International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 04, Issue 02, February 2019,
https://doi.org/10.23958/ijirms/vol04-i02/574

Case Report

Vitamin B12 Deficiency an Unusual Cause of Fever: A Case Report

Shyama[1], P. Kumar [2], Surabhi [3]

[1]Assistant Professor, Department of General Medicine, AIIMS PATNA
[2]Assistant Professor, Department of Pediatrics, AIIMS Patna
[3]Assistant Professor, Department of Pathology, AIIMS Patna

**Corresponding author* – Shyama, drshyamaneeraj@gmail.com

Received 25 January 2019; Accepted 22 February 2019; Published 24 February 2019

Abstract

Introduction: An unusual case of a 19 year old female, presenting with fever, pallor and hepatosplenomegaly for one month. She had microcytic anemia on peripheral smear examination but her bone marrow aspiration & biopsy revealed a hypercelluar marrow with megaloblastic erythroid hyperplasia. Resolution of fever within 48 hours of Vitamin B12 supplementation, initiated in view of the megaloblastic bone marrow picture & low serumVitamin B12 level, suggests a causal association. ***Conclusion:*** Vitamin B12 deficiency seems to be an unusual cause of PUO (Pyrexia of unkown origin) which should be ruled out in every case of PUO.

Keywords: ***Megaloblastic anemia, Vitamin B12 deficiency, Pancytopenia, Pyrexia of unknown origin (PUO).***

1. Introduction

Deficiencies of vitamin B12 and/or folate can cause megaloblastic anemia (macrocytic anemia with other features due to impaired cell division).

Hematopoietic precursor cells are among the most rapidly dividing cells in the body and hence are most sensitive to abnormal DNA synthesis caused by vitamin B12 and folate deficiencies.

There are two major effects of Vitamin B12 deficiency and folate on hematopoiesis

1. Megaloblastic changes.
2. Ineffective erythropoiesis

Association of fever with Vitamin B12 deficiency anemia has been well documented in past.4-6, even though it is not there on the list enumerating causes of PUO.

Although Vitamin B12 deficiency rarely presents as the sole cause of fever, it remains an important and often overlooked cause of the same. These cases are often treated as cases of PUO, leading to wastage of precious time as well as money.

Here we report a case of Vitamin B12 deficiency presenting as fever, which subsided after 48 hrs of initiation of parenteral Vitamin B12 therapy.

Case Report

A 19 Year old female was admitted in the department of General Medicine, AIIMS Patna (INDIA) with complaints of Fever for one month.

Fever was of moderate grade (102˚F-103˚F), two or three episodes daily associated with chills. Every episode was followed by a fall in temperature after about 1-2 hours with excessive sweating. There was no associated nausea or vomiting initially but recently she complained of vomiting on & off for 10 days. There was no pain abdomen or loose motions.

She was treated outside with antibiotics for enteric fever but her fever didn't resolve.

On examination there was pallor and hepatosplenomegaly.

On investigations (Table-1), there was microcytic anemia with leucopenia. Thrombocytes were borderline (low) normal

All her investigations including ELISA for typhoid, PBS for malaria, RK-39 for kala-azar were inconclusive. Chest X ray was within normal limits.

Bone marrow aspiration and biopsy was planned in view of unexplained fever, hepatosplenomegaly, bicytopenia i.e. microcytic hypochromic anemia with leucopenia on peripheral smear. Her bone marrow biopsy (Figure 1-4) revealed

hypercellular marrow with megaloblastic erythroid hyperplasia. There was low serum Vitamin B12 level, normal serum folate level.

She also had low serum iron and high TIBC but her serum ferritin level was high contrary to the expectation. High levels of serum ferritin, reflecting reticuloendothelial iron may be found in megaloblastic anemia due to the shift in iron from haemoglobin to reticuloendothelial stores8.

