An Uncommon Variant of Acute Myeloid Leukemia: Acute Erythroid Leukemia

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Case Studies

Questions

1. How has the classification of this leukemia been recently revised by the WHO?
2. What are this patient’s most striking clinical and laboratory findings?
3. What additional tests were done to establish a diagnosis? Would additional immunophenotyping be beneficial?
4. Could molecular testing help establish a diagnosis? What aberrant molecular mechanisms might underlie the etiology and pathophysiology of this leukemia?
5. Lenalidomide was chosen to treat this patient. What are some other novel treatments for refractory acute myeloid leukemia (AML)?

Possible Answers

1. Acute erythroid leukemia (AEL) is a rare variant of AML affecting primarily older adults (>50 years). After several revisions by the WHO, AML with predominantly erythroid features can be classified either as erythroleukemia or as a pure erythroid malignancy. Erythroleukemia remains the more frequently diagnosed form of the disease. For inclusion in this category, 50% or more of all nucleated bone marrow cells should be erythroblasts and 20% or more of the remaining non-erythroid cells should be myeloblasts. If there are less than 20% blasts, the diagnosis is refractory anemia with an excess of blasts (RAEB).<sup>1,2</sup> Dyserythropoiesis at all stages of development is characteristic. Dyserythropoiesis is not limited to the erythrocytic line and can manifest in granulocytes and megakaryocytes.<sup>1,2</sup> In these latter 2 cell lines, the dyserythropoiesis is likely to be subtle and not a distinctive feature of the leukemia, although this patient displayed both dysmyelopoiesis and dysmegakaryopoiesis. Pure erythroid leukemia

Abbreviations

AML, acute myeloid leukemia; AEL, acute erythroid leukemia; RAEB, refractory anemia with an excess of blasts; CAD, coronary artery disease; LDH, lactate dehydrogenase; PAS, Periodic acid-Schiff; MPO, myeloperoxidase; JAK2, Janus kinase 2; FLT3, fms-related tyrosine kinase 3; RUNX1, runt-related transcription factor 1; NPM1, nucleophosmin; AMMoL, acute myelomonocytic leukemia; miRNAs, micro RNAs; CR, complete remission; HDAC, histone deacetylase; FTIs, farnesyltransferase inhibitors; DNR, daunorubicin; AraC, cytarabine; BM, bone marrow

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displays a neoplastic proliferation of immature bone marrow cells predominately committed to the erythroid series with a lack of a myeloid component. In this rare variant, >80% of the immature cells must be committed to erythroid lineage.1,2

2. A 65-year-old Asian/Caucasian female with a long history of stable CAD presented to her physician complaining of general malaise of several weeks duration. She felt generally healthy, but she was becoming increasingly short of breath and easily fatigued. Diagnostic studies were conducted on her as an outpatient. She was determined to be markedly anemic with combined leukopenia and thrombocytopenia. Since there was concern for the possibility of an underlying leukemia or myeloproliferative disorder, she was admitted to a local hospital for a more thorough evaluation and hematologic consultation. A CBC and differential done on this patient’s peripheral blood shortly after her admission was characteristic of acute erythrocytic leukemia (AEL). Specifically, it was remarkably pancytopenic and displayed nonspecific erythrocyte morphologic abnormalities such as poikilocytosis, anisocytosis, basophilic stippling, hypochromasia, and nucleated RBCs. The WBCs were slightly shifted left (Table 1) with dysplastic changes including occasional, pseudo Pelger-Huët cells (Image 1A). Moreover, her platelets were decreased in number, giant, and hypogranular. Other laboratory testing revealed this patient to have an increased lactate dehydrogenase (LDH) level, indicative of early cell death.

