Low Blast Count Myeloid Disorders With Auer Rods

A Clinicopathologic Analysis of 9 Cases

Monte S. Willis, MD, PhD, Robert W. McKenna, MD, LoAnn C. Peterson, MD, James E. Coad, MD, and Steven H. Kroft, MD

Key Words: Refractory anemia with excess blasts; RAEB-2; RAEB-T; Auer rods; Myelodysplastic syndrome; Acute myelogenous leukemia

DOI: 10.1309/WB79MFV6FCDJH2EG

A b s t r a c t

Auer rods are a hallmark of acute myeloid leukemia but occasionally are seen in myelodysplastic syndromes (MDSs) or chronic myelomonocytic leukemia, rarely in cases with fewer than 5% blasts. The significance of this finding is unclear. We report 9 cases of this unusual phenomenon. All patients had cytopenias, isolated to a single lineage in 4. Circulating blasts were present in 8 cases (rare to 2.5%). Bone marrow blasts ranged from 0.4 to 4.9%; 1% to 32% of blasts contained Auer rods. There were variable degrees of dysplasia; 1 case closely mimicked refractory anemia with ringed sideroblasts. Cytogenetic studies in 8 cases showed clonal changes in 4. In 5 patients, acute myelogenous leukemia (AML) developed 6, 6, 5, 13, and 24 months after diagnosis; the patients subsequently died. Three patients died at 1, 1, and 8 months without progression to AML, and only 1 was alive at 10 months. MDSs with fewer than 5% blasts and Auer rods seem to be a heterogeneous group, but rapid progression to death or AML in most cases suggests that Auer rods signify an aggressive biology in MDSs with a low blast count.

The presence of Auer rods in myeloid blasts commonly is considered a hallmark of acute myeloid leukemia. However, classification schemes have permitted the presence of Auer rods in some forms of myelodysplastic syndrome (MDS) or related disorders. Specifically, in the French-American-British (FAB) classification, Auer rods may be present in refractory anemia with excess blasts in transformation (RAEB-T), and in the recent World Health Organization (WHO) classification, they may be seen in RAEB type 2 (RAEB-2) and in chronic myelomonocytic leukemia type 2 (CMML-2). In fact, the mere presence of Auer rods is sufficient for the diagnosis of these entities, regardless of the blast count. This is based on the assumption that Auer rods indicate a more aggressive disease when present in the setting of an MDS, although there are few data to support this view.

Within the WHO scheme, the large majority of MDS cases containing Auer rods would otherwise fall into the RAEB-1 or RAEB-2 categories based on blast count. However, rare cases of MDS or CMML are encountered in which Auer rods are present but the blast count is less than 5%. The significance of this phenomenon is unknown. We herein report the clinicopathologic features of 9 such cases.

Materials and Methods

We identified 9 cases of MDS with fewer than 5% blasts with Auer rods by searching the files of the University of Texas Southwestern Medical Center (Dallas), Northwestern University Medical Center (Chicago, IL), and West Virginia University (Morgantown). Clinical, pathologic, and laboratory data were reviewed for all cases.
Bone marrow core specimens were fixed in B-5 or 10% neutral buffered formalin, washed, decalcified, and processed. Paraffin-embedded sections of the core biopsy (4-µm sections) were stained with H&E. Direct smears, particle crush, buffy coat, and touch preparations were prepared and stained with Wright or Wright-Giemsa and Prussian blue stains as previously described.4,5

Differential cell counts were performed on peripheral blood (minimum of 200 cells) and bone marrow (500 cells) specimens. In addition, the percentage of marrow blasts containing Auer rods was assessed in 100 consecutive marrow blasts.

Dysplasia in the peripheral blood and bone marrow was graded in each myeloid lineage by 3 observers (M.S.W., R.W.M., and S.H.K.) at a multiheaded scope as follows: absent or nonspecific, mild, moderate, or severe. Nonspecific changes were of the sort commonly encountered in patients without primary marrow abnormalities, eg, mild anisocytosis and occasional nonspecific poikilocytes, such as elliptocytes or target cells; mild megaloblastoid changes in erythroid precursors such as may be seen in states of increased RBC turnover or with commonly administered drugs; and mild abnormalities of nuclear segmentation in association with toxic neutrophil changes.

