Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medicine

Megaloblastic Anemia Presenting as Pyrexia of Unknown Origin

Dhananjaya M[1], Rajendrakumar Parakh[2*], Poojashree J[3], Raghavendra Chavan[4]

[1]Associate Professor, [2]Professor, [3,4]Post Graduate Student, Shri Dharmasthala Manjunatheshwara University, Sattur, Dharwad-580009, Karnataka, India

DOI: 10.36347/sjams.2021.v09i07.006 | **Received:** 29.05.2021 | **Accepted:** 06.07.2021 | **Published:** 11.07.2021

***Corresponding author:** Dr. Rajendrakumar Parakh

Abstract **Original Research Article**

Background: **A**n uncommon cause of pyrexia is Vitamin B12 deficiency. Megaloblastic anemia is common in India, but its presentation as pyrexia of unknown origin data is insufficient. We did a prospective study on pyrexia of unknown origin where megaloblastic anemia was the cause. ***Materials and methods*****:** A study of 74 cases with megaloblastic anemia in adults above 18 years of age during 2 years (January 2019 to December 2020) was conducted at tertiary care hospital. ***Results:*** There were 74 patients presenting with PUO and pancytopenia and was diagnosed to have megaloblastic anemia secondary to vitamin B12 and folate deficiency based on peripheral smear. Fever and easy fatigability were the main presenting symptoms. 15 patients had fever of 102 F and fever of more than 2 months. The pyrexia subsided following the vitamin B12 supplementation. Other causes of PUO infective, inflammatory/autoimmune, endocrine causes of pyrexia were excluded by appropriate investigations. ***Conclusion:*** Patients presenting with PUO and pancytopenia should be carefully evaluated for simple vitamin B12 deficiency in order to prevent unnecessary use of antibiotics. Megaloblastic anemia due to vitamin B12 deficiency is a reversible cause of pyrexia that should be considered in any patient who presents with pyrexia of unknown origin.

Keywords: Pyrexia of unknown origin, Megaloblastic Anemia, Vitamin B12, Pancytopenia.

INTRODUCTION

Megaloblastic anemias are a group of disorders due to ineffective hematopoiesis in the marrow. Most common cause for megaloblastic anemia is nutritional deficiencies due to vitamin B12 or folate. Other causes of megaloblastic anemia are inherited disorders of DNA synthesis, or following drug therapy [1]. Pyrexia in megaloblastic anemia is rare but commonly seen in patients.

Megaloblastic anemia as the cause of pyrexia of unknown origin can be found in small proportion of cases, for which differentiation from other causes has to be done after exhaustive laboratory investigations [2-6].

Any patient with pyrexia and pancytopenia has to be evaluated for Megaloblastic anemia (vitamin B12, folate deficiency) which is a reversible cause of pyrexia of unknown origin. Usually fever is low grade; however high grade fever may be seen in those patients who present with more severe anemia and hematological disease. The Proposed 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 this study was to highlight this aspect of megaloblastic anemia presenting as pyrexia of unknown origin with a brief review of literature and create awareness among practicing clinician.

MATERIALS AND METHODS

This study was conducted in tertiary care hospital of North Karnataka during a period of two years (January 2019 to December 2020). The inclusion criteria were a hemoglobin level <10g/dl and/or a mean corpuscular volume (MCV) >95 fL along with peripheral blood film findings consistent with pancytopenia, macrocytosis, and hypersegmented neutrophils.

Exclusion criteria were Patients with dimorphic anemia, age less than 18 years, infective etiology associated with anemia were excluded.

A proforma was used to document demographic data, clinical presentation, and 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 causes of recurrent pyrexia were excluded by appropriate investigations (Blood for TC, ESR, ASO titer, and blood film for malarial parasite, Widal test, RA factor, liver function test, renal function test, complete urine examination, chest X ray and others).

Patients were started on vitamin B12 supplementation and only those who improved have been taken in the study.

