Could Vitamin B12 Deficiency Mimic Erythroleukemia?

Jenan Obaid, MBBCh, BAO* Wilfredo Gracia, MD**
Abbas Ali, MBBCh, BAO*** Abdulrahman Barakat, MBBCh*

Erythroleukemia is a rare form of acute myeloblastic leukemia (AML) as described by the World Health Organization (WHO); the condition represents less than 5% of all AML cases. It is a great challenge to establish the diagnosis. One of the principal differential diagnosis is megaloblastic anemia due to vitamin B12 deficiency.

A fourteen-year-old Bahraini female was initially diagnosed with vitamin B12 deficiency based on the clinical history, blood count, smear findings and vitamin B12 level. The lack of response to supplementation with vitamin B12 injections raised suspicion of bone marrow disease. A subsequent bone marrow biopsy confirmed the diagnosis of erythroleukemia. After establishing the diagnosis with bone marrow biopsy, the patient was referred to the oncology center to receive chemotherapeutic treatment.

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Erythroleukemia, sometimes referred to as Di Guglielmo syndrome; it is a rare form of acute leukemia related to AML family. The disease was initially described by Giovanni Antonio Di Guglielmo in 1917, who described the condition as being composed of immature erythroid and myeloid cells with a pure normoblastic proliferation[1].

The condition represents less than 5% of all AML cases, and could occur at any age; some studies have shown a bimodal distribution with a high peak in the sixth or seventh decade of life, and a smaller peak below the age of 20[2-4].

The disease was significantly revised since the criteria was established. The disease was classified by the French-American-British (FAB) Cooperative Group in 1976 and recently by WHO[5,6].

In 2008, WHO classified the disease into two subcategories: erythroleukemia with myeloid/erythroid component and pure erythroid leukemia (PEL). Erythroleukemia with myeloid/erythroid component was 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 non-erythroid cell population. Pure erythroid leukemia was defined when immature cells undergo a neoplastic proliferation (undifferentiated or pro-erythroblastic in nature) exclusively involving the erythroid component (>80% of bone marrow cells) with no significant myeloblastic involvement observed[7].

In the 2016 WHO classification, the first category was merged into AML with myelodysplastic related changes and retains the category of pure as the only form of acute erythroid leukemia[6].

The most common clinical presentation is pancytopenia with extensive marrow involvement. Furthermore, hepatosplenomegaly has been reported in approximately 40% of cases with erythroleukemia and a subset of cases present with extramedullary disease[8,9]. Erythroleukemia has a very poor prognosis, poor response to conventional chemotherapy and a median survival of 3 months[10].

Vitamin B12 is an essential cofactor in the cell metabolism and DNA synthesis and is crucial for erythropoiesis. Its deficiency increase erythroblast apoptosis resulting in anemia or even pancytopenia which can be very difficult to differentiate from hematologic malignancy. Although rare among children, it is a common condition among elderly patients, pregnant and vegetarians[11,12].

The aim of this report is to present a case of acute erythroleukemia which was masked and delayed due to co-existence of vitamin B12 deficiency in a young vegetarian patient.

THE CASE

A fourteen-year-old Bahraini female presented with one-month history of epigastric pain associated with nausea, vomiting, dizziness and fatigue. Further investigation revealed an intentional weight loss of approximately 10 kilograms over a span of 6 weeks.

Her dietary history elucidated that the patient had a very poor diet for the past one and a half year, consisting mostly of rice and vegetables, avoiding fish, meat and poultry products. Her medical, surgical, and family histories were unremarkable.

* Registrar
** Consultant
*** Intern
Department of Internal Medicine
King Hamad University Hospital
Kingdom of Bahrain
E-mail: jenan.obaid@khuh.org.bh

Clinical examination revealed non-contributory findings except for tenderness in the epigastric region. Basic investigations revealed a hemoglobin level of 58 g/L, normocytic, normochromic, WBC of $2.26x10^9$/L and a platelet count of $84x10^9$/L. The reticulocyte count was normal and the peripheral blood smear revealed nucleated RBC and few circulating blasts, mild macrocytosis, poikilocytes, polychromatophils and stippling basophils. Renal and liver function, electrolytes and iron profile were normal.