Mild, moderate, and severe changes were defined based on quantitative and qualitative criteria. For example, mild dysplasia could constitute mild cytologic changes seen in a substantial minority (eg, one third to one half) of the cells of a given lineage or moderate cytologic changes seen in fewer than one third of cells. Similarly, moderate dysplasia could constitute mild cytologic changes in the majority of cells, moderate cytologic changes in a substantial minority of cells, or severe cytologic changes in a smaller minority. A designation of severe dysplasia would be applied when moderate changes affected the majority of cells or severe changes affected a substantial minority. Cytologic changes considered to be dysplastic were as described in the WHO classification.6 The grading of the severity of such changes in a given cell was by necessity subjective. Ringed sideroblasts were defined according to the WHO criteria.6

**Results**

The 9 patients included 6 males and 3 females, ages 8-79 years (median, 58.6 years). All patients had cytopenias: 3 with isolated anemia, 1 with anemia and thrombocytopenia, 1 with leukopenia and thrombocytopenia, 1 with isolated thrombocytopenia, and 3 with pancytopenia ([Table 1](#Table1)).

**Peripheral Blood Findings**

In the peripheral blood, small numbers of blasts were identified in 8 of 9 patients (rare to 2.5%) ([Table 1](#Table1)), and Auer rods were identified in peripheral blood blasts in 6 patients. Small numbers of circulating immature granulocytes were seen in 5 patients (metamyelocytes and myelocytes), and monocytosis was present in 2 patients (case 7, 1,200/µL [1.2 × 10³/µL]; case 9, 3,440/µL [3.44 × 10⁹/L]). No eosinophilia or basophilia was identified in any patient. Of the 9 cases, 7 demonstrated granulocyte dysplasia (4 mild, 3 moderate), and 3 showed platelet dysplasia (2 mild, 1 moderate) ([Table 2](#Table2)). Eight cases had mild or moderate anisopoikilocytosis, with dacrocyes in 6 and RBC dimorphism in 1 (case 3). Examples of the peripheral blood findings are illustrated in ([Image 1](#Image1)). Case 9 manifested no evidence of peripheral blood dysplasia in any lineage.

**Bone Marrow Findings**

Between 0.4% and 4.9% bone marrow blasts were identified in bone marrow aspirates, and 1% to 32% of the blasts contained Auer rods (median, 11%) ([Table 3](#Table3)). Of the 9 patients, 6 had hypercellular bone marrow samples, 2 hypocellular, and 1 normocellular. The myeloid/erythroid ratio was normal in 6 cases; in 2 cases it was increased, and in 1 case it was decreased ([Table 3](#Table3)). Bilineage dysplasia was identified in 4 cases, pandysplasia in 3, and unilineage...
dysplasia in 2 cases. The unilineage dysplasia in case 3 was characterized by mild erythroid dysplasia, dimorphic erythrocyte morphologic features in the blood, and 25% ringed sideroblasts. No more than moderate dysplasia was identified in the erythroid and granulocytic lineages in any case. In the 7 cases with multilineage dysplasia, 5 showed the most prominent changes in the megakaryocytic lineage (Image 2). Iron stains were performed in 7 cases, and increased storage iron was identified in 4, whereas decreased or absent storage iron was seen in 2. Two patients had ringed sideroblasts: 25% of the erythroid precursors in case 3 (Image 3) and occasional in case 5.

**Table 2**
Grading of Peripheral Blood Dysplasia in Initial Blood Smears

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Granulocyte Dysplasia</th>
<th>RBC Dysplasia (Anisopoikilocytosis)</th>
<th>Platelet Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Mild</td>
<td>Absent or nonspecific</td>
</tr>
<tr>
<td>3</td>
<td>Absent or nonspecific</td>
<td>Mild</td>
<td>Absent or nonspecific</td>
</tr>
<tr>
<td>4</td>
<td>Mild</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>5</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Absent or nonspecific</td>
</tr>
<tr>
<td>6</td>
<td>Moderate</td>
<td>Mild</td>
<td>Absent or nonspecific</td>
</tr>
<tr>
<td>7</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Absent or nonspecific</td>
</tr>
<tr>
<td>8</td>
<td>Moderate</td>
<td>Absent or nonspecific</td>
<td>Absent or nonspecific</td>
</tr>
<tr>
<td>9</td>
<td>Absent or nonspecific</td>
<td>Absent or nonspecific</td>
<td>Absent or nonspecific</td>
</tr>
</tbody>
</table>