RESULTS

This study was conducted in tertiary care hospital of North karnataka during a period of two years (January 2019 to December 2020). There were 112 cases of severe anemia during the study period out of which 74 cases had megaloblastic anemia with hyper segmented neutrophils in peripheral smear and fit into the inclusion criteria. Majority of patients were from rural areas (49 out of 74). There were 38 males and 36 females. The majority of the cases were among 21-40 years (38 out of 74). Majority had duration of illness lasting for more than 2 weeks. Majority of patients were pure vegan. There was no history of rash, arthralgia, urinary or bowel disturbances. There was no significant past history.

On examination there was marked pallor. There was no icterus, lymphadenopathy, rashes or eschar. There was bald glossy tongue and hyperpigmentation of knuckles. Cardiovascular system examination revealed soft 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 easy fatigability were the main presenting symptoms. 38 patients had fever of 99 – 102 F and 16 had high grade fever. 14 patients had fever lasting for <7 days, 38 had fever from 7-21 days and 12 had fever lasting > 3 weeks. Other symptoms were generalized weakness 35, dysnea in 31, vomiting 15, loose stools 10, and bleeding tendency in 5 patients TABLE.

Peripheral smear showed megaloblastic anemia with pancytopenia and typical hypersegmented neutrophils in peripheral smear. FIGURE all the basic sepsis workup was negative. Bone marrow was not done. Initially patient was started on single IV antibiotic. Based on reports patient was started on vitamin B12 supplementation. 43 patients improved within 48 hours and remaining improved within 72 hours. Antibiotic was stopped and patients were discharged within next two days. Patients were followed up after 4 weeks and there was improvement in hemoglobin and platelet count.

Table-1: Clinical characteristics of megaloblastic anemia patients presenting as pyrexia

AGE	16-20	8
	21-40	38
	41-60	12
>60		16
SEX	Male	38
	Female	36
TEMPERATURE		
99-102		58
>102		16
DURATION OF FEVER		
< 7 days		14
7-21 days		38
>21 days		12
SYMPTOMS		
Fever		44
Breathlessness		31
Easy fatigability		35
Vomiting		15
Loose stools		10
Bleeding tendency		5

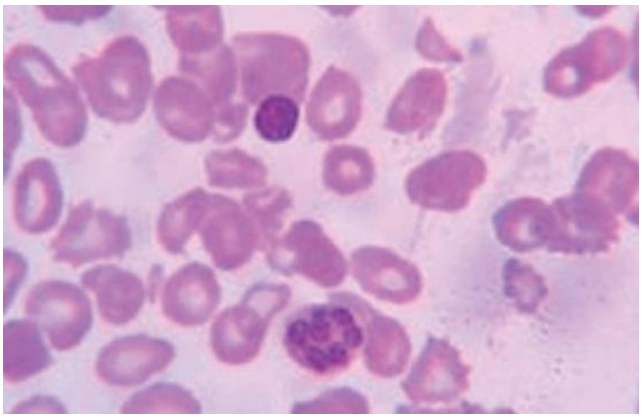

Fig-1: Peripheral smears showing macrocytic anemia with hypersegmented neutrophils

DISCUSSION

Fever is one of the clinical features of megaloblastic anemia [5]. Studies have shown that fever occurs in about 50%to 60 % of patients with megaloblastic anemia c [7-9]. Usually this is low grade fever and high grade fever is seen in those patients who have severe anemia [10, 11]. The exact cause of pyrexia in megaloblastic anemia is not known and previously it has been hypothesized that it may reflect a defect in oxygenation to the temperature regulatory centers in the brain. [11] Another proposed mechanism is that megaloblastic anemia can cause striking intramedullary hemolysis and possibly ineffective leucopoiesis and thrombopoiesis.

Thus increased activity in bone marrow may be related to systemic pyrexia [7, 11]. Severity of pyrexia depends on degree of anemia and responds quickly to correction of anemia. For those with high fever, 2 to 4days are required for temperature to become normalize. In patients with folic acid deficiency there is a tendency for temperature to take slightly longer to drop below 37.8 ºC [10, 11].

