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Vitamin B_{12} Deficiency Presenting as Pyrexia of Unknown Origin: A Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. Author SK designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors SKG and NG managed the analyses of the study. Author SK managed the literature searches. All authors read and approved the final manuscript.

Case Report

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ABSTRACT

Vitamin B_{12} deficiency is an uncommon cause of fever. Here we describe a case of a 16-year-old male who presented with pyrexia of unknown origin from one and half month subsequently on investigation patient diagnosed to nutritional megaloblastic anemia secondary to severe vitamin B_{12} deficiency after exclusion of other infective, neoplastic or inflammatory causes. Megaloblastic anemia (vitamin B_{12}, folate deficiency) is a reversible cause of pyrexia that should be considered in any patient who presents with pyrexia from long time and pancytopenia.

Keywords: Pyrexia of unknown origin, megaloblastic anemia; pancytopenia.

1. INTRODUCTION

Vitamin B_{12} and folic Acid deficiency are rare but treatable cause of fever of unknown origin that responds well to the treatment. 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

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hemolysis and possibly ineffective leucopoiesis and thrombopoiesis. This increased activity in the bone marrow may be related to systemic pyrexia.

2. CASE PRESENTATION

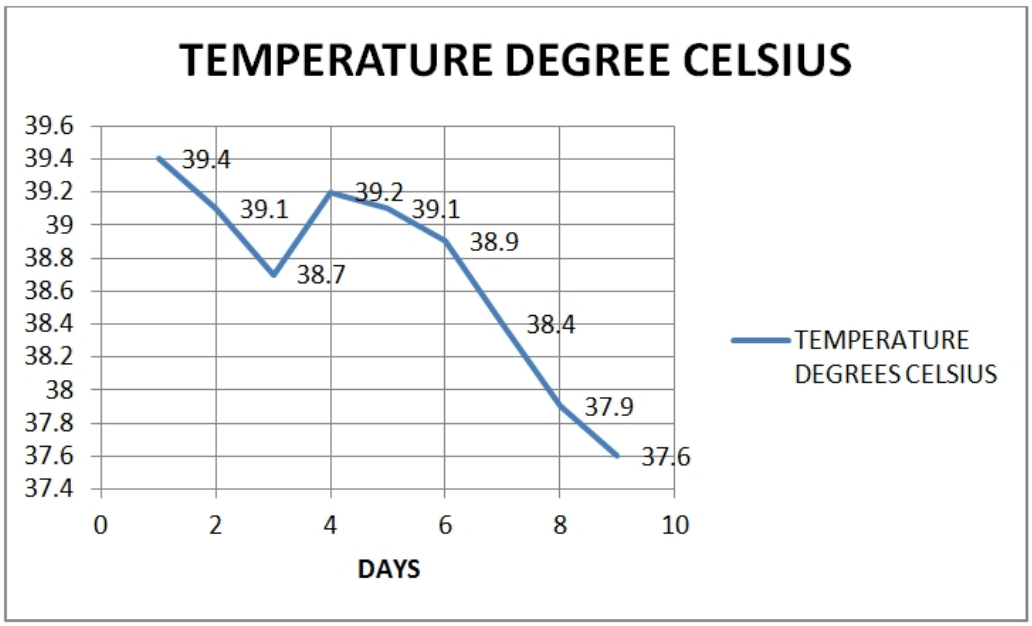
A 16-year-old male of Indian origin who is pure vegetarian since birth presented to our medical unit II in maharaja agrasen medical college with history of fever for last 6 week which was intermittent in nature and was of high grade (up to 103^0F).It was associated with rigors and chills. There was no history of associated rash, cough, headache, vomiting, arthralgia any bowel and bladder disturbance, yellowness of sclera or altered sensorium. Patient has no significant history of any chronic illness like tuberculosis or past history of any exposure to tuberculosis. There was no history of any regular medication but patient has history of taking antipyretic irregularly and cefexime 200 mg BD for 5 day, 20 days back and levofloxacin 500mg OD 7 day back for three days. At the time of admission in hospital, patient was put on intravenous broad spectrum antibiotics with provisional diagnosis of pyrexia secondary to underlying sepsis of unknown origin and one unit whole blood transfusion was done on day 1. On physical examination, the patient was conscious, oriented to time place and person. His pulse rate was 116/minute; regular, and of good volume, BP was 126/76 mmHg. Oxygen saturations were 99% without oxygen with no signs of respiratory distress. The patient was febrile with temperature 39.4 ºC and had marked pallor, bald glossy tongue and hyper pigmentation of knuckles. Cardiovascular system examination revealed loud S1 and ejection systolic murmur in pulmonary area. Abdominal examination showed mild splenomegaly but not other organomegaly or ascites. Neurological examination was normal with no evidence of neck stiffness or skin rashes. The profile of complete haemogram at the time of admission is shown in Table 1.

