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Case Report

Pure Erythroid Leukemia in a Sickle Cell Patient Treated with Hydroxyurea

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Abstract
We present a very rare case of pure erythroid leukemia arising in a young patient with sickle cell disease being treated with hydroxyurea for almost 5 years. Diagnosing and managing this rare condition has been a challenge and the majority of patients with pure erythroid leukemia have a very poor prognosis with survival in months despite treatment. This form of leukemia could be therapy related and in our case, hydroxyurea may have been responsible for the development of this aggressive condition.

Introduction

Pure erythroid leukemia (PEL) is a rare entity which mostly evolves from prior myelodysplastic syndrome (MDS) or myeloproliferative neoplasms; however, it can also arise de novo. As per the 2016 WHO revision of myeloid neoplasms, PEL is the sole form of acute erythroid leukemia. Most cases of PEL have complex cytogenetic abnormalities and a grave prognosis with survival of few months.

Only a few case reports of leukemia/MDS secondary to the use of hydroxyurea have been published in the literature and it has been concluded in some studies that hydroxyurea is nonleukemogenic in sickle cell anemia patients. However, its use has been associated with a cytogenetic evolution with the development of acute myeloid leukemia/MDS in patients with

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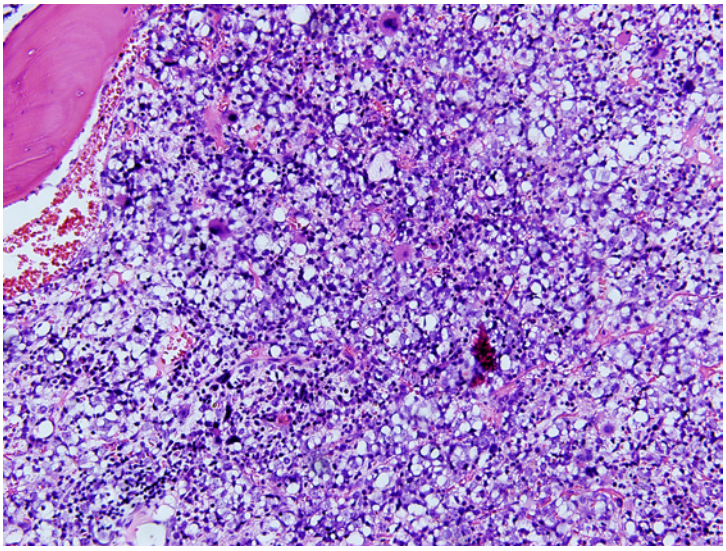

Fig. 1. Low-power field shows hypercellular marrow (almost 100% cellularity) with sheets of large pleomorphic mononuclear cells, increased plasma cells and mono/hypolobated megakaryocytes (hematoxylin and eosin stain, ×20).

myeloproliferative disorders. There is no clear association of PEL with prior treatment; however, genomic instability and poor outcome may suggest therapy-related pathogenesis. Hydroxyurea use may be related to the development of this complex disorder in certain patients.

Case Presentation

A 29-year-old female with a history of sickle cell anemia on hydroxyurea (20 mg/kg/day) for the last 5 years was admitted to the hospital with acute sickle cell crisis. She was found to be anemic with Hgb of 6.1 g/dL and thrombocytopenic with platelet counts of 30,000/μL. Her platelet count during the last admission about a month ago was 186,000/μL. The patient complained of generalized pain on admission and was started on pain medications and was also given 3 units PRBC transfusion which improved her hemoglobin level to 10.1 g/dL. Upon further questioning, the patient was also experiencing gum bleeding and hematuria for the last few days.

Absolute reticulocyte count was 11, 000/μL with a reticulocyte percentage of 0.6. Other laboratory work showed LDH of 261 IU/L, fibrinogen of 451 mg/dL, haptoglobin of 141 mg/dL, negative heparin-induced antibody and negative direct antiglobulin test. Parvovirus B19 IgM antibody was negative. Vitamin B_{12}, serum folate and methylmalonic acid levels were within normal limits. Hemoglobin electrophoresis, which was done after the transfusions, showed hemoglobin A1 of 77.9% and hemoglobin S of 14.6%. Other workup for thrombocytopenia including infectious etiology was negative.

The patient was started on intravenous immunoglobulin and prednisone for thrombocytopenia without any improvement. Because of persistent thrombocytopenia and drop in reticulocyte count compared to her previous values with no apparent cause, bone marrow biopsy was performed.