It is essential to examine the bone marrow in order to diagnose AEL since the morphology of the peripheral blood is striking but not exclusive of other hematopathologies. The bone marrow had an increased cellularity of 95%-100% with 80% of the cells devoted to erythroid lineage and 20% restricted to myeloid lineage. The cells displayed trilineage dysplasia with erythroid dysplasia as the most pronounced. Dysmegakaryopoiesis (MPO) and Sudan Black B. The morphological appearance of the patient’s bone marrow was characteristic of, but not exclusive to, AEL, so cytochemical stains, immunophenotyping, and cytogenetic studies helped establish a diagnosis.

Cytochemically, the bone marrow erythroblasts displayed diffuse Periodic acid-Schiff (PAS) staining reactions. Periodic acid-Schiff staining reactions are usually positive in AEL and display either a block or diffuse pattern in the erythroblasts. The diffuse pattern seen in this patient usually reflects more mature erythroblasts.3 An iron stain revealed increased iron stores but no indication of ringed sideroblasts. As expected, the putative myeloblasts were positive for myeloperoxidase (MPO) and Sudan Black B.

The erythroblasts of AEL show variable expression of the usual erythrocyte-associated antigens depending on the existing degree of differentiation. Most erythroblasts typically express CD71 (transferrin receptor), but some patients, including the patient in this case, have aberrantly dim CD71 expression.4,5 Seventy percent of this patient’s cells stained positive for CD71 (transferrin receptor), but some patients, including the patient in this case, have aberrantly dim CD71 expression.4,5 Seventy percent of this patient’s cells stained positive. Other laboratory testing revealed this patient to have an increased lactate dehydrogenase (LDH) level, indicative of early cell death.

3. The morphological appearance of the patient’s bone marrow cells was characteristic of, but not exclusive to, AEL, so cytochemical stains, immunophenotyping, and cytogenetic studies helped establish a diagnosis.

Cytogenetic testing carried out in this patient revealed her to have a complex karyotype with multiple numerical and structural chromosomal abnormalities, including a del(5q), -16, and -17. These findings place her in a prognostically unfavorable group.3,6

4. Assessment of molecular findings in AEL cases remains an area of diagnostic testing that has not been carried out extensively, due to the infrequency of the diagnosis. Interestingly, the prevalence of mutations in Janus kinase 2 (JAK2), TP53 tumor suppressor gene, and in fms-related tyrosine kinase 3...
(FLT3) are sharply contrasted in AEL and in the other subtypes of AML. Although aberrant runt-related transcription factor 1 (RUNX1) shows the same persistent trend in AEL as in the rest of the AMLs, JAK2, FLT3, and TP53 mutations are more frequently found in AML except AEL.5,6 Mutation of the nucleophosmin gene (NPM1) is commonly seen in other subtypes of AML and presents in approximately 20% of AEL cases. The discrepant findings in gene mutations between AEL and other AMLs suggests the etiology and pathogenesis of AEL are specific to the subtype.3

The etiology of erythroleukemia remains elusive, but the likelihood that it develops secondary to chemotherapeutic treatment or exposure to mutagenic agents is significant. Acute erythroid leukemia may also develop from myeloproliferative disease or myelodysplastic syndrome. Interestingly, the erythroid/myeloid subtype of AEL can gradually change to several AMLs not otherwise specified; AML minimally differentiated, AML without maturation, AML with maturation, or acute myelomonocytic leukemia (AMMoL).3

Aberration of any of the key regulators of erythropoietic proliferation and differentiation might contribute to the development of erythroleukemia. Deviant transcription factors instrumental in regulating erythroid differentiation/proliferation or aberrant interaction of growth factors and signaling pathways essential for normal erythropoiesis could lead to the development of malignancy.7,8 Recently it has been found that erythroid differentiation is regulated by micro RNAs (miRNAs), a class of small RNAs regulating gene expression.7,8 The list of putative transcription factors, growth factors, downstream signaling proteins, and other cellular molecules that might be aberrant in erythroleukemia is under investigation, and research in this area will provide insights concerning the etiology of AEL and will likely result in greatly improved treatment options.

