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Erythroleukemia with Complex Cytogenetic Abnormalities: A case report with review of literature

KEYWORDS: Acute Erythroleukemia, Flow cytometry, Cytogenetic abnormality

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ABSTRACT *Acute Erythroleukemia (AEL) is a rare type of hematopoietic neoplasm, having a prevalence of 3-5% of all Acute Myeloid Leukemia (AML). We present a case report of acute erythroleukemia, a rare type of AML, with complex cytogenetic abnormalities.*

A 54-year old male presented with low grade fever and significant weight loss. Complete hemogram and a peripheral smear revealed pancytopenia with 18% blasts. It also showed features of hemolysis. Bone marrow (BM) study showed erythroid hyperplasia with erythroblasts constituting 85% of all nucleated cells and 21% myeloid blasts among non-erythroid cells. Flow cytometry revealed 23% blasts positive for CD33, CD34, CD117, CD36 and HLA-DR. Cytogenetic study revealed hypotetraploidy with numerous structural abnormalities indicating poor prognosis.

Introduction

The term Acute Erythroleukemia (AEL) /AML-M6 is defined as proliferation of dysplastic erythroid elements mixed with blasts of myeloid origin. The recent World Health Organization (WHO) classification has a category of acute myeloid leukemia not otherwise categorized, which includes acute erythroid leukemia (M6) of two subtypes: M6a-erythroleukemia (erythroid/myeloid) and M6b-pure erythroid leukemia. [1]

Erythroleukemia (erythroid/myeloid) is defined by the presence of >50% erythroid precursors of all nucleated cell population and >20% myeloblasts among the non-erythroid cell population in the bone marrow. Pure erythroid leukemia represents a neoplastic proliferation of immature erythroid cells (undifferentiated or proerythroblastic in appearance) constituting >80% of BM cells, with no significant myeloblastic component. [2]

We report a rare case of acute erythroleukemia which had complex cytogenetic abnormalities.

Case report

A 54 year old male, businessman by occupation, presented with complaints of fever since 2 days, easy fatigability, and loss of weight and appetite of 2 months duration. Fever was low grade and continuous. There was significant weight loss of 6 kg in the previous 2 months. He consumed alcohol and smoked occasionally, and denied any history of toxin exposure or medications.

On examination, he was pale and emaciated. He had no bleeding tendency, gum hypertrophy or bone tenderness. Vitals were stable. There was mild hepatosplenomegaly without significant lymphadenopathy.

Hematological investigations revealed hemoglobin of 4.7gm/dl, hematocrit 13.8%, total count 2400 cells/cumm and platelets of 30,000/cumm. The peripheral smear showed normocytic normochromic RBC picture with numerous spherocytes, schistocytes, polychromatophils, occasional erythroblasts and 18% myeloblasts. Biochemical parameters showed an elevated serum LDH, Uric acid & total bilirubin. Renal function test and liver function tests were within normal limits.

The bone marrow yielded a hypercellular aspirate with increase in erythroid precursors showing megaloblastic changes. The total erythroblast count was 85% of all nucleated cells. Of this, the proerythroblasts comprised 35%. Dyspoietic erythroid cells showing multinucleation, nuclear budding and nuclear to cytoplasmic dysynchrony were noted. Myeloblasts comprised 21% of non erythroid cells. Megakaryocytes were normal in number and morphology. PAS (Periodic acid stain) showed diffuse and punctate positivity in few abnormal erythroblasts. Perls stain revealed few sideroblasts; however no ringed sideroblasts were seen. The bone marrow biopsy revealed a hypercellular packed marrow. The intertrabecular spaces were infiltrated by blasts having scant cytoplasm, high nuclear to cytoplasmic ratio, round nucleus with fine chromatin and 1-2 prominent nucleoli. Numerous erythroblasts were also evident. Myelopoiesis was suppressed and a few megakaryocytes are seen. Flow cytometry analysis of the bone marrow revealed 23% blasts. The myeloid nature of the blast cell population was confirmed by phenotypic markers (CD34, CD117, and CD33). The erythroid nature of the blast cells belonging to this series was confirmed by immunologic markers (CD45dim and CD36). B cell and T cell markers were negative.