As patient confessed, she has not been eating non-vegeterian food for a long period and was not even having milk& milk products (effectively a vegan), thus poor nutrition was probably the culprit.

To rule out impaired absorption, IgA anti-tTG, anti-parietal cell antibody, anti-intrinsic factor antibody titres were done, all of which later came negative.

On the basis of her low Vitamin B12 we gave her injectable vitamin B12 1000 microgram once daily following which she became afebrile after 48 hrs with two dose of parenteral Vitamin B12.

She was then discharged on parenteral Vitamin B12 regimen of once weekly for 4 weeks followed by once monthly. On follow up, after three months patient was doing well and her hemogram was within normal limits (Table 2)

Table 01

TLC N/L/E/M/B (%)	1.98×10^9 /L (LOW) 65/29/00/06/00
PLATELETS	150×10^9 /L
Hb	6.5 g/dl
MCV	77.10 fl
MCH	24.00 pg
MCHC	31.10 g/dl
ESR	40 mm
CRP	0.20 mg/dl(normal)
PBS	MICROCYTIC HYPOCHROMIC ANEMIA WITH LEUCOPENIA NO HEMOPARASITES /ATYPICAL CELLS SEEN
URINE ROUTINE	WITH IN NORMAL LIMITS
DENGUE NS1 Ag & DENGUE IgG ,IgM TYPHIDOT IgM,IgG, MALARIA Ag RK39(kala-azar)	ALL WERE NEGATIVE
LFT	
S BILIRUBIN (TOTAL)	0.45 mg/dl
SGPT/SGOT	43/73 U/L
TOTAL PROTEIN	7.10 g/dl
ALBUMIN	3.31 g/dl
PT/INR	14.5 s/1.14
aPTT	25
RFT	RFT
S CREATININE	0.86
BLOOD UREA	22
S SODIUM	144
S POTASSIUM	4.4
S CALCIUM	8.0
Serum Vitamin B12	152 mg/dl (low)
Serum folate	8.68 ng/ml.
s.Ferritin	725 ng/ml (high)
s. Iron	25 microgm/dL (low)
TIBC	419 microgram/dL (high)
IgA t-TG antibody	Negative
Intrinsic factor IgG antibody	Negative
USG abdomen	Mild Hepatosplenomegaly
Bone marrow biopsy	Hypercellular marrow, Trilineage hematopoiesis Megaloblastic erythroid hyperplasia

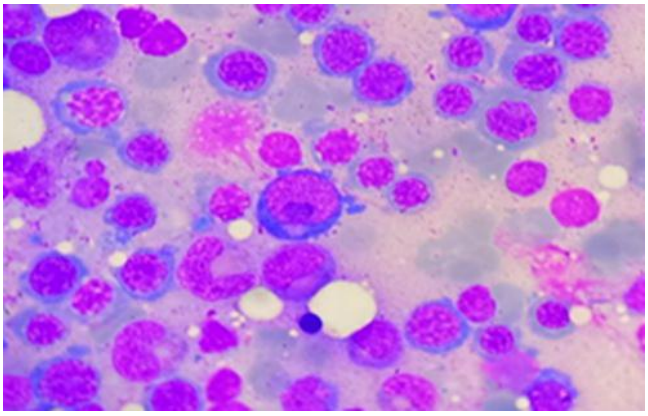

Figure 1

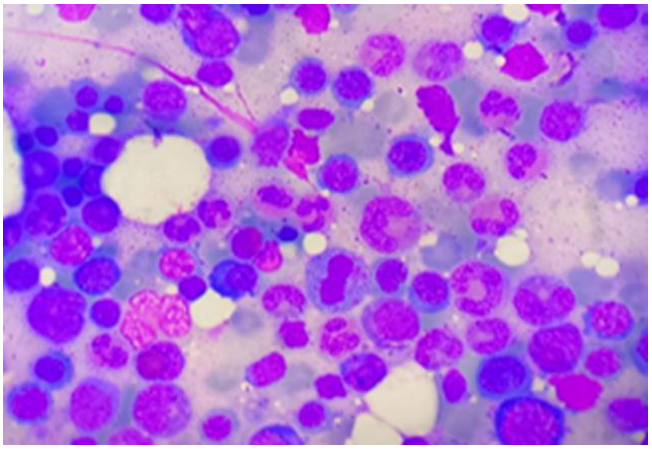

Figure 2

Figure 1&2: Bone marrow aspiration showing numerous megaloblasts and giant metamyelocytes and band

