Peripheral Acute Leukemia: High Peripheral but Low-Marrow Blast Count

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We report five patients who had >30% peripheral blasts and <30% marrow blasts. By the current standards these cases would be classified as myelodysplastic syndrome. Four of five patients progressed to acute leukemia within approximately 1.5 months of developing >30% peripheral blasts. Two of these four patients had evidence of acute leukemia by criteria other than marrow involvement at the time of presentation: one patient had evidence of multifocal dermal involvement; and the other patient had a cytogenetic abnormality, t(18;21), found predominantly in acute leukemia. The fifth patient developed acute leukemia 2 years after initial presentation with >30% peripheral blasts. Although our series of patients is small, it does suggest that patients who have >30% peripheral blasts should be considered an acute leukemia, even with <30% marrow blasts.

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THE FRENCH-AMERICAN-BRITISH (FAB) Cooperative Group devised diagnostic criteria for myelodysplastic syndromes (MDS), acute nonlymphocytic leukemia, and acute lymphocytic leukemia.1,3 Classification of the MDS is recent and, as with all new classification schemes, may require modification. MDS are classified according to the percentage of blasts in the marrow or blood and the number of circulating monocytes. For example, refractory anemia with excess blasts in transformation (RAEBT) is defined as having any of the following: >5% peripheral blasts, 20% to 30% bone marrow (BM) blasts, and/or the presence of unequivocal Auer rods. Chronic myelomonocytic leukemia (CMML) has an absolute monocytosis of >1 x 10^9/L, often with granulocytosis with or without dysgranulopoiesis. There are <5% blasts in the peripheral blood and generally <5% in the BM, although the marrow can have 5% to 20% blasts. According to FAB criteria, the diagnosis of acute leukemia (M1 through M5) can be made if there are <50% erythroblasts and >30% of the nucleated BM cells are blasts. The diagnosis of M6 is more complicated and requires >50% erythroblasts and >30% of the nonerythroid cells be blasts. Cases that contain >30% peripheral blasts and >30% BM blasts require clarification. We have identified five such cases, which, because of clinical behavior or cytogenetic features, we believe represent acute myelogenous leukemia (AML) rather than MDS.

MATERIALS AND METHODS

We reviewed 1,411 cases of chronic leukemia, MDS, or acute leukemia from the BM files at The University of Texas M.D. Anderson Cancer Center (UTMDACC) from the last 4½ years (1984 to 1988). Five cases had <30% blasts in a good-quality BM aspirate (500 cells counted) and a concomitant peripheral blast count >30% (100 cells counted). The charts were reviewed for therapy and clinical data. Slides on the five cases were reviewed by two of the authors (James D. Cason and Sanford A. Stass) who were in concordance on the percentages of blasts. Cytogenetic and ultrastructural studies were carried out as previously described.4 Immunophenotyping was carried out by flow cytometry according to a previously described method5-11 using antibodies against the following antigens: CD3, CD4, CD8, CD10, CD13, CD14, CD20, CD33, CD34, and HLA-DR. Cytogenetic studies were carried out using routine methods.12-14 The samples were incubated overnight at 37°C in Ham's F-10 medium (GIBCO, Grand Island, NY) supplemented with 10% fetal bovine serum (FBS; Armour Pharmaceuticals, Kankakee, IL) and Pen-Strep antibiotics (GIBCO). Harvesting of the cultures and slide preparation were done according to established procedures. A maximum of 25 well-spread Giemsa-banded metaphases were analyzed from each culture. Karyotypes were prepared on at least two metaphases of each cell type using the International System for Human Cytogenetic Nomenclature (ISCN 1985).15

PATIENTS

Diagnostic laboratory data for each of the five patients are shown in Table 1.

Patient 1. Patient 1 was a 61-year-old man who was diagnosed in 1981 as having polycythemia vera. The patient was initially treated with phlebotomy and then with melphalan; however, this therapy was stopped after ten days due to thrombocytopenia. In July 1986 the patient was referred to UTMDACC. He presented with 26% blasts in his marrow aspirate and 42% blasts in his peripheral blood and was diagnosed as having RAEBT (7/24/86). On August 13, 1986 he had 56% blasts in his aspirate and was diagnosed as having AML. The patient was started on daunorubicin. By the end of August 1986, he had failed daunorubicin therapy and was started on cytosine arabinoside and VP-16-213. He went into complete remission in November 1986, and the patient has remained in remission for 2 years.