Cytogenetic analysis of the bone marrow sample was performed. 23 metaphases were analyzed and 11 of them karyotyped which showed hypotetraploidy with numerous structural abnormalities. Karyotype: 82-85,XY+,Y,+Y,i(1)(p10), +del(6)(q23)X2,+add(11)(p13), add(12)(p13),+5mar.

However the patient refused treatment and was discharged against medical advice.

Discussion

Acute erythroleukemia is an uncommon type of acute myeloid leukemia (AML) constituting less than 5% of all AML cases. [1] Di Guglielmo reported the original cases of erythroleukemia in 1917. He described a syndrome composed of an association of immature erythroid and myeloid elements and a disease characterized by a pure normoblastic proliferation. Ever since, its classification and description has been changing over time. Dameshek and Baldini in 1969, postulated 3 phases of the disease as an erythremic phase, an erythromyeloblastic phase and lastly the myeloblastic phase. The FAB classification in 1985 and the present WHO classification of 2008, categorizes this disease into 2 sub types. They are Erythroleukemia M6a (erythroid/myeloid leukemia) and Pure erythroid leukemia M6b. [2, 3]

The Erythroleukemia (M6a) is more common and is defined

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by the presence of 50% or more erythroid precursors and 20% or more myeloid blasts in the non erythroid component. The pure erythroid leukemia (M6b) is composed of 80% or more immature erythroblast with no significant myeloblastic component.[2] Most of the AEL develop de novo, accounting for approximately 1% of all de novo AML, and the disease is not associated with any identifiable risk factors. The common antecedent causes for secondary erythroleukemia are Myelodysplastic syndrome (refractory anemia with excess of blasts or refractory cytopenia with multilineage dysplasia), Myeloproliferative neoplasms (Chronic myelogenous leukemia with erythroblastic crisis), exposure to toxins such as benzene, chemotherapy, immunosuppressants or ionizing radiation.[4]

Acute erythroid leukemia is a disease of adults that primarily affects people older than 50 years with a male preponderance. The clinical features are relatively non specific and include pallor, fever and hepatosplenomegaly. [2, 4]

The diagnosis of AEL requires morphologic examination of the bone marrow with flow cytometry for confirmation. The examination of peripheral blood smears can sometimes be misleading because more often blood smears show pancytopenia and are completely devoid of blasts. The present case also showed pancytopenia with 18% of blasts in the peripheral blood. [1, 3]

Nonspecific red blood cell abnormalities may be present, such as anisocytosis, poikilocytosis, anisochromia, basophilic stippling, schistocytes, and erythrocytes that are poorly hemoglobinized. Severe hemolysis may sometimes occur. This case showed mild hemolysis comprising of schistocytes, spherocytes, and polychromatophils with an elevated total bilirubin values. Anemia, leucopenia and thrombocytopenia, either singly or in combination, is also a common manifestation.[4,5]

Bone marrow aspirate and imprint smears shows erythroid hyperplasia with predominantly medium to large erythroblasts with basophilic cytoplasm and megaloblastic nucleus. The cytoplasm in the more immature cells frequently contains poorly demarcated vacuoles, which may coalesce. Dyspoiesis in the form of multinucleation, budding, bizarre nuclear forms and basophilic stippling can be seen. Dysgranulopoiesis and megakaryocytic dyspoiesis can also be seen. [3, 4, 7, 8] The atypical erythroblasts show coarse granular positivity with PAS staining. The Perls stain shows ring sideroblasts in few cases. [1.3]

Immunophenotyping of AEL is best performed by flow cytometry because a wider array of antibodies is available than in immunohistochemistry. Erythroblasts express erythrocyte-associated antigens; this expression correlates with the degree of differentiation or maturation of the neoplastic cells. Erythroblasts usually express CD71 (transferring receptor), but occasionally CD71 expression can be aberrantly dim. Erythroblasts variably express hemoglobin A, glycophorin A, spectrin, ABH blood group antigens, and HLA-DR, and are negative for myeloid-associated markers such as MPO. The Gerbich blood group (Gero) antibody, carbonic anhydrase 1, and CD36 can be expressed by more immature erythroblasts. The myeloblasts of the erythroleukemia subtype express myeloid-associated markers including CD13, CD33, CD117 (KIT), and MPO, with or without expression of CD34 and HLA-DR. [4, 8]

