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Case report

PYREXIA DUE TO MEGALOBLASTIC ANEMIA: AN UNUSUAL CASE

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ABSTRACT

Postmenopausal vegetarian female presented with short febrile illness associated with generalized weakness Clinical and investigative findings evidenced megaloblastic anemia Since none of investigations could pinpoint the cause for pyrexia and patient did not respond to empirical antibiotic and conservative antimalarial therapy, megaloblastic anemia itself was suspected to be cause for febrile episode Patient was treated with parenteral B12 and oral folic acid for megaloblastic anemia and she responded to it and became afebrile within 72 hours. Subsequently megaloblastic anemia was correlated to be cause of febrile illness.

Keywords: Megaloblastic anemia, Pyrexia of unknown origin, B12 and folic acid deficiency

INRTODUCTION

Megaloblastic anemias are a group of disorders which are most commonly caused by nutritional deficiencies of either vitamin B_{12} or folate or both, inherited disorders of DNA synthesis or following certain drug therapy. Megaloblastic anemia rarely may be a cause of pyrexia which may be difficult to differentiate from pyrexia of unknown origin (PUO) even after exhaustive laboratory investigations.[1] The aim of the present article is to highlight megaloblastic anemia as a rare cause of fever and create awareness amongst practicing physicians about a treatable condition.

CASE PRESENTATION

A 55 year old postmenopausal vegetarian female presented with complaints of fever, nausea, vomiting and dry cough of 7 days duration. The fever was intermittent, mild to moderate grade and associated with generalized weakness, easy fatigability and loss of appetite. There was no history of burning micturation, arthralgia or skin rash. There was no history of recent travel to malarial endemic zone or exposure to any patient suffering from communicable diseases e.g. Tuberculosis, etc.

Clinical examination revealed a pulse rate of 110 per minute, blood pressure of 120/70 mm Hg (supine x right arm) and oral temperature of 101°F. She had moderate pallor and mild icterus. There was no significant lymphadenopathy, dyspnoea or skin rashes. Examination of cardiovascular, respiratory, abdomen and nervous system examinations were within normal limits. X-ray chest was within normal limit and ultrasound abdomen revealed no significant abnormalities.

Routine hematological evaluation revealed low hemoglobin (Hb); 6 G%, low hematocrit; 18% , low total leukocyte count (TLC): 4000c/mm with P60L37E02M01, low total platelet count (TPC):100000 c/mm, high reticulocyte count: 3.5% and high mean corpuscular volume (MCV): 115 fL . Peripheral smear showed pancytopenia with a moderate degree of anisopoikilocytosis and a good number of macrocytes, macro-ovalocytes and

hypersegmented neutrophils. Bone marrow aspiration from the left anterior superior iliac spine revealed marked hypercellularity, florid erythroid hyperplasia with an altered myeloid to erythroid ratio (1:2), megaloblastic dyspoiesis and numerous giant metamyelocytes. Perl stain showed adequate marrow iron stores without any ring sideroblasts. There was no evidence of blast prominence, granulomas, hemoparasites, malignancy or increased reticulin. The bone marrow morphology was suggestive of megaloblastic anemia which was confirmed biochemically by low levels of serum vitamin B_{12} 59.6 pg/mL (reference; 180- 900), low folic acid 3.9 ng/mL (reference; 4-24) and markedly elevated serum lactate dehydrogenase (LDH) 7500 IU/L (reference: 225-420]. The patient's routine liver and renal function tests were within normal limits except for mild unconjugated hyperbilirubinemia with total bilirubin: 4.2 mg/dL (reference: 0.2-1.2), direct: 0.4 mg/dL and indirect: 3.8 mg/dl. Her routine microbiological (blood culture), serological, autoimmune, inflammatory (serum C-reactive protein) and endocrine work-up were negative. Normal viral titre along with the absence of reactive lymphocytes in the peripheral smear ruled out the possible viral etiology.