Patient 2. A 61-year-old man presented to his private physician with a 1-month complaint of increasing weakness. His hemoglobin level was 5.0 g/dL. The patient was referred to UTMDACC for therapy. The patient was found to have RAEBT (2/4/88) with 17% marrow blasts and the presence of Auer rods. The peripheral blood contained 3% blasts at this time. The patient was begun on fludarabine phosphate, which was stopped 1 month later (March 1988) due to toxicity. The patient was changed to cytosine arabinoside and daunomycin. On May 12, 1988 the patient developed a peripheral blast count of 56%, while the aspirate contained 15% marrow blasts. On June 30, 1988 the aspirate contained 36% blasts, and the patient was begun on doxorubicin hydrochloride, cytosine arabinoside, and prednisone. The patient did not achieve a complete remission and continues to have elevated blast counts in the marrow aspirates.

Patient 3. The patient was a 75-year-old diabetic man who in November 1986 was diagnosed by his private physician to be anemic, with BM containing increased erythroid elements. No further information is available regarding this BM sample. The
patient was treated with pyridoxine hydrochloride. The patient developed multiple skin nodules in September 1987 measuring 0.5 to 1 cm in diameter. Right thigh and chin nodules were biopsied, and a diagnosis of AML with dermal involvement was made. The patient was referred to UTMDACC for therapy. A BM aspirate showed 17% blasts in the BM aspirate and 35% blasts in the peripheral blood. In September 1987, the patient developed multiple skin nodules measuring 0.5 to 1 cm in diameter. Right thigh and chin nodules were biopsied, and a diagnosis of AML with dermal involvement was made. The patient was referred to UTMDACC for therapy. A BM aspirate showed 17% blasts in the BM aspirate and 35% blasts in the peripheral blood. Due to the presence of Auer rods and the finding of a cytogenetic abnormality ([t(8;21)], the patient was given therapy appropriate for AML. She has remained in complete remission with a BM aspirate most recently aspirated August 24, 1989.

**Patient 4.** The patient was a 33-year-old woman with a 1-month history of increasing fatigue. Upon examination by her outside physician, she was found to be anemic and thrombocytopenic. Blasts with Auer rods were present in the peripheral smear. The hemoglobin value was 4.4 g/dL, the platelet count was 12,000/μL, and the white count was 20,000/μL. She had 17% blasts in the BM with rare Auer rods and was diagnosed as having RAEBT on July 1, 1986. Due to a persistence of increased peripheral blasts (33%) and the finding of a cytogenetic abnormality ([t(8;21)], the patient was given therapy appropriate for AML. She has remained in complete remission with a BM aspirate most recently aspirated August 24, 1989.

**Patient 5.** The patient was a 66-year-old woman who presented in 1985 with a 1-month history of fatigue. The patient was referred to UTMDACC. There were 17% blasts in the BM aspirate and 35% blasts in the peripheral blood. Due to the presence of Auer Rods and >5% blasts in the peripheral blood, a diagnosis of RAEBT was made October 9, 1985; however, the possibility that this represented AML was suggested in a comment. The patient was treated with cytosine arabinoside and went into complete remission. She relapsed 1 year later (1986) as RAEBT. Complete remission was again achieved using cytosine arabinoside and daunomycin. One year after the first relapse (11/12/87) the patient developed a second relapse, with 40% blasts in the BM aspirate. She was diagnosed as AML 2 years after initial presentation with >30% blasts in the peripheral blood. The patient died in complete remission documented by a BM aspiration a few weeks prior to death (12/23/87).

**RESULTS**

All patients except patient 2 initially presented with >30% peripheral blasts (range 31% to 42%); and <30% marrow blasts (range, 17% to 26% blasts) (see Table 1). Patient 2 had 15% marrow blasts and 56% peripheral blasts approximately 3 months after initial presentation and 1½ months before the diagnosis of AML. Patients 2, 4, and 5 had blasts that contained Auer rods. All patients except patient 2 had blasts that were peroxidase positive. Patient 2 was myeloperoxidase deficient; however, the blasts in this patient were chloroacetate esterase positive. Patient 3 also had blasts that were butyrate esterase positive. The periodic acid-Schiff stain was negative for a block-staining pattern in all cases, and the terminal deoxynucleotidyl transferase was negative in all patients. Electron microscopy confirmed the presence of myeloblasts in all patients as well as the presence of myeloperoxidase-containing granules in patient 2 (myeloperoxidase negative by light microscopy). Immunophenotyping of marrow blasts at the time of presentation revealed that all patients were negative for CD3 (pan T-cell antibody), CD8 (suppressor T-cell subset), and CD10 (common acute lymphoblastic leukemia antigen [CALLA]), and CD20 (pan B-cell antibody). All the patients were positive for CD33 (myeloid marker) and for HLA-DR. Patients 1 and 2 were positive for CD14 (monocytic marker), and all patients except patient 2 were positive for CD13 and CD34 (myeloid marker). Cytogenetic studies were carried out on all patients. The results are summarized in Table 1.