5. New regimens and novel agents are being explored in an attempt to improve outcomes in patients with refractory or relapsed AML. High-dose cytarabine (Ara-C) is a standard treatment for relapsed or refractory AML; however, following increased Ara-C with mitoxantrone has resulted in significantly improved remission rates. Recent phase II studies indicate that treatment with fludarabine, high-dose Ara-C, G-CSF, and mitoxantrone is a promising treatment option for relapsed or refractory AML patients.10,11 The addition of chemoimmunotherapy to standard induction protocols has resulted in positive treatment outcomes. CD33

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**Image 1.** Dyshematopoiesis in peripheral blood and bone marrow aspirate, Wright Giemsa (×100). (A) A pseudo Pelger-Huët cell exemplifies dysmyelopoiesis in the peripheral blood. (B, C) Bone marrow aspirate reveals mostly erythroid precursors displaying dyserythropoiesis (multinucleate forms, cytoplasmic irregularities). (D) Dysmegakaryopoiesis displayed by this mononuclear megakaryocyte in the bone marrow aspirate.
therapy. Novel agents are being investigated for efficacy to significantly improve patient response to standard induction therapy. One such agent is gemtuzumab ozogamycin, conjugated to calicheamycin FTIs, which has proven to be effective in the treatment of AML, especially in those with poor cytogenetic findings that appear to be well correlated with AEL. The most frequently encountered abnormalities include monosomy 5, del(5q), monosomy 7, del(7q), trisomy 8, and complex karyotypes. The patient presented here displayed a complex karyotype with multiple numerical and structural chromosomal abnormalities, including -16, -17, and del(5q). Unfortunately, these karyotype findings placed her into a prognostically unfavorable group as complex aberrant karyotype, 5q deletions, and several other abnormalities (-5, -7, del(7q), inv(3q), and t(3;3)) are all associated with unpromising outcomes.

The patient was started on the standard induction therapy of daunorubicin (DNR) 45 mg/m² intravenously for 3 days and (Ara-C) 100 mg/m² by continuous infusion for 7 days. Fourteen days later another bone marrow (BM) biopsy was performed, revealing residual disease. Morphologically, 10% of the nucleated cells of the BM were erythroblasts and abnormal myeloid precursors. Cytogenetically, her complex karyotype persisted. After another cycle of induction therapy failed to induce remission, the patient chose to try a novel regimen of chemotherapy. The patient began treatment with oral lenalidomide 50 mg/day for 14 days, followed by 30 days’ rest, then oral lenalidomide 50 mg/day for 21 days. Bone marrow examination done after a second cycle of treatment showed 40% cellularity with <5% blasts. Cytogenetic analysis revealed 46,XX in all 20 metaphases examined. Following this favorable BM result, the patient began receiving a low maintenance dose (10 mg) of oral lenalidomide daily for 21 days. Five months later, the patient continues to follow her maintenance dose schedule and continues to be in CR.

### Table 2. Bone Marrow Report

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<th>Specimen(s) Submitted</th>
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<td>1. LPSC BM BX 1.4 cm</td>
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<td>2. Bone marrow aspirate</td>
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### Patient Treatment and Outcome

It was felt that the ability to treat this patient successfully was going to be difficult because of her complex karyotype. While there are no known chromosome abnormalities specific and unique to AEL, certainly there are abnormal cytogenetic findings that appear to be well correlated with AEL. The most frequently encountered abnormalities include monosomy 5, del(5q), monosomy 7, del(7q), trisomy 8, and complex karyotypes. The patient presented here displayed a complex karyotype with multiple numerical and structural chromosomal abnormalities, including -16, -17, and del(5q). Unfortunately, these karyotype findings placed her into a prognostically unfavorable group as complex aberrant karyotype, 5q deletions, and several other abnormalities (-5, -7, del(7q), inv(3q), and t(3;3)) are all associated with unpromising outcomes.

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Case Studies


