was able to discriminate between low-risk and high-risk patients (Fig 3B).

A second indicator of disease course found was the degree of erythroid marrow proliferation, as provided by the measurement of EIT. Most patients had high values for EIT, which indicated an expanded erythroid marrow under the stimulus of erythropoietin. Some patients, however, had normal or nearly normal values for EIT (less than three times basal) in the presence of anemia. This picture is called relative marrow failure and indicates a reduced ability of the erythroid marrow to proliferate under the stimulus of anemia.41 Because the iron supply to the erythron and presumably erythropoietin production were adequate in these patients, relative marrow failure likely reflected a defect in the stem cell compartment. The results obtained suggest that the more impaired the erythroid proliferation, the greater the propensity for bone marrow failure and/or leukemic transformation and the worse the prognosis. In accordance with this conclusion, Jacobs and Clark42 have found that the degree of erythroid proliferation seen in the initial marrow aspirates of patients with myelodysplastic syndrome was related to prognosis, those with erythroid hyperplasia having the longest survival. We want to emphasize that the ferrokinetic measurement of erythroid marrow function can be carried out in a few hours in a clinical setting.19,43

Although chromosomal abnormalities were found in only a minority of cases, these disease characteristics potentially appeared another prognostic marker. Monosomy 7 was associated with leukemic evolution in two cases, whereas trisomy

From www.bloodjournal.org by guest on October 21, 2017. For personal use only.
8 was found in three subjects with subsequent long survival (125+, 92+, and 32+ months) without leukemic transformation. This is in keeping with recent findings obtained by Yunis et al.10 using refined chromosomal analysis (high-resolution chromosome banding). In their study, patients diagnosed as having IRSA with normal chromosomes had a highly favorable prognosis and stable clinical course. In contrast, patients with IRSA and monosomy 7, deletion 20q, or complex defects had a high-grade disease with survival of less than 1 year.

A common feature of the natural history of IRSA in our patients was the worsening of anemia with a consequent need for blood transfusions sooner or later. Iron overload was present in nearly all patients at presentation, but it became clinically manifested only in those who received blood transfusions, and clinical manifestations correlated with both initial transferrin saturation and the number of units of blood transfused. This indicates that, although there was iron loading through increased iron absorption due to erythroid expansion,14 transfusion iron loading was the main factor in the development of hemochromatosis in these patients. Widespread organ dysfunction has been found to occur in most adult patients with acquired anemia and transfusion dependence after accumulation of iron from about 100 units of blood.15 It is likely to become clinically manifested earlier in patients with IRSA due to the increased PIT, which produces active reticuloendothelial iron release and predominantly parenchymal iron overload.14 Because hemochromatosis in IRSA shortens the median survival, patients who need regular blood transfusions, or at least those who would otherwise have a good prognosis, should be given iron chelation therapy.

Although IRSA is a heterogeneous condition, its natural history as outlined by this study is in agreement with the model proposed by Jacobs and Clark12 to describe the progression of the myelodysplastic syndromes. The initial phase of IRSA, which in many patients is stable for several years, is characterized by erythroid hyperplasia and ineffective erythropoiesis with no or minimal phenotypic involvement of the other cell lines. Patients with stable disease and no need for blood transfusions are very likely to be long survivors. The proliferative activity of the erythroid marrow, however, tends to decrease with time, which leads to appearance of a need for blood transfusions. A subset of patients who usually have evidence of other cell line involvement at presentation may develop bone marrow failure with or without the emergence of blast cells and final evolution into ANLL.

REFERENCES

Refractory cytopenias: Clinical course according to bone marrow cytology and cellularity. Blut 54:153, 1987
Natural history of idiopathic refractory sideroblastic anemia

M Cazzola, G Barosi, PG Gobbi, R Invernizzi, A Riccardi and E Ascari

Updated information and services can be found at:
http://www.bloodjournal.org/content/71/2/305.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml