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CASE REPORT

Development of Myelodysplastic Syndrome and Acute Myeloid Leukemia 15 Years after Hydroxyurea Use in a Patient with Sickle Cell Anemia

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Abstract: We report a 41 year old male with sickle cell disease who developed a myelodysplastic syndrome and acute myeloid leukemia with complex karyotype involving chromosomes 5, 7 and 17 after 15 years of hydroxyurea treatment. He responded poorly to induction chemotherapy with cytarabine/idarubicin followed by high dose cytarabine and succumbed to neutropenic sepsis. Multiple systematic reviews, observational studies and clinical trials were conducted to identify the toxicity profile of hydroxurea. Only six cases of leukemia/myelodysplastic syndrome were identified in patients with sickle cell anemia treated with hydroxyurea. Subsequently, it was concluded that hydroxyurea is not leukemogenic. However, it was noted that most of the published studies had only up to 9 years of follow-up. Our patient was started on hydroxyurea in 1990, before the widespread use of the drug and took hydroxyurea for 15 years. His presentation may reflect an outcome otherwise not yet observed because of the short follow-up of prior studies. We believe that the leukemogenic risk of hydroxyurea should be discussed with the patients and their families. Studies evaluating the adverse effects of hydroxyurea should have longer follow-up before definitive conclusions are drawn.

Keywords: hydroxyrea, myelodysplastic syndrome, acute myeloid leukemia

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Case Report

A 21 year old African–American male first presented to the adult hematology service with frequent sickle cell crises. Despite multiple exchange transfusions his sickle cell disease (SCD) continued to require hospitalization for management of painful crises. The patient did not have any significant past medical history but his sister had Gaucher disease. At age 26, he was begun on hydroxyurea (HU). Significant improvement in his crises occurred with reduction in hospital admissions, from more than 14 admissions per year to 3 admissions per year. The patient took HU for 15 years. The dose of HU ranged from 1.5 to 2 grams per day. At age 41, the drug was discontinued because of refractory pancytopenia. A bone marrow biopsy revealed Refractory Anemia with Excess Blasts-2 according to the World Health Organization classification (Fig. 1). Myeloblasts (15% of myeloid cells) were CD33, CD34, CD117 and CD68 positive by immunohistochemistry. Flow cytometry was not performed because the aspirate was dry. The patient was referred for a second opinion and a repeat bone marrow biopsy was performed 34 days after the first biopsy which showed progression of myelodysplastic syndrome to acute myeloid leukemia (AML) with 68% myeloblasts on flow cytometry. All 20 cells examined from the bone marrow aspirate had 42XY with complex cytogenetics including, t(5;18), del(7)(q21) and –17 (Fig. 2). A peripheral blood sample revealed a white blood cell count of 14×10^9/L with 41% blasts. The patient underwent induction chemotherapy with cytarabine and idarubicin. A peripheral blood flow cytometry done 2 months after induction chemotherapy due to persistent pancytopenia revealed the presence of CD33+/CD34+/CD117+ myeloblasts (2.6%). Subsequent treatment included high dose cytarabine with a goal of remission prior to bone marrow transplantation. His hospital course was complicated by pancytopenia, sepsis, subarachnoid hemorrhage and respiratory failure. He died at age 41.

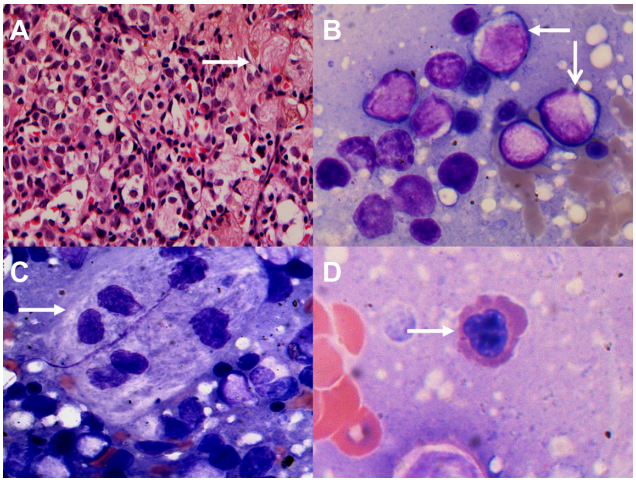

Figure 1. Bone marrow biopsy and aspirate. (**A**) Low power magnification showing a hypercellular marrow for age (>90%) and Gaucher/Pseudo-Gaucher cells (arrow). (**B**) High power magnification showing blasts with large nuclei and prominent nucleoli. (**C**) High power magnification showing a dysplastic megakaryocyte with multiple small lobes seemingly disconnected. (**D**) High power magnification showing a dysplastic eryrthroblast with nuclear budding.

Discussion

HU is the only approved medication for the treatment of sickle cell disease. It has been shown to significantly modify the course of SCD with up to a 40% reduction in mortality after 9 years of follow-up.[1] Most adverse effects of hydroxyurea are mild and include: rash, hyperpigmentation, nail changes, cutaneous ulcerations, alopecia, mucositis, nausea, vomiting, diarrhea, fever, fatigue, myelosuppression, drowsiness, and headache. Other rare adverse effects include: hepatic failure, renal failure, interstitial pneumonitis and azoospermia. Because HU impairs the repair of damaged DNA, clinicians have been concerned that long term exposure to HU may lead to an accumulation of acquired DNA mutations and eventual leukemic transformation.