Bone marrow biopsy revealed marrow with 100% cellularity with cellular elements comprising of a predominantly immature erythroid cell population, morphologically consistent with pronormoblasts and without evidence of any maturing forms (Fig. 1–3).

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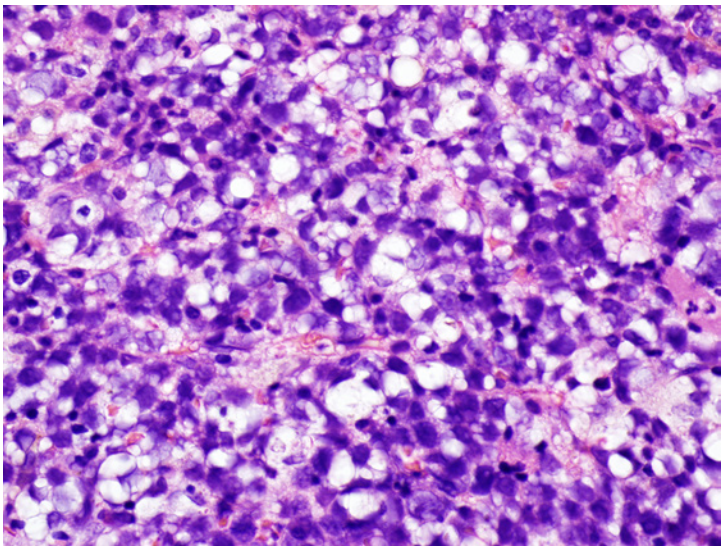

Fig. 2. Sheets of large pleomorphic mononuclear cells, the majority with dark chromatin and scant cytoplasm; a subset exhibits finely dispersed chromatin with the presence of nucleoli (hematoxylin and eosin stain, ×60).

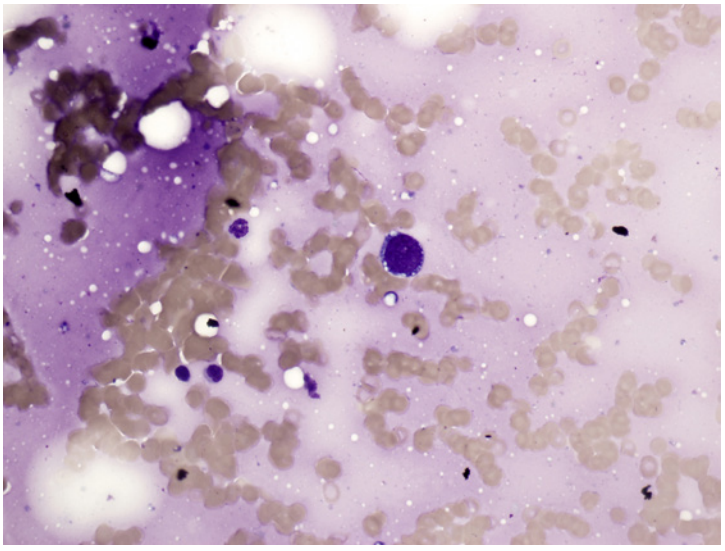

Fig. 3. Left shifted erythropoiesis with predominantly atypical enlarged pronormoblastic forms with irregular cytoplasmic vacuolations (Leishman stain, ×60).

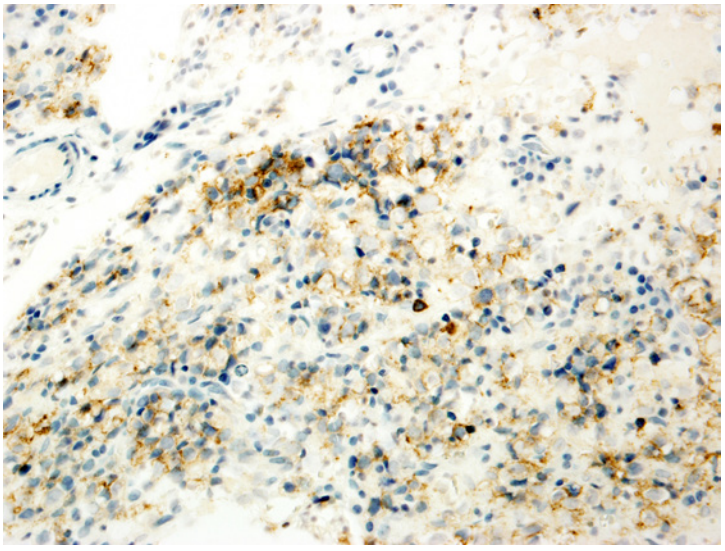

Fig. 4. Sheets of immature cells positive for E-cadherin (E-cadherin stain, ×60).