Our article also favors this point and the improvement in fever is presumed to be due to improvement in bone marrow erythropoiesis. Patients presenting with fever, anemia, neutropenia and thrombocytopenia are usually treated on the lines of febrile neutropenia with broad spectrum antibiotics, which if caused by megaloblastic anemia leads to unnecessary antibiotics and investigations. 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 improvement even after 2-3 days of initiating vitamin B12 and folate therapy should suggest the possibility of another etiology for fever [12].

This article intends to create awareness among the treating clinician to consider megaloblastic anemia as a cause of pyrexia avoiding unnecessary use of wide spectrum antibiotics. Vitamin B12 deficiency should be considered as one of the cause of PUO [13].

This study has several limitations. We could not get vitamin B12 and folic acid level and bone marrow examination for all patients because majority of the patients are from poorer section of population. Based on clinical and peripheral smear examination we treated the patient and all improved within 48 hours. Follow up of all the patients after 4 weeks showed improvement in hemoglobin and no recurrence of fever during this period.

CONCLUSION

Megaloblastic anemia is a known and treatable cause of fever. Infections and inflammatory conditions are important causes of fever in patients of pancytopenia have to be ruled out and megaloblastic anemia should be considered as a possibility of fever. Peripheral blood smear is a simple and easily available, low cost helps in screening these patients at an early stage. 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. Based on these results treatment can cause a rapid improvement and avoids the need of unnecessary antibiotics and further investigation.

REFERENCES

1. Kucukardali, Y., Oncul, O., Cavuslu, S., Danaci, M., Calangu, S., Erdem, H., ... & Fever of Unknown Origin Study Group. (2008). The spectrum of diseases causing fever of unknown origin in Turkey: a multicenter study. *International journal of infectious diseases*, *12*(1), 71-79.
2. Aslinia, F., Mazza, J. J., & Yale, S. H. (2006). Megaloblastic anemia and other causes of macrocytosis. *Clinical medicine & research*, *4*(3), 236-241.
3. Tahlan, A., Bansal, C., Palta, A., & Chauhan, S. (2008). Spectrum and analysis of bone marrow findings in anemic cases. *Indian journal of medical sciences*, *62*(8), 336-339.
4. McKee Jr, L. C. (1979). Fever in megaloblastic anemia. *Southern medical journal*, *72*(11), 1423-4.
5. Carpenter, C. L., & Patalas, E. D. (2000). Case 40-2000: A 38-year-old woman with gastric adenocarcinoma. *New England Journal of Medicine*, *343*(26), 1951-1958.
6. Khanduri, U., & Sharma, A. (2007). Megaloblastic anaemia: prevalence and causative factors. *National Medical Journal of India*, *20*(4), 172-175.
7. Gatenby, P. B. B., & Lillie, E. W. (1960). Clinical analysis of 100 cases of severe megaloblastic anaemia of pregnancy. *British medical journal*, *2*(5206), 1111.
8. Khosya, S., Gothwal, S. K., & Gharpure, N. (2013). Vitamin B12 Deficiency Presenting as Pyrexia of Unknown Origin: A Case Report. *Annual Research & Review in Biology*, 226-231.
9. Carpenter, C. L., & Patalas, E. D. (2000). Case 40-2000: A 38-year-old woman with gastric adenocarcinoma. *New England Journal of Medicine*, *343*(26), 1951-1958.
10. Davidson, S. (1957). Clinical picture of pernicious anaemia prior to introduction of liver therapy in 1926 and in Edinburgh subsequent to 1944. *British medical journal*, *1*(5013), 241.
11. Singanayagam, A., Gange, N., Singanayagam, A., & Jones, H. (2008). Folate deficiency presenting as pyrexia: a case report. *Cases journal*, *1*(1), 1-3.
12. Negi, R. C., Kumar, J., Kumar, V., Singh, K., Bharti, V., Gupta, D., ... & Raina, S. (2011). Vitamin B12 deficiency presenting as pyrexia. *The Journal of the Association of Physicians of India*, *59*, 379-380.
13. Fauci, B. (2008). Fever of unknown origin. In: Jeffrey A Gelfand, Michael V Callahan (eds.).*Harrison's principles of Internal Medicine*.18thed.ND; McGraw Hill, 158-164.