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Research Article

Megaloblastic Anemia Secondary to Vitamin B12 and Folate Deficiency Presenting As Acute Febrile Illness and Pyrexia of Unknown Origin: A Prospective Study from Tertiary Care Hospital

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Abstract: Megaloblastic anemia is not uncommon in India, but data is insufficient regarding its presentation as pyrexia. There are many case reports on this topic but very few large sample size studies. We did a prospective study to document such data for patients with megaloblastic anemia secondary to vitamin B12 and folate deficiency presenting as pyrexia of unknown origin. A study of 34 cases with megaloblastic anemia in adults above 15 years of age during 1 year (September 2012 to August 2013) presenting as pyrexia was conducted at SDM College of Medical Sciences and Hospital, Dharwad, Karnataka state, India. There were 34 patients with megaloblastic anemia secondary to vitamin B12 and folate deficiency based on peripheral smear who presented with fever. Fever and dyspnoea were the main presenting symptoms. 28 patients had fever of 99 – 102 F and 6 had moderate to high grade fever (>102 F). 17 patients had fever lasting for less than 7 days, 13 had fever from 7 to 20 days and 4 had fever for more than 21 days .Other symptoms were generalized weakness 25 (73.5%), vomiting 10(29.4%), loose stools 8 (23.5%), and bleeding tendency in 4(11.76%) patients. The pyrexia subsided following the intramuscular injection of vitamin B12 and oral folic acid administration. All the other infective, inflammatory, autoimmune, drugs, endocrine and malignant cause of pyrexia were excluded by appropriate investigations. All patients presenting with pyrexia should be carefully evaluated for possible vitamin B12 and folate deficiency in order to prevent the unnecessary use of antibiotics and investigations. Megaloblastic anemia (vitamin B12, folate deficiency) is a reversible cause of pyrexia that should be considered in any patient who presents with pyrexia especially in those with long duration.

Keywords: Pyrexia, Megaloblastic Anemia, Vitamin B12, Folic acid, Pancytopenia, Hypersegmented neutrophils.

INTRODUCTION

Megaloblastic anemia is a group of disorders characterized by peripheral blood cytopenia which results due to ineffective hematopoiesis in the marrow. They are usually caused by nutritional deficiencies (most common) of either vitamin B12 or folate; or both, inherited disorders of DNA synthesis, or following certain drug therapy [1]. Pyrexia in megaloblastic anemia is not an uncommon manifestation.

However, megaloblastic anemia secondary to vitamin B12 and folate deficiency, solely as the cause of pyrexia, can be found in only a small proportion of cases, for which differentiation from other causes of fever and fever of unknown origin (FUO) may be difficult even after exhaustive laboratory investigations [2-6].

Megaloblastic anemia (vitamin B12, folate deficiency) is a reversible cause of pyrexia that should be considered in any patient who presents with pyrexia, macrocytosis and pancytopenia. Usually fever is low grade; however high grade fever may be seen in those patients who present with more severe hematological disease. The proposed underlying mechanism is that megaloblastic anemia causes intramedullary hemolysis and possibly ineffective leucopoiesis and thrombopoiesis. This increased activity in the bone marrow may be related to systemic pyrexia.

The aim of the present article was to highlight this aspect of megaloblastic anemia presenting as pyrexia as well as pyrexia of unknown origin with a brief review of the existing literature and create awareness among practicing physicians about a treatable condition.

MATERIALS AND METHODS

This study was conducted in tertiary care hospital of North Karnataka during a period of one year (September 2012 to August 2013).

The inclusion criteria for the study are hemoglobin level <10g/dl, mean corpuscular volume (MCV) >100 fL , peripheral blood film findings consistent with megaloblastosis (pancytopenia, macrocytosis, hypersegmented neutrophils) and those patients who had shown significant improvement to vitamin B12 and folic acid supplementation symptomatically on the 2nd day and hematologically on the 7th day.