Complex karyotype with multiple structural abnormalities is usually associated with poor prognosis. The most frequent abnormalities include monosomy 5 or del (5q), monosomy 7 or del (7q) and trisomy 8. Complex karyotypes (3 or more cytogenetic abnormalities) also have been reported in AEL cases. [2, 4, 7, 8] The cell of origin of acute erythroleukemia of any subtype is a multipotent stem cell. This cell shows varying degrees of erythroid and granulocyte lineage maturation. The poor remission rate and short survival characteristic of this disorder are dependent upon high pronormoblast to myeloblast ratio within diagnostic bone marrow aspirates, high proliferative index, "unfavourable" cytogenetic aberrations, and high incidence of P-glycoprotein expression (the multidrug resistant phenotype). [6] Acute erythroid leukemia overlaps with Myelodysplastic syndromes that are erythroid rich and other types of AML with increased erythroid precursors. Other differentials include megaloblastic anemia and reactive erythroid hyperplasia following therapy or administration of erythropoietin. [2, 4]

Conclusion

Acute Erythroleukemia is a rare hematopoietic neoplasm characterized by uncontrolled proliferation of abnormal erythroid precursors and myeloblasts. Based on morphology, it has to be differentiated from other neoplastic and non neoplastic conditions. Immunophenotyping and cytogenetic studies are required for assessing the prognosis. However, it has an overall poor prognosis among the other AMLs.

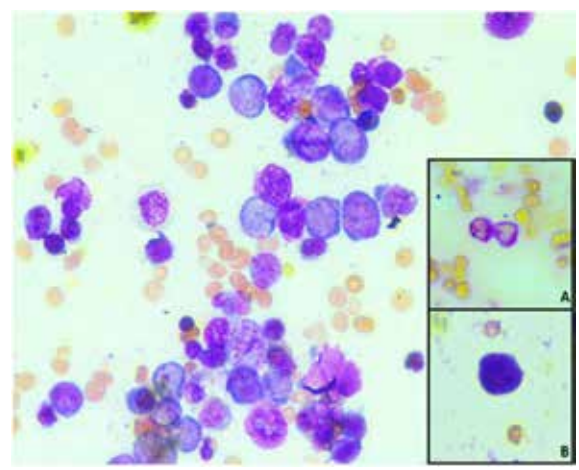

Figure 1: Bone marrow aspirate showing erythroid hyperplasia comprising of proerythroblasts and abnormal erythroblasts. Inset (A) shows coarse granular positivity in PAS stain (PAS stain 40x). Inset (B) shows myeloblast (Leishman stain 40x)

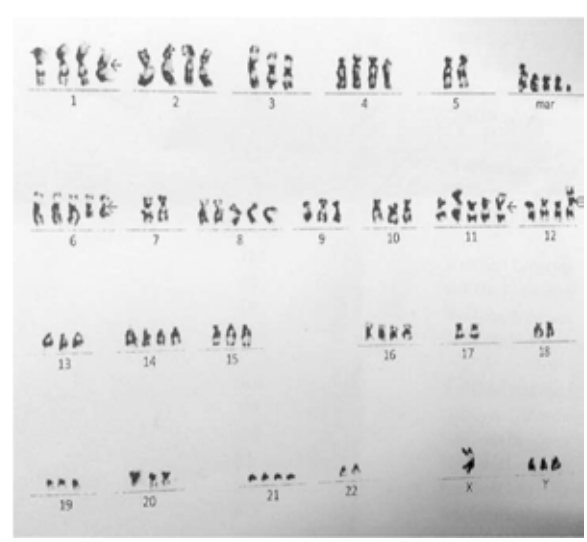

Figure 2: Karyotype showing multiple cytogenetic abnormalities.

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