**Image 2** Peripheral blood findings. A (Case 5), Moderate anisopoikilocytosis with dacrocyes and ovalocytes, dysplastic neutrophil (inset, lower right), and a circulating blast (inset, upper right) (Wright-Giemsa, original magnification ×165; insets, Wright-Giemsa, original magnification ×330). B (Case 7), Neutrophil dysplasia (Wright-Giemsa, original magnification ×330). C (Case 7), Circulating blast containing an Auer rod (Wright-Giemsa, original magnification ×330).
Cytogenetics, International Prognostic Scoring System Scores, and Clinical Course

Cytogenetic studies were performed successfully on the bone marrow samples in 8 cases: 4 had normal karyotypes only and 4 had clonal abnormalities, all of which were intermediate-risk abnormalities. An International Prognostic Scoring System (IPSS) score was calculated for the 8 patients with successful cytogenetic studies. A score of 0 (low risk) was found in 3 patients and a score of 0.5 to 1.0 (intermediate-1 risk) was found in 5 (Table 4).

Clinical follow-up information is provided in Table 4. In cases 2, 3, 7, and 9, the disease progressed to acute myeloid leukemia (AML) 6, 6, 5, and 13 months, respectively, after initial examination. One patient (case 2) died 4 months after the AML diagnosis and 3 months after allogeneic bone marrow transplantation, and 3 patients (cases 3, 7, and 9) died 10, 7, and 2 months, respectively, after the AML diagnosis and conventional chemotherapy. One patient (case 5) underwent allogeneic transplant 10 months after diagnosis, the disease progressed to AML 14 months later, and the patient died 1 month after transformation. Death occurred at 7, 1, and 4 months after diagnosis without progression to AML in cases 1, 4, and 6, respectively. Only 1 patient (case 8) was alive 10 months after diagnosis with stable disease (Table 4).

Discussion

Although Auer rods are an accepted feature of some MDSs, their biologic and clinical significance in this setting are unclear. In the original description of RAEB in 1976, the FAB group suggested that the presence of Auer rods correlated with prognosis. Later, the FAB defined RAEB-T as 20% to 29% blasts in the bone marrow and/or 5% to 29% blasts in the peripheral blood and/or the presence of Auer rods in the blasts, together with morphologic evidence of dysplasia. This category was created to identify patients believed to have a shorter clinical course and/or a higher probability of evolution to AML. The allowance for Auer rods in MDS represented a significant deviation from the prevailing opinion at the time that Auer rods represented AML, regardless of blast count.

The current WHO guidelines define RAEB as an MDS with 5% to 19% myeloblasts in the bone marrow and further divide this category into RAEB-1 (5%-9% blasts in the bone marrow and <5% blasts in the peripheral blood) and RAEB-2 (10%-19% blasts in the bone marrow and/or 5%-19% blasts in the peripheral blood and/or the presence of Auer rods). RAEB-T is not recognized in this scheme because cases with 20% blasts or more are considered AML. CMML is no longer classified by the WHO as an MDS (as it was in the FAB classification), but rather as a myelodysplastic/myeloproliferative disease. Nevertheless, the WHO subdivides CMML into types 1 and 2 according to a scheme nearly identical to that used for RAEB.

Seymour and Estey studied the prognostic significance of Auer rods in MDS classified according to the FAB scheme. These authors identified Auer rods in 33% of 208 patients with RAEB-T. Of these, 42% contained fewer than 20% marrow blasts (and, thus, were classified as RAEB-T on the basis of the presence of Auer rods) and 58% contained 20% to 29% blasts. These investigators found that patients with RAEB-T with Auer rods (regardless of blast count) had a higher incidence of
diploid karyotypes and a lower incidence of adverse cytogenetic abnormalities than RAEB or Auer rod–negative RAEB-T cases. The group with Auer rods also demonstrated a superior overall survival compared with Auer rod–negative RAEB-T, even within groups defined by similar cytogenetic abnormalities. However, among patients who did not receive AML induction therapy, Auer rod–positive RAEB-T cases progressed to AML (defined as ≥30% blasts) at a higher rate than those with Auer rod–negative RAEB-T (58% vs 34%). This increase was due primarily to the high rate of transformation seen in patients with Auer rods with more than 20% blasts (which would be classified as acute leukemia in the WHO scheme). These results also were confounded by the inclusion of patients with inv(16) or t(8;21) in the Auer rod–positive group. Finally, when Auer rod–positive cases with fewer than 20% blasts were compared with RAEB cases, the former also were found to have a better overall survival.