The exclusion criteria for the study are age less than 15 years, patients with dimorphic anemia, proven other known etiologies and those patients who had not shown significant improvement to vitamin B12 and folic acid supplementation symptomatically on the second day and hematologically on the 7th day.

A proforma was used to document demographic data, clinical presentation, dietary history, past history of anemia, blood transfusions and drugs. Details of physical examination were obtained from medical records of patients. With informed consent, two blood samples were collected from each patient, 2 ml in EDTA for complete blood counts (CBC) and 5 ml clotted blood for serum. Other common causes of pyrexia were excluded by appropriate investigations (complete haemogram and reticulocyte count, ASO titer, blood film for malarial parasite, Widal test, Brucella agglutination test, Weil Felix test, dengue serology, Leptospira serology, RA factor, blood culture, liver function test, renal function test, complete urine examination, chest radiograph, Ultrasound abdomen and pelvis and others).

RESULTS

This study was conducted in tertiary care hospital during a period of one year (September 2012 to August 2013). There were 112 cases of macrocytic anemia during the study period out of which 62 cases had megaloblasts with hyper segmented neutrophils in peripheral smear. Only 34 cases fit into the inclusion criteria and were studied. Majority of patients were from rural areas (29 out of 34 i.e., 85.29%). There were 26 males and 8 females. The majority of the cases belonged to the age group of 21-40years (18 out of 34 i.e., 52.94%).Majority had duration of illness lasting for 2 weeks. All the patients were vegetarian since birth. There was no history of cough, headache, rash, arthralgia, urinary or bowel disturbances. There was no history of visit to malaria endemic area and no significant past history.

Table 1: clinical characteristics of megaloblastic anemia patients presenting as pyrexia

<table>
<tr><th></th><th></th><th>Number of Patients</th></tr>
<tr><td>Age (in years)</td><td>16-20
21-40
41-60
>60</td><td>5
18
10
1</td></tr>
<tr><td>Sex</td><td>Male
Female</td><td>26
8</td></tr>
<tr><td>Temperature</td><td>
99-102 F
>102 F</td><td>
28
6</td></tr>
<tr><td>Symptoms</td><td>Fever</td><td>34
<table><tr><th>Period</th><th>< 7days</th><th>7-20days</th><th>> 21 days</th></tr><tr><td>No. of patients</td><td>17</td><td>13</td><td>4</td></tr></table></td></tr>
<tr><td></td><td>Breathlessness
Easy fatigability
Vomiting
Loose stools
Bleeding tendency</td><td>31
25
10
8
4</td></tr>
</table>

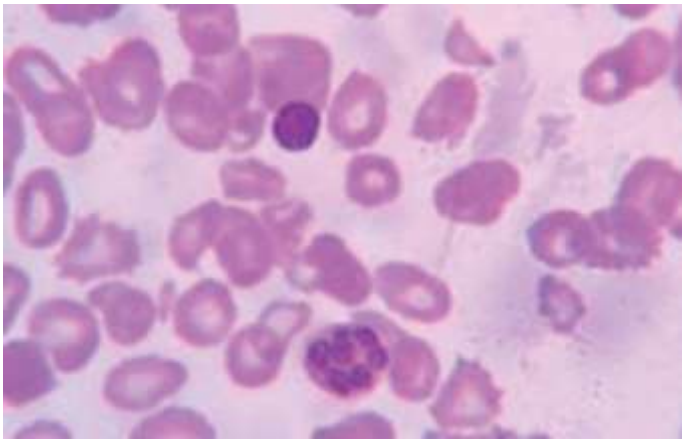

Fig. 1: Peripheral smear showing macrocytic anemia with hypersegmented neutrophils

On examination there was marked pallor. There was no icterus, lymphadenopathy, rashes or eschar. There was presence of bald glossy tongue and hyperpigmentation of knuckles. Cardiovascular system examination revealed loud S1 and ejection systolic murmur in pulmonary area. Abdominal examination showed mild to moderate splenomegaly in majority of patients. Chest and nervous system examination was normal.

