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ERYTHROLEUKEMIA IN AN ADOLESCENT MALE WITH SHORT STATURE AND HYPOGONADISM: A RARE ASSOCIATION

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ABSTRACT

Short stature is extremely rare to be associated with acute erythroid leukemia particularly in the presence of hypogonadism and hormonal abnormality. We present a case of an adolescent male patient who had short stature, hypogonadism and hormonal abnormalities. Complete blood counts showed evidence of pancytopenia with presence of blasts in peripheral blood. On Bone marrow aspirate, a diagnosis of Erythroleukemia (erythroid/myeloid) was made. Acute erythroid leukemias are rare type of acute leukemias characterized by a predominant erythroid population and comprise less than 2-7% of all acute myeloid leukemias. This case is presented due to rarity of Erythroleukemia in young age. In addition, association of erythroleukemia with short stature, hypogonadism and various hormonal abnormalities has not been reported so far.

INTRODUCTION

Variants of normal growth include familial short stature, constitutional delay of growth and puberty, and small for gestational age with catch-up growth. Pathological causes of abnormal growth include many systemic diseases and their treatments, growth hormone deficiency, and a series of genetic syndromes, including Noonan syndrome and Turner syndrome.[1] However, clinical presentation of erythroleukemia associated with short stature is extremely rare.

Acute erythroid leukemia (AEL) is a rare form of acute myeloid leukemia (AML). It accounts for less than 2-7% of all AML cases. [2] Di Guglielmo described the original case of acute erythroleukemia in 1917 as a syndrome composed of immature erythroid and myeloid elements characterized by a pure normoblastic proliferation.[3]According to World Health Organization (WHO) classification, 2 subtypes of Acute erythroid leukemia are recognized based on the presence or absence of a significant myeloid (granulocytic) component. The first subtype, pure erythroid leukemia is defined as a neoplastic proliferation of immature erythroid lineage cells (undifferentiated or proerythroblastic) comprising >80% of bone marrow cells with no evidence of a significant myeloblastic component (corresponding to AML-M6a of FAB classification). The second subtype, erythroleukemia is defined by the presence in the bone marrow of more than 50% erythroid precursors in the entire nucleated cell population and more than 20% myeloblasts in the nonerythroid cell population (corresponding to AML-M6b of FAB classification).[2]

CASE REPORT

A 17 year old male patient presented with complaints of multiple episodes of vomiting and easy fatigability, headache and on and off high grade fever. Three months back the patient was diagnosed with communicating hydrocephalus with tuberculous meningitis and was started on anti-tubercular treatment. On examination, the patient was found to have short stature and underdeveloped secondary sexual characteristics including absence of facial and axillary hair, sparse pubic hair and small sized bilateral testes. Pallor was noted on general physical examination. However, rest of the general and systemic examination was within normal limits.

On further evaluation of short stature and underdeveloped secondary sexual characteristics, a hormonal profile was done which revealed low levels of testosterone and high levels of prolactin. Follicle Stimulating Hormone and Leutinizing Hormone were found to be within normal limits. A hypothyroid profile was revealed; however, other biochemical parameters including liver and kidney function tests did not show any abnormality. The hormone profile is summarized in Table 1. A CT-scan of head showed evidence of a communicating hydrocephalus and ruled out presence of any neoplasm which could lead to hyperprolactinemia. Ultrasonogram abdomen revealed a calculus of 7.9 mm size in left kidney, but was otherwise unremarkable.