Vitamin B12 level was 152 (normal range: 211-911), increased homocysteine serum level 37.9 µmol/L (<15 µmol/L), whereas methylmalonic acid, parietal cells and intrinsic factor antibodies were within normal limits. Gastroscopy was normal.

The patient's clinical presentation and laboratory results led to a provisional diagnosis of vitamin B12 deficiency. She was given B12 intramuscular injection.

During follow-up, further CBC results revealed that the patient had not shown any significant improvement, which raised the suspicion of bone marrow disease as the cause of pancytopenia.

Bone marrow aspiration and biopsy revealed a hypercellular marrow, a severe hyperplasia of the erythropoietic system with dysplastic features (megaloblastic changes and multiple nuclei), and approximately 70% of erythroid blasts of all nucleated cells. The blast population was cytochemical MPO positive.

The immunophenotyping by flow cytometry expressed CD13 (heterogeneous), CD33, CD34 (dim), CD117 (dim) and HLA-DR (heterogeneous). The karyotyping results were normal (46, XX [25]), see figure 1.

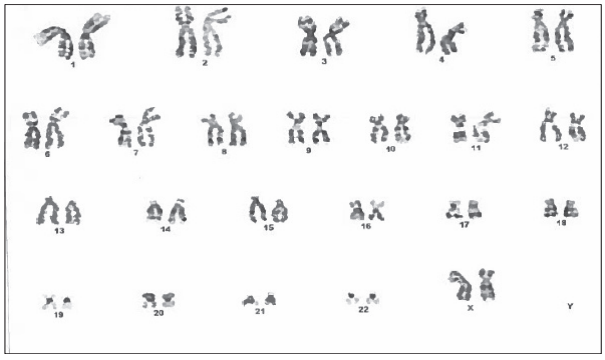

Figure 1: Patient's Karyotype

DISCUSSION

Acute erythroleukemia is a rare disease, comprising only 5% of all AML, and is rarely seen in patients below the age of 20 years. Similarly, vitamin B12 deficiency is rare among children[11,13]

Vitamin B12 deficiency could induce a significant change in the bone marrow, which in turn could mimic the diagnosis of leukemia. Several cases have been reported of the concomitant presentation of vitamin B12 deficiency with leukemia, and the difficulty of distinguishing them[14,15].

Our patient had a history of very poor oral intake and strict vegetarian diet for one year and a half, which was the cause of vitamin B12 deficiency. A study reported that vitamin B12 depletion occurs in vegetarians irrespective of the type of diet they are on, age, or residential area[16].

The need for the treatment of vitamin B12 deficiency prior to labeling a patient with erythroleukemia has thus been well demonstrated in a case presented by Kappeler and Gubser, where the diagnostic signs completely disappeared following B12 replacement[15].

Our case was labeled as vitamin B12 deficiency and was treated accordingly with a course of vitamin B12 injection. However, the hematological abnormalities persisted which raised the suspicion of bone marrow malignancy.

Bone marrow aspiration and biopsy revealed a characteristic morphologic pattern of erythroleukemia with the myeloid component. The marrow was replaced by approximately 70% of dysplastic erythroid blasts displaying a typical immunophenotype, although the most typical markers for erythroblasts (CD 36 and glycophorin A) were not tested in our patient. The remaining blast population was MPO positive. The morphology and immunophenotype by flow cytometry confirmed the diagnosis of erythroleukemia (myeloid/erythroid component).

In our patient, the cytogenetic study was normal, which is in contrast with the majority of the studies. That shows a significant number of genetic aberrations including abnormalities on either chromosome 5 or 7 and complex karyotype, although no specific mutation has been described[3,17]. In a recent study, Wang et al found TP53 mutation in 100% of 10 patients with PEL indicating that this mutation could play a role in the pathogenesis, complex karyotype and genomic instability in PEL[18].

CONCLUSION

Clinical guidelines are mandatory for the proper management of patients with erythroleukemia. It is also very important to address other co-factors that may mimic or hinder the diagnosis, such as vitamin B12.

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