Fever and dyspnea were the main presenting symptoms. 28 patients had fever of 99 – 102 F and 6 had moderate to high grade fever (>102 F). 17 patients had fever lasting for <7 days, 13 had fever from 7-20 days and 4 had fever > 21 days. Other symptoms were generalized weakness 25 (73.5%), vomiting 10(29.4%), loose stools 8 (23.5%), and bleeding tendency in 4 (11.76%) patients.

Peripheral smear showed megaloblastic anemia. There were typical hyeprsegmented neutrophils in peripheral smear. Some smears showed pancytopenia. All the basic work up for sepsis was negative. Initially patient was started on empirical IV antibiotics. Based on culture reports, antibiotics were stopped and vitamin B12 and folate supplementation was started. All patients showed symptomatic improvement within 48 hours and hematologically by the 7th day. Patients were discharged after 7 days, their hematological values being documented. They were then followed up after 2 weeks and 4 weeks later and there was improvement in their complete blood counts.

DISCUSSION

Pyrexia is a feature of megaloblastic anemia which as been shown in many studies. It is shown that fever occurs in about 40% of patients with megaloblastic anemia caused by deficiency of either Vitamin B12 or folic acid or both [5,7-9]. Usually this is low grade fever and occasionally high grade fever can be seen in those patients with severe anemia [10, 11]. The exact cause of pyrexia is not known. But it has been suggested that it may reflect a defect in oxygenation to the temperature regulatory centers in the hypothalamus or due to release of chemicals due to intramedullary hemolysis and hence increased activity in bone marrow may be related to systemic pyrexia [7, 11].

Some patients may have prolonged pyrexia for more than 21 days causing fever of unknown origin. In megaloblastic anemia due to B12 or folic acid deficiency, the fever subsides within 2 to 4days after giving B12/folic acid supplementation.

Our study has also shown improvement in fever following supplementation of vitamin B12 or folic acid due to improvement in bone marrow erythropoiesis. Patients presenting with fever and pancytopenia are usually treated with broad spectrum antibiotics, which if caused by megaloblastic anemia leads to unnecessary antibiotics. There is also a prolonged hospital stay and burden to family members. Megaloblastic anemia, though rare, is a treatable cause of pyrexia. However persistence of fever for several days or its failure to improve even after 2-3 days of initiating vitamin B12 and folate therapy should suggest the possibility of other etiology.

This article intends to create awareness among the treating physician to consider megaloblastic anemia as a cause of pyrexia avoiding unnecessary investigations and use of antibiotics.

On review of literature for the differential diagnosis of pyrexia of unknown origin, megaloblastic anemia is not considered as one among them yet. [12] This article strongly recommends the necessity to consider megaloblastic anemia due to B12 or folic acid deficiency as cause of fever of unknown origin.

This study has some limitations. We could not get vitamin B12 and folic acid levels as they were not available in our hospital. We did not do bone marrow examination for all patients. The majority of the patients coming to our hospital are from poorer section of society. Considering this, based on clinical and peripheral smear examination, we treated the patient and all showed improvement within 48 hours. All the

patients were followed up after 2 weeks and 4 weeks with significant improvement in hemoglobin. There was no recurrence of fever during this period.

CONCLUSION

Megaloblastic anemia is a known and treatable cause of fever. After ruling out infections and inflammatory conditions, which are important causes of fever, megaloblastic anemia should be considered as a possible cause especially in tropical countries. Easy availability and low cost of peripheral blood smear helps in screening these patients at an early stage. Based on the peripheral smear report treatment is initiated. Measurement of B12 and folate levels should be requested as part of a screen sent for any patient who has pyrexia of unknown origin with moderate to severe anemia without any other cause. Treatment based on these results can cause a rapid improvement and avoids the need of unnecessary antibiotics and further investigations.

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