To clarify the toxicity profile of HU, the Johns Hopkins University Evidence-based Practice Center reviewed numerous randomized clinical trials, observational studies, and case reports of patients with MPD or SCD on HU. In the MPD group, there were no increased cases of leukemia/MDS in patients on HU compared to patients not receiving the drug.[2] To our knowledge and based on the John Hopkins review, only six patients with SCD on HU were reported to subsequently develop leukemia/MDS: a 10 year old female with a Philadelphia chromosome acute lymphoblastic leukemia (ALL) after 1.5 years of HU treatment,[3] a 14 year old male with ALL after 3 months of HU treatment,[4] a 21 year old female with acute promyelocytic leukemia after 8 years of HU treatment,[5] a 25 year old female with AML after 2 years of HU treatment,[6] a 27 year old female with AML/MDS after 8 years of HU treatment,[7] and a 42 year old female with AML after

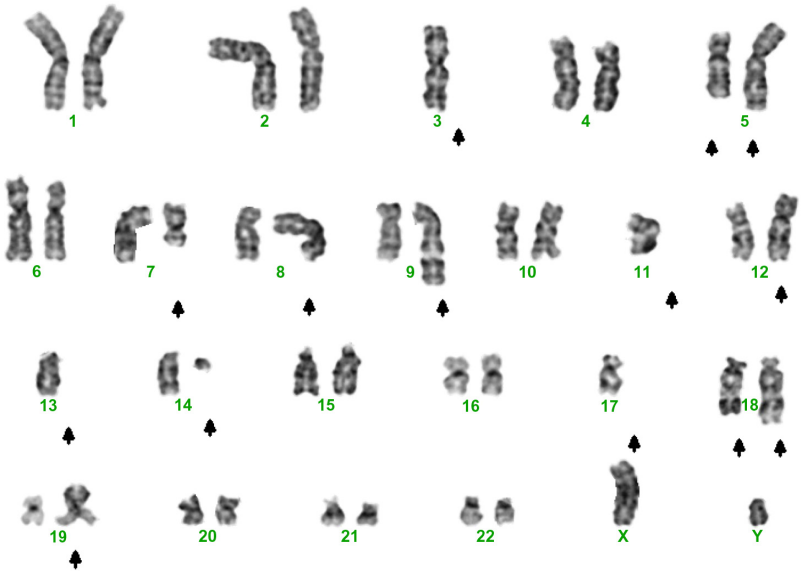

Figure 2. 42, XY, –3, +der(5)t(5;18)(p12;q11.2), del(7)(q21), add(8)(p23), der(9)t(9;14)(q34;q11), –11, add(12)(p13), –13, del(14)(q11), –17, add(18)(q22), der(18)t(11;18)(q14;q23), der(19)t(5;19)(p12;p12) karyotype.

6 years of HU treatment.[8] Cytogenetic analysis was only reported in the 25 year old female, who had a normal karyotype. Based on this large review, it was concluded that there was evidence, qualified as being low grade, that HU treatment is not associated with leukemia.[2] The evidence was qualified as low grade as most of the studies reviewed had only 9 years of follow-up. To our knowledge, only one study had more than 9 years follow-up. In this single center trial, 26 patients were followed-up for more than 15 years, 12 of whom were followed for 17 years. Of 131 patients enrolled in this study and taking HU, none developed MDS, leukemia or cancer.[9] Our patient was treated with HU for 15 years. Given the extended duration of follow-up, his presentation may reflect an outcome otherwise not yet observed in most of the previous studies which are shorter in duration. He was not exposed to radiation or chemicals, did not have a myeloproliferative disorder, or any underlying identifiable genetic predisposition that explains his progression to AML/MDS at the age of 41. Pseudo-Gaucher cells may be found in the bone marrow biopsies of patients with MDS or leukemia which explain the pseudo-Gaucher cells seen in the patient's bone marrow.[10] Gaucher disease is not known to be a predisposing factor for the development of AML/MDS.[11] The unique aspect of our case is that complex karyotype involving chromosome 5, 7 or 17 were never reported in a sickle cell patient on HU treatment. Chemotherapy or radiation induced leukemia/MDS is associated with monosomy or deletion of long arm of chromosome 5 or 7.[12–14] Recently, deletion of the whole chromosome 17 or its short arm was found to be specifically associated with HU treatment in patients with MPDs.[15–18] This "17p$^-$ syndrome" results from deletion of the tumor suppressor gene p53.[16–18] Our patient had not only monosomy 17 consistent with HU related MDS but had also, deletion 7q, and multiple other complex structural rearrangements suggestive of chemotherapy induced leukemia/MDS. HU is currently used in children with SCD. Numerous observational and randomized clinical trials conducted in children, demonstrated decreases in the rates of hospitalization, painful crises, acute chest syndrome, stroke, and cognitive development without affecting growth.[19] Many children with SCD are being enrolled in clinical trials involving HU treatment. We are concerned that this population will be exposed to HU for a long period of time which may increase its potential leukemogenic risk. Our case highlights the observation that short-term studies cannot provide strong evidence for toxicities that may require years to be observed. We believe that the leukemogenic risk of hydroxyurea should be discussed with the patients and their families. Studies evaluating the adverse effects of HU should have longer follow-up before definitive conclusions are

drawn. Physicians and patients should consider all risks and benefits prior to initiating HU treatment.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

Written informed consent was obtained from the patient's father for the publication of this case report.

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