**DISCUSSION**

According to current FAB criteria, the presence of <30% blasts in the BM aspirate is not considered diagnostic of acute leukemia, assuming a good-quality aspirate. We present five cases in which the BM aspirate contained <30% blasts while the peripheral blood contained >30% blasts. In attempting to classify these cases we encountered a dilemma:
(1) ignore the peripheral blasts beyond 30% and classify according to the BM aspirate differential, or (2) recognize these cases as a distinct subgroup not clearly addressed previously. Several factors led us to conclude that rather than being classified as myelodysplastic (one case was called AML), the patients should have been classified as acute leukemia. As is evident from Table 1, our diagnoses at the time of presentation was prior to the recognition of the peripheral variant of acute leukemia; however, upon review we would suggest using all the data available to classify the disease.

Our results suggest that patients who have <30% blasts in the marrow but >30% blasts in the blood in fact have AML. Thus patients 1 and 2 developed overt AML within approximately 1½ months of developing >30% peripheral blasts. The third patient developed extramedullary leukemia in multiple skin sites while the aspirate contained <30% blasts. Patient 4 was found to have a cytogenetic abnormality seen predominantly in AML\(^1\)\(^-\)\(^4\) \((t(8;21))\) and only rarely in MDS\(^2\)\(^-\)\(^8\) a finding responsible in large part for this patient's treatment for AML. Only patient 5 did not have features suggestive of AML (eg, medullary leukemia or a typical cytogenetic abnormality) and did not develop AML shortly after presentation. In all other patients the presence of peripheral blasts predicted an impending acute leukemia phase.

We estimated blasts by examination of BM biopsies, although this proved difficult. However, in no case could we definitely quantitate >30% myeloblasts in the biopsy. Delacretaz et al\(^24\) believed they could accurately subclassify MDS cases on the basis of the biopsy; however, they were using plastic-embedded tissue, whereas we use paraffin-embedded tissue. They found a discrepancy in diagnosis between aspirate and biopsy in only four of their 30 cases.

Several authors\(^2\)\(^-\)\(^5\) have done multiparameter studies looking at the importance of various factors in the prognosis of MDS. Most authors\(^3\)\(^-\)\(^8\)\(^,\)\(^10\)\(^-\)\(^13\) have found that the presence of circulating blasts adversely affected survival. Coiffet et al\(^10\)\(^-\)\(^13\) found that the percentage of blasts in the BM smear had the strongest correlation with length of survival, although the presence of circulating blasts also unfavorably influenced survival. No correlation was found between absolute numbers or percentage of peripheral blasts and survival, although they did report the average length of survival in those without blasts was 875 days, whereas those with circulating blasts averaged only 163 days. Tricot et al\(^15\) found there was a statistically significant difference in survival between those with and without circulating blasts. No correlation was made between absolute blast count and prognosis. Four of our patients had absolute blast counts of >3,500 blasts/\(\mu\)L. All of these patients progressed to overt leukemia within approximately 1 month of a peripheral count >30% blasts. The one patient with an absolute blast count <3,500 blasts/\(\mu\)L (patient 5) did not immediately progress to acute leukemia but did eventually progress to acute leukemia after a 2-year course as a RAEBT. We could find no reports that examined the relationship between absolute circulating blast count and prognosis and no reports of patients with >30% circulating blasts and <30% blasts in the BM.

Cytogenetic studies are increasingly being recognized as important in the prognosis of MDS and acute leukemias.\(^2\)\(^0\)\(^-\)\(^23\) Jacobs et al\(^24\) found a significant correlation between karyotypic abnormalities at the time of diagnosis of MDS and progression to acute nonlymphocytic leukemia (ANLL). Also in their study trisomy 8 was the most common cytogenetic abnormality, which is commonly present in de novo ANLL\(^18\) and in primary MDS at the time of transformation to ANLL.\(^17\) Our patient 2 had loss of the Y chromosome without other cytogenetic abnormalities, which is uncommon. One report\(^32\) described 13 patients with AML with loss of the Y chromosome and found that that loss was associated with an aggressive clinical course. Our patient 5 had a numerical aberration of chromosome 13, which has rarely been described in association with AML.\(^33\) As noted above, cytogenetic studies are important; however, classification still requires enumeration of the blast count.

Although our series is small, our results lead us to recommend diagnosing patients who present with <30% marrow blasts and >30% circulating blasts as having acute leukemia, especially if the absolute peripheral blast count is >3,500 blasts/\(\mu\)L.

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