Another study of 52 patients with RAEB-T investigated outcomes with or without therapy. Of these patients, 44% met the criterion of RAEB-T based on the detection of Auer rods alone. Differences in overall survival were not identified based on Auer rods, but better survival was seen in patients with Auer rods when the analysis was limited to patients older than 45 years who received induction therapy.

The vast majority of cases of MDS with Auer rods in the WHO scheme would qualify as RAEB-1 or RAEB-2 based on blast counts. However, rare cases of patients with Auer rods and fewer than 5% bone marrow blasts are encountered. The
cases detailed in the present study seem to be a heterogeneous group based on morphologic features, cytogenetics, and clinical course.

All of our patients fell into the low or intermediate-1 IPSS groups; this is similar to the findings of Nangia et al. This result is, of course, not surprising, given that the marrow blast count is a factor in the calculation of the IPSS score. Nevertheless, because the IPSS is used widely as a predictor of prognosis in MDS, it is of interest to compare the survival of our patients with that seen historically in the IPSS risk groups. The predicted median survival of all patients (all ages) with a low-risk score is 5.7 years, whereas patients with an intermediate-1 risk score have a 3.5-year median survival. The risk of AML evolution at 1 and 2 years is less than 5% for low-risk IPSS cases and approximately 10% and approximately 20% for intermediate-1 cases. In our series, 3 of 9 patients died within 7 months of diagnosis without disease progression to AML. In an additional 5 patients, the disease progressed to AML in 6 to 24 months, and all patients died 1 to 10 months from transformation. For the 1 surviving patient in our series, only 10 months of follow-up are available. Therefore, although the small number of cases in the study

Image 3: Myelodysplastic syndrome (MDS) demonstrating Auer rods and closely resembling refractory anemia with ringed sideroblasts (RARS) was seen in case 3 at diagnosis. The disease progressed to AML in 6 months. Peripheral blood findings included a normal WBC count without granulocyte dysplasia (not shown), RBC dimorphism (A), and rare circulating blasts (<1% of differential) (A, inset) (Wright-Giemsa, original magnification ×330). The bone marrow showed mild erythroid dysplasia (B), 2.6% myeloblasts, of which 14% contained Auer rods (C), and ringed sideroblasts (25% of erythroblasts) (D) (B-C, Wright-Giemsa, original magnification ×330; D, Prussian blue, original magnification ×330).
precludes definitive conclusions, it seems that our patients experienced a more aggressive course than would be predicted from the IPSS score.

Because of the apparent aggressive course in the majority of our patients, it becomes important to distinguish these cases from low-grade MDS or even nonneoplastic conditions. The Auer rods can be overlooked easily because they may be present in as few as 1% of the blasts.

Notably, 5 of our patients had no more than mild dysplasia in the granulocytic and erythroid lineages. However, 4 of these 5 cases manifested moderate or marked megakaryocytic dysplasia, making diagnosis of MDS relatively straightforward. These, as well as 3 additional cases in our series, would be classified as refractory cytopenia with multilineage dysplasia (RCMD; 4 patients) or RAEB-1 (2 patients, based on >1% peripheral blood blasts) in the WHO scheme if the Auer rods were not detected. RCMD has been shown to have a more unfavorable course than refractory anemia or refractory anemia with ringed sideroblasts (RARS). Thus, even if Auer rods had not been identified, these would not be classified as low-grade MDS.

One case in our series, however, showed classic findings of RARS, including isolated mild anemia with RBC dimorphism, mild dyserythropoiesis without granulocytic or megakaryocytic dysplasia, and 25% ringed sideroblasts (RARS). Thus, even if Auer rods had not been identified, these would not be classified as low-grade MDS.