Peripheral smear showed RBC were predominantly macrocytic, oval macrocytes, with few microcytic, hypo chromic and segmented neutrophils with thrombocytopenia suggestive of dimorphic anemia with predominant megaloblastic anemia and pancytopenia. Biochemical examination (RFT, LFT) was completely normal. Urine microscopy, gram stain, sputum for acid fast bacilli (AFB) and KOH mount were normal. Three sets of blood cultures were taken from different sites (before commencement of antibiotics) but all were negative after 5 days culture. Chest X-ray was normal and ultrasonography of abdomen showed mild splenomegaly only. Plasma lactate dehydrogenase (LDH) values was found 750U/L, His G6PD and Coombs test were negative. Patients antinuclear antibodies, thyroid profile and C-reactive protein were normal .Vitamin B_{12} level was 108 pg/ml (normal 1200-800 pg/ml), antibody to intrinsic factor and parietal cell antibodies were absent and Folate level was 5.04µg/L (normal). Iron studies were normal. Initial peripheral blood film (Fig. 1) and subsequent bone marrow examination (Fig. 2) confirmed a severe megaloblastic picture, consistent with Vitamin B_{12} deficiency due to nutritional deficiency in pure vegetarian male. Vital signs remained stable throughout the admission but patient remained febrile during his stay at hospital up to 6 days (chart-1). Patient was started on injection 1000 mcg hydroxocobalamin IM once daily after diagnosis. Six day after starting treatment of megaloblastic anemia, patient became afebrile and remained so thereafter. Patient's antibiotics were stopped and he was discharged after three days. On follow up after two weeks, patients hematological examination revealed improved in Peripheral blood counts (Table 1). Subsequent measurement of B_{12} and folate levels at follow-up outpatient appointment showed normalization (Table 1).

Table 1. Serial haemogram before and after treatment

Parameters	Admission	7th day of admission	2 weeks after vitamin B_{12} and folic acid
Hb (g %)	2.6	4.0	9.7
MCV (80 - 100 fl)	108	107	89
MCH (26- 34 pg)	30.2	36	31
MCHC (31 -37 g/dL)	33.6	33	34
TLC (cells/cumm)	3,100	3,600	9,200
DLC			
Polymorphs	30	36	62
Lymphocytes	66	61	34
Eosinophills	2	2	2
Monocytes	2	1	2
Platelets (per cumm)	43,000	53,000	1,44,000
ESR (mm 1st hr.)	12	11	10
Vit B_{12} level (normal 200 - 800 pg/mL pg/mL)	108	165	210
Folic Acid level (normal 5.0 mg/L)	5.04	N/A	N/A