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Myeloid series was markedly decreased, and megakaryocytes showed frequent dysmegakaryopoiesis. Pronormoblasts/proerythroblasts were diffusely positive for E-cadherin, glycophorin A and CD71 (Fig. 4). It was difficult to quantitate the percentage of erythroid lineage cells due to the lack of aspirate; however, it was estimated, based on immunostains in core biopsy, that they represented a major component of cellular elements (at least 80%) in the marrow. Furthermore, preliminary cytogenetic analysis revealed the deletion of chromosome 5q with evidence of clonal evolution. Combined morphologic, immunophenotypic and cytogenetic features supported the diagnosis of pure erythroid leukemia.

The patient was started on induction chemotherapy at a different institution but unfortunately, she succumbed to her illness after a few months.

Discussion

The 2016 WHO classification of myeloid neoplasms defines PEL as neoplastic proliferation of mature erythroblasts with more than 80% immature erythroid precursors in bone marrow of which more than 30% are proerythroblasts and with no significant myeloblast component (less than 20%) [1]. Diagnosing PEL has always been a challenge due to a lack of specific immunophenotype studies. Many erythroid markers such as CD71, CD235a, glycophorin A, hemoglobin A, and E cadherin have been utilized in the diagnosis of PEL. These markers are either nonspecific and stain both erythroid precursors and anucleate mature red blood cells like CD235a, or stain nonerythroid malignant cells in other malignancies like CD71. Traditional markers of erythroid lineage like glycophorin A and hemoglobin A are often absent in early pronormoblasts that decreases the sensitivity for diagnosis [2]. More recently, alpha hemoglobin stabilizing protein (AHSP) and ferritin H have shown to be more specific markers of erythroid precursors in PEL. AHSP does not stain blasts in other nonerythroid acute leukemias [3]. Similarly, ferritin H, which is a marker of early erythroid precursors, is specific for pure erythroid leukemia blasts, plasma cells, and macrophages [4]. Additionally, some cases of PEL may express myeloid or T cell markers adding to further confusion in the diagnosis.

The majority of the cases of PEL demonstrate abnormal karyotype, which is mostly complex genetic alteration [2]. Both de novo and secondary PEL cases show a complex karyotype with chromosomes 5 and 7 being the most frequently involved abnormalities [5]. Some of the cytogenetic abnormalities like del 5q, del 7q or del 17p are recurring myeloid associated while others like 7p abnormalities could be non-myeloid associated. PEL has also been associated with a higher frequency of TP53 mutations compared to other leukemias. More than one TP53 abnormality could be pathognomonic for PEL [6], while lower rates of FLT3, NMP1 or NRAS mutations have been observed in PEL compared to other leukemia cases.

A systematic review of clinical trials, observational studies and case reports did not show any evidence of increased cases of leukemia or secondary cancers in patients taking hydroxyurea for sickle cell disease or myeloproliferative disorders. Even studies with up to 17 years of follow-up did not reveal leukemogenesis or carcinogenesis in adult sickle cell patients treated with hydroxyurea [7, 8]. However, there have been cases of leukemia or MDS reported with the use of hydroxyurea, mainly limited to case reports [9–12]. Another series noted a higher incidence of hematological evolution to acute leukemia and MDS than previously reported, with 40% of cases occurring after 12 years of follow-up [13]. 17p deletion associated acute myeloid leukemia and MDS have been seen in patients with myeloproliferative disorders treated with hydroxyurea [14, 15].

A couple of cases of erythroid leukemia have been reported with the use of hydroxyurea in sickle cell disease after about 4 and 14 years of exposure [16, 17]. This is only the third case

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of PEL reported in the literature associated with the use of hydroxyurea. PEL has also been reported with other therapies [18, 19]. While there is no known clear etiology for the development of this rare and aggressive disease, complex genetic abnormalities seen in these cases may suggest therapy-related cause and the use of hydroxyurea or other anti-metabolites may be responsible for these changes. Better understanding of pathogenesis of PEL is needed to determine if there is any significant association with the use of anti-neoplastic agents.

Statement of Ethics

Informed consent was obtained from the patient for the publication of the case report. Written informed consent was provided by the parents after the patient's demise for publication of the case including images.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

All authors were involved in the preparation of this article. All authors have read and approved the final manuscript.