The final 2 cases in this series would have been classified as CMML-1 if Auer rods had not been present. CMML usually follows an aggressive course, with a median survival of 20 to 40 months.

It should be noted that the WHO classification does not specifically provide guidelines for the disposition of cases that otherwise would be classified as RCMD but that contain Auer rods; it only specifies that cases of RAEB with Auer rods should be classified as RAEB-2. Most pathologists likely would extrapolate this criterion to classify cases with fewer than 5% blasts and Auer rods as RAEB-2. While the aggressive disease course in our patients would seem to justify this approach, analysis of larger numbers of cases would be required to make firm recommendations regarding classification. It is conceivable that the presence of Auer rods signifies a distinct biology in these neoplasms, perhaps warranting classification in a separate MDS category. Further study is required to address this possibility.

Myeloid neoplasia with Auer rods and fewer than 5% blasts is a rare phenomenon that seems to be clinically, morphologically, and cytogenetically heterogeneous. The clinical behavior seems worse than would be expected based on the IPSS score, and, thus, it seems important to identify the rare Auer rods in these cases.

The final 2 cases in this series would have been classified as CMML-1 if Auer rods had not been present. CMML usually follows an aggressive course, with a median survival of 20 to 40 months.

It should be noted that the WHO classification does not specifically provide guidelines for the disposition of cases that otherwise would be classified as RCMD but that contain Auer rods; it only specifies that cases of RAEB with Auer rods should be classified as RAEB-2. Most pathologists likely would extrapolate this criterion to classify cases with fewer than 5% blasts and Auer rods as RAEB-2. While the aggressive disease course in our patients would seem to justify this approach, analysis of larger numbers of cases would be required to make firm recommendations regarding classification. It is conceivable that the presence of Auer rods signifies a distinct biology in these neoplasms, perhaps warranting classification in a separate MDS category. Further study is required to address this possibility.

Myeloid neoplasia with Auer rods and fewer than 5% blasts is a rare phenomenon that seems to be clinically, morphologically, and cytogenetically heterogeneous. The clinical behavior seems worse than would be expected based on the IPSS score, and, thus, it seems important to identify the rare Auer rods in these cases.

The final 2 cases in this series would have been classified as CMML-1 if Auer rods had not been present. CMML usually follows an aggressive course, with a median survival of 20 to 40 months.

It should be noted that the WHO classification does not specifically provide guidelines for the disposition of cases that otherwise would be classified as RCMD but that contain Auer rods; it only specifies that cases of RAEB with Auer rods should be classified as RAEB-2. Most pathologists likely would extrapolate this criterion to classify cases with fewer than 5% blasts and Auer rods as RAEB-2. While the aggressive disease course in our patients would seem to justify this approach, analysis of larger numbers of cases would be required to make firm recommendations regarding classification. It is conceivable that the presence of Auer rods signifies a distinct biology in these neoplasms, perhaps warranting classification in a separate MDS category. Further study is required to address this possibility.

Myeloid neoplasia with Auer rods and fewer than 5% blasts is a rare phenomenon that seems to be clinically, morphologically, and cytogenetically heterogeneous. The clinical behavior seems worse than would be expected based on the IPSS score, and, thus, it seems important to identify the rare Auer rods in these cases.

The final 2 cases in this series would have been classified as CMML-1 if Auer rods had not been present. CMML usually follows an aggressive course, with a median survival of 20 to 40 months.

It should be noted that the WHO classification does not specifically provide guidelines for the disposition of cases that otherwise would be classified as RCMD but that contain Auer rods; it only specifies that cases of RAEB with Auer rods should be classified as RAEB-2. Most pathologists likely would extrapolate this criterion to classify cases with fewer than 5% blasts and Auer rods as RAEB-2. While the aggressive disease course in our patients would seem to justify this approach, analysis of larger numbers of cases would be required to make firm recommendations regarding classification. It is conceivable that the presence of Auer rods signifies a distinct biology in these neoplasms, perhaps warranting classification in a separate MDS category. Further study is required to address this possibility.

Myeloid neoplasia with Auer rods and fewer than 5% blasts is a rare phenomenon that seems to be clinically, morphologically, and cytogenetically heterogeneous. The clinical behavior seems worse than would be expected based on the IPSS score, and, thus, it seems important to identify the rare Auer rods in these cases.
References