Pending laboratory investigative reports and in view of neutropenia, the patient was started empirically with broad spectrum intravenous antibiotics (Ceftriaxone) which was given for a period of 05 days, but the patient continued to be febrile even after 05 days of antibiotic. Thereafter she was given course of antimalarial (Artisunate) for period of five days. But she still continued to remain febrile, even after 10 days of hospitalisation and none of investigations were contributory to determine the cause of fever Therefore, in view of the positive laboratory investigations pointing towards megaloblastic anemia along with the absence of any positive contributory findings, the patient was started on injection vitamin $B_{12:}$ 1000µg IM and folic acid: 5mg oral daily. Pyrexia settled on day 13^{th} day of hospitalisation within 03 days of vit B12 and folic acid treatment which was further continued and in view of low Hb, she was transfused with 2 units of packed cell volume. The patient improved symptomatically after being prescribed vitamin B_{12} and folic acid supplements, following which the patient was discharged in a stable condition. Routine follow-up at two months showed normalization of vitamin B_{12} and folate levels as well as improvement in hematological parameters (hemoglobin; 12gm, MCV; 87fL) without any febrile episode.

DISCUSSION

Dramatic response to nutritional supplements in our case supports that the pyrexia was attributable directly to megaloblastic anemia secondary to vitamin B_{12} and folate deficiency rather than anything else, as was ruled out by appropriate available diagnostic modalities. As per the modified Petersdorf criteria[2], FUO is defined as: 1) a temperature exceeding 101^0 F 2) duration of the fever of more than three weeks and 3) evaluation of three outpatient visits or three days in hospital. Our patient satisfied two out of the three criteria (1 and 3).

In a study by Tahlan etal[3], the incidence of low-grade fever in nutritional megaloblastic anemia varied from 28% to 60%. Another study from Northern India described persistent low-grade fever in 70% of the females with B_{12} and/or folate deficiency.[4] McKee[5] reviewed 122 patients of nutritional megaloblastic anemia for the presence of pyrexia (temperature≥100°F) and found that 40% pyrexia was attributable solely to the megaloblastic disease. In the majority of the patients, fever subsided 24 to 72 hours after supplementation of vitamin B_{12} and/or folate, suggesting the rapid correction of ineffective hematopoiesis.. Negi et al[6] reported a case of anicteric male with pyrexia (100.2^0f), bicytopenia and macrocytosis secondary to B_{12} deficiency Singanayagam et al.[7] reported a young male with pyrexia of 6 weeks duration , severe pancytopenia and mild hyperbilirubinemia secondary to folate deficiency. The present report described a case of megaloblastic anemia in a postmenopausal vegetarian female patient who presented with low-grade pyrexia, pancytopenia, macrocytosis (115 fL), very high LDH: 7500 IU/L (reference range: 225-420 IU/L) and mild unconjugated hyperbilirubinemia secondary to combined deficiency of B_{12} (59.6 pg/mL) and folate (3.9 ng/mL). Pyrexia subsided within 03 days after initiation of supplementation therapy.

The exact cause of fever in megaloblastic anemia is unknown and at present, seems more hypothetical rather than conclusive. An association of pyrexia and megaloblastic anemia appears to be causal, whereas in other types of anemias, it seems more coincidental.

Megaloblastic anemia is a panmyelosis characterized by hypercellular marrow and ineffective hematopoiesis. Premature destruction of hematopoietic precursors possibly releases intracellular substances which might function as systemic pyrogens. As was suggested by the researchers, dramatic response to B_{12} and/or folate supplementation (within 72 hours) strongly supports the above said hypothesis. Alternatively, the defective oxygenation at the thermoregulatory centre of the hypothalamus might be the explanation for pyrexia. However, lack of correlation between neurological manifestation and pyrexia in megaloblastic disease does not support this theory[5] Moreover studies have also shown that a rise in temperature might cause depletion of folate stores, both in red blood cells and serum, leading to disturbance of folate metabolism. So whether pyrexia is the cause of folate deficiency or vice versa is yet to be fully understood

CONCLUSION

All patients presenting with pyrexia, megaloblastic anemia and cytopenia should be carefully evaluated for possible vitamin B_{12} and folate deficiency in order to prevent delay in diagnosis, initiate appropriate curative treatment and unnecessary use of antibiotics and other empirical medication

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