References

1 Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
2 Reinig EF, Greipp PT, Chiu A, Howard MT, Reichard KK. De novo pure erythroid leukemia: refining the clinicopathologic and cytogenetic characteristics of a rare entity. Mod Pathol. 2018;31(5):705–17.
3 Raess PW, Paessler ME, Bagg A, Weiss MJ, Choi JK. α-Hemoglobin-stabilizing protein is a sensitive and specific marker of erythroid precursors. Am J Surg Pathol. 2012;36(10):1538–47.
4 Wang W, Grier DD, Woo J, Ward M, Sui G, Torti SV, et al. Ferritin H is a novel marker of early erythroid precursors and macrophages. Histopathology. 2013;62(6):931–40.
5 Lessard M, Struski S, Leymarie V, Flandrin G, Lafage-Pochitaloff M, Mozziconacci MJ, et al. Cytogenetic study of 75 erythroleukemias. Cancer Genet Cytogenet. 2005;163(2):113–22.
6 Montalban-Bravo G, Benton CB, Wang SA, Ravandi F, Kadia T, Cortes J, et al. More than 1 TP53 abnormality is a dominant characteristic of pure erythroid leukemia. Blood. 2017;129(18):2584–7.
7 Voskaridou E, Christoulas D, Bilalis A, Plata E, Varvagiannis K, Stamatopoulos G, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). Blood. 2010;115(12):2354–63.
8 Steinberg MH, McCarthy WF, Castro O, Ballas SK, Armstrong FD, Smith W, et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. Am J Hematol. 2010;85(6):403–8.
9 Wilson S. Acute leukemia in a patient with sickle-cell anemia treated with hydroxyurea. Ann Intern Med. 2000;133(11):925–6.
10 Baz W, Najfeld V, Yotsuya M, Talwar J, Terjanian T, Forte F. Development of myelodysplastic syndrome and acute myeloid leukemia 15 years after hydroxyurea use in a patient with sickle cell anemia. Clin Med Insights Oncol. 2012;6:149–52.

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DOI: 10.1159/000508361

11 Rauch A, Borromeo M, Ghafoor A. Leukemogenesis of hydroxyurea in the treatment of sickle cell anemia. Blood. 1999;94:415.
12 Al Jam'a AH, Al Dabbous IA, Al Khatti AA, Esan FG. Are we underestimating the leukemogenic risk of hydroxyurea. Saudi Med J. 2002;23(11):1411–3.
13 Kiladjian JJ, Rain JD, Bernard JF, Briere J, Chomienne C, Fenaux P. Long-term incidence of hematological evolution in three French prospective studies of hydroxyurea and pipobroman in polycythemia vera and essential thrombocythemia. Semin Thromb Hemost. 2006;32(4 Pt 2):417–21.
14 Merlat A, Lai JL, Sterkers Y, Demory JL, Bauters F, Preudhomme C, et al. Therapy-related myelodysplastic syndrome and acute myeloid leukemia with 17p deletion. A report on 25 cases. Leukemia. 1999;13(2):250–7.
15 Sterkers Y, Preudhomme C, Laï JL, Demory JL, Caulier MT, Wattel E, et al. Acute myeloid leukemia and myelodysplastic syndromes following essential thrombocythemia treated with hydroxyurea: high proportion of cases with 17p deletion. Blood. 1998;91(2):616–22.
16 Taylor JG, Darbari DS, Darari DS, Maric I, McIver Z, Arthur DC. Therapy-related acute myelogenous leukemia in a hydroxyurea-treated patient with sickle cell anemia. Ann Intern Med. 2011;155(10):722–4.
17 Aumont C, Driss F, Lazure T, Picard V, Creidy R, De Botton S, et al. Myelodysplastic syndrome with clonal cytogenetic abnormalities followed by fatal erythroid leukemia after 14 years of exposure to hydroxyurea for sickle cell anemia. Am J Hematol. 2015;90(7):E131–2.
18 Imataki O, Takeuchi A, Uchida S, Yokokura S, Uemura M, Kadowaki N. Pure erythroid leukemia in a polymyositis patient treated with azathioprine. Rare Tumors. 2018;10:2036361318773847–3.
19 Sadrzadeh H, Hasserjian R, Fathi AT. Pure erythroid leukemia evolving from a therapy-related myelodysplastic syndrome secondary to treatment for chronic lymphocytic leukemia. Am J Hematol. 2013;88(3):240–1.