TEMPERATURE CHARTING



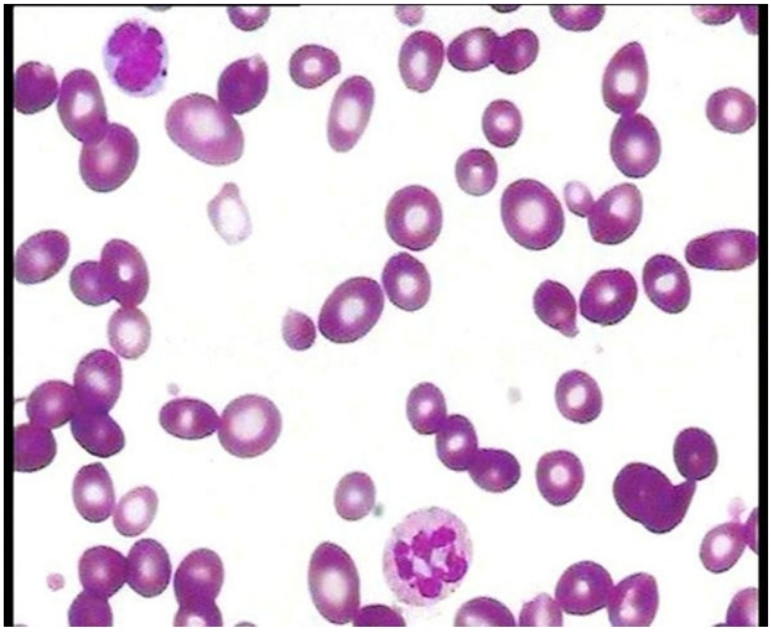


Fig. 1. Peripheral blood smears showing dimorphic picture and pancytopenia.

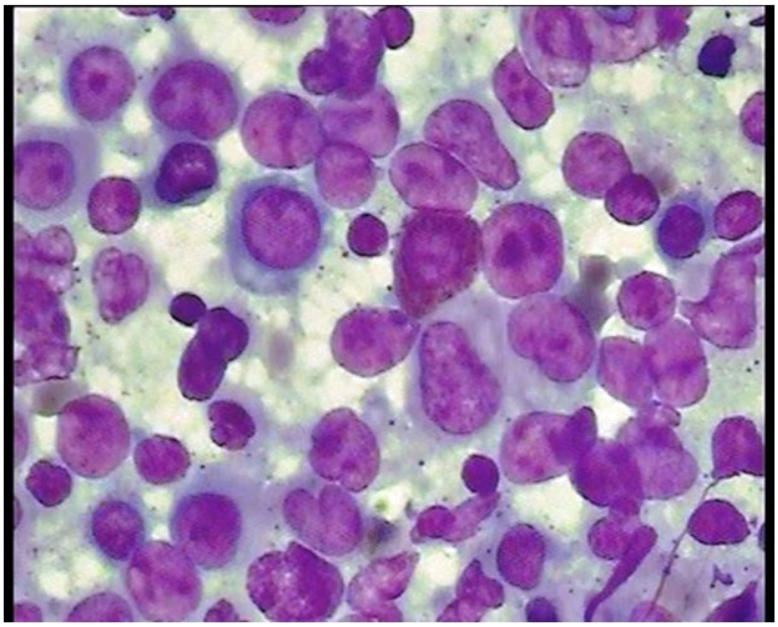


Fig. 2. Bone marrow revealing megaloblastic erythropoiesis.

3. DISCUSSION

Pyrexia is a feature of megaloblastic anemia that has been described previously in the literature [1]. Studies have shown that fever occurs in about 40% of patients with

megaloblastic anemia caused by deficiency of either vit. B_{12} or folic acid or both [1-3] Usually this is low grade, high grade fever is seen in those patients who have more severe anemia[4,5]. 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 centres in the brain [5]. Another proposed mechanism is that megaloblastic anemia cause striking intramedullary hemolysis and possibly ineffective leucopoiesis and thrombopoiesis. Thus increased activity in bone marrow may be related to systemic pyrexia. [1,5]. Severity of pyrexia usually correlates with degree of anemia and improve very quickly after 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 [6,7]. Our case report 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. 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 B_{12} and folate therapy should suggest the possibility of another etiology for fever [1]

4. CONCLUSION

Megaloblastic anemia is rare but a known and treatable cause of fever. After ruling out Infections and inflammatory conditions, which are important causes of fever in patients of pancytopenia, we should consider this possibility to be the etiological cause of fever. Easy availability and low cost of peripheral blood smear helps in screening these patients at an early stage. Measurement of B_{12} 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. After measurement of vit B_{12} and folic acid levels, a trial of treatment based on these results can cause a rapid improvement; avoid the need of unnecessary antibiotics and investigation.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CONFLICT OF INTEREST

Authors have declared that no competing interests exist.

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