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Therapy-Related Acute Myelogenous Leukemia in a Hydroxyurea-Treated Patient With Sickle Cell Anemia

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Background

Hydroxyurea is an antimetabolite that minimizes pain and prolongs survival in patients with sickle cell anemia (1). It is not widely prescribed because of concerns about late effects, including cancer (2), and its leukemogenic risk is extrapolated from its reported risk in myeloproliferative disorders (3). Few cases of leukemia in patients with sickle cell anemia have been described, and only half of them report cytogenetics (4). Acute myelogenous leukemia (AML) in patients with sickle cell anemia receiving hydroxyurea treatment is exceptionally rare, but data on its true incidence are insufficient (1, 2). Whether AML in hydroxyurea-treated patients with sickle cell anemia is coincidental or related to therapy remains an unanswered question (2).

Objective

To report a unique combination of sickle cell anemia, hydroxyurea treatment, and short-latency leukemia of erythroid origin that presented a diagnostic challenge and underscored leukemogenic potential.

Methods and Findings

A 33-year-old man with sickle cell anemia began treatment with hydroxyurea, 9.0 mg/kg daily, after 1 year of ambulatory pain and recurrent priapism requiring hospitalization. At baseline, the patient had a leukocyte count of $14\,700 \times 10^9$ cells/L, hemoglobin level of 7.2 g/dL, and fetal hemoglobin level of 5.1%. Four years later, he was receiving hydroxyurea, 18 mg/kg daily, and the response was excellent (maximum fetal hemoglobin level, 35.6%; maximum mean corpuscular volume, 131.0 fL), although administration was interrupted by onset of transient neutropenia (Figure, panel A). The patient was later hospitalized and received transfusions for the acute chest syndrome. Hydroxyurea was withheld due to onset of neutropenia 2 weeks later. Follow-up again showed profound neutropenia (absolute neutrophil count, 0.120×10^9 cells/L), a leukocyte count of 0.670×10^9 cells/L, and a platelet count of $102\,000 \times 10^9$ cells/L. Peripheral blood smear showed 44% blasts, consistent with normoblasts, megaloblastic changes, and marked dyserythropoiesis in numerous circulating nucleated erythrocytes (Figure, panel B). We ruled out delayed transfusion reaction and folate or B12 deficiency. Bone marrow biopsy showed hypercellularity with myeloid hypoplasia and erythroid hyperplasia with markedly left-shifted maturation and an increased erythroblast count. There was no increase in myeloblast count. Immunocytochemistry showed that blasts were positive for spectrin, hemoglobin, and CD117 and were negative for myeloperoxidase, CD34, glycophorin, terminal deoxynucleotidyl transferase, CD68, and factor VIII (von Willebrand factor), indicating malignant cells of early erythroid origin (Figure, panel B). Standard flow cytometry showed less than 2% myeloblasts. Pure erythroid leukemia (Di Guglielmo disease or French-American-British M6b AML) was suspected; however, massive erythroid recovery due to

marrow in fractions occurring during the acute chest syndrome was also in the differential diagnosis. Cytogenetic analysis showed that 14 out of 20 marrow metaphase cells were abnormal, with significant karyotypic heterogeneity. The composite karyotype had 44 to 46 chromosomes with a recurring unbalanced rearrangement of chromosome arm 5q, deletion of chromosome arm 7q, loss of chromosomes 15 to 22 and Y, and 5 marker chromosomes, suggesting the myelodysplastic syndrome or AML. Clonal abnormalities enabled diagnosis of pure erythroid leukemia. Induction therapy with cytarabine and idarubicin produced a cytogenetic remission. Sibling-matched stem cell transplantation after cyclophosphamide therapy, fludarabine therapy, and irradiation was unsuccessful, and relapse occurred 4 months later. Flow cytometry demonstrated that 33% blasts were coexpressing CD117, CD38, and CD33. Bone marrow biopsy showed sheets of erythroblasts. Neither salvage chemotherapy nor donor lymphocyte infusion yielded a response. The patient died 9 months after diagnosis.

Discussion

To our knowledge, this is the first case of sickle cell anemia associated with AML of erythroid origin and a complex karyotype that meets the immunophenotype criteria for pure erythroid leukemia and, of note, therapy-related AML following the 2008 World Health Organization classification (5). This case is unique for development after 50 months of hydroxyurea treatment compared with an average AML latency of 8 years in myeloproliferative disorders. Short latency and genomic instability suggest a therapy-related cause, although complex karyotype AML is not characteristic of hydroxyurea treatment in the absence of a myeloproliferative disorder (3, 5). The potential role of antimetabolites in therapy-related AML and suggestions for expanding hydroxyurea treatment to children and others with sickle cell anemia not meeting current U.S. Food and Drug Administration guidelines highlight the need for long-term studies with bone marrow cytogenetics to determine whether these rare cases represent true therapy-related AML in patients with sickle cell anemia (2, 5). Even if risk for therapy-related AML was proven, it would need to be weighed against the intrinsic mortality of untreated sickle cell anemia.

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Figure 1. Case synopsis of AML, with images from peripheral blood and bone marrow
 AML = acute myelogenous leukemia; ANC = absolute neutrophil count; HbF = fetal hemoglobin; MCV = mean corpuscular volume; MPO = myeloperoxidase. **A.** Timeline with events listed. Graphs illustrate ANC, HbF level, MCV, and hydroxyurea dose over 6 years. The red triangles indicate red blood cell transfusions (E _ exchange; S _ simple), and the blue squares indicate interruption of hydroxyurea therapy. Time from the start of hydroxyurea therapy to diagnosis was 50 months. **B.** Images from peripheral blood, marrow, and immunocytochemistry at diagnosis.