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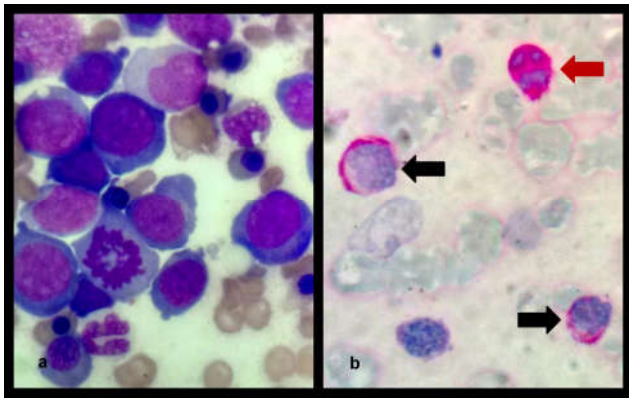
A complete blood count was done which revealed pancytopenia, with hemoglobin=3.1g/dl, total leukocyte count= 3500/µL and platelet count= 25000/µL. Peripheral blood examination revealed presence of 10-14% blasts, some of which showed few fine cytoplasmic granules, and 4-10 nucleated RBCs/100 WBCs. In view of the peripheral blood findings, a possibility of Myelodysplastic syndrome and Subleukemic leukemia was considered and Bone marrow aspiration was done. Marked erythroid hyperplasia with erythroid precursor cells comprising 55% of all nucleated cells was noted in Bone marrow aspiration smears. Myeloid blasts comprised 39% of all non-erythroid cells. (Figure a) Erythroid cells showed features of dyserythropoiesis including megaloblastic change and multinucleation. Megakaryocytes were adequate but showed dysplastic changes including few hypolobated forms. A distinct cytoplasmic positivity was noted within erythroid precursor cells on Periodic acid-Schiff staining on bone marrow aspirate smears which strongly indicated the neoplastic origin of these cells particularly in conjunction with the aforesaid morphological findings. (Figure b) Therefore, a diagnosis of Acute Erythroleukemia (erythroid/myeloid) was made.

Table 1 Hormone profile of the patient

Hormone	Level (ref range)
FSH	3.6 mIU/ml (1.55-9.74)
LH	2.9 mIU/ml (1.8-7.8)
Prolactin	22.8ng/ml (3-18.6)
Testosterone	2.3nmol/L (4.56-28.2)
Estradiol	95.5pmol/L (19.7-242)
TSH	>100mIU/L (0.5-5)
T3	1.0 pg/ml (2-4.4)
T4	0.4 ng/dl (0.6-2.2)



a Bone marrow aspirate showing both myeloid and erythroid blasts. Erythroid precursors comprised more than 50% of all nucleated cells. **b** Neoplastic erythroblasts highlighted by Periodic-Schiff positivity (black arrows). A neutrophil (red arrow) act as internal control in the field.

DISCUSSION

Erythroleukemia primarily affects males over 50 years of age. 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] In the present case however, the patient is adolescent and he did not have any previous history of hematological neoplasm or exposure to radiations/ toxins/ chemotherapy suggestive of a de-novo process.

In a report of two cases of acute erythroid leukemia by Hasserjian *et al*, hypogonadism and bilateral undescended testes were noted in one of the adult patients. However, association with short stature or other hormonal abnormalities was not observed. [5] In another case report, Werner Syndrome (adult Progeria) associated with erythroleukemia was noted. In this case, the short stature of the patient was found to be part of Werner syndrome. However, no evidence of hypogonadism was observed. [6] Presence of pancytopenia, with low circulating blasts is typical of acute erythroid leukemia, as also seen in the present case. Very few patients present with elevated total leukocyte count. The diagnosis require a bone marrow examination, special stains and in difficult cases, immunophenotyping and molecular studies. In cases with undifferentiated blasts, AML with minimal differentiation, acute lymphoblastic leukemia and acute megakaryoblastic leukemia needs to be excluded. However, in our case neoplastic erythroblasts could be identified by using cytochemical stain (PAS) Periodic acid-Schiff.

The increase in both myeloid blast cells and erythroblasts in AML-M6a indicates the involvement of an early stem cell in the pathogenesis of this disease. [7] Previous reports have demonstrated multiline age involvement in cases of AML-M6a. In fact it has been argued by some authors that AML-M6a is a clonal myeloid disorder similar to MDS but presents with a major erythroid component, whereas AML-M6b represents a 'true erythroleukemia', where only erythroid cells are involved in the malignant clone.[8],[9]

In conclusion, short stature is extremely rare to be associated with acute erythroid leukemia. Association of erythroleukemia with short stature, hypogonadism and various hormonal abnormalities has not been reported so far.

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