Table 02

CBC	
Hemoglobin (g/dl)	11.8
TLC	7900/mm^3
DLC	
Neutrophils	68.2 %
Lymphocytes	22.3 %
Eosinophil	7.5 %
Moncytes	2.0 %
Basophil	0
MCV	86.2 fl
MCH	29 pg
MCHC	33.6 g%
Platelet count	1.4 lakh/mm^3

Discussion

The dramatic response in fever to parenteral Vitamin B12 supplementation in this patient suggests that fever may have been because of Vitamin B12 deficiency.

Patient was already adequately treated with empirical antibiotics for enteric fever and antimalarial. Presence of fever with splenomegaly and bicytopenia (leucopenia & anemia) also made Kala-azar, one of the differentials. As serology for kala-azar (RK-39) came negative, and other tests done to find the cause of fever were not conclusive, a bone marrow biopsy was done.

Bone marrow picture of erythroid hyperplasia coupled with low serum vitamin B12 led us to initiate the parenteral Vitamin B12 therapy, to which Patient responded dramatically by being afebrile within 48 hrs.

Although the incidence of low-grade fever in nutritional megaloblastic anemia varies from 28% to 60%, 1fever as a presenting symptom of vitamin B12 deficiency is rare. Only few case reports were found where vitamin B12 deficiency was attributed as the sole cause of pyrexia.2-5

In a study on megaloblastic anemia as a cause of PUO by Bushra Siddiqui et al7, they found 4 out of their 15 (26.6%) patients who came with megaloblastic anemia associated with fever had no improvement with antibiotics but experienced marked improvement in fever within 48 h of administration of vitamin B12 and folate.

Kevin Manuel et al.3 described a case of megaloblastic anemia in a middle-aged female patient, who presented with low-grade pyrexia, pancytopenia, macrocytosis (114.3 fL), very high LDH (10,550 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).

Negi et al.4 reported a case of anicteric male with pyrexia (39.7°C), bicytopenia, and macrocytosis (MCV=105 fL) secondary to B12 deficiency (105 pg/mL).

Singanayagam et al.5 reported a young male with pyrexia of 6 weeks' duration (38.8°C), severe pancytopenia, and mild hyperbilirubinemia secondary to folate deficiency (1.2 ng/mL, reference range: 5-24 ng/mL) and low normal vitamin B12 (202 pg/mL).

Another study from Northern India described persistent low-grade fever in 70% of the females with B12 and/or folate deficiency.6

McKee, 7 reviewed 122 patients of nutritional megaloblastic anemia for the presence of pyrexia (temperature≥37.8°C [100°F]). In 49/122 (40%), pyrexia was attributable solely to the megaloblastic disease

In present case, a 19 year old female patient, had fever for one month, hepatosplenomegaly, bicytopenia, microcytic anemia on PBS and megaloblastic erythroid hyperplasia on bone marrow biopsy, low vitamin B12, normal serum folate.

Her fever subsided within 48 hrs of initiation of vitamin B12 supplementation like that of the above reference cases, which may be because of the rapid correction of ineffective haematopoiesis, suggesting a causal association.

Now as we didn't supplement folic acid owing to her normal serum folate level, it can be assumed that fever here was solely due to Vitamin B12 deficiency

Vitamin B12 deficiency rarely presents as the sole cause of fever, but still remains an important and often overlooked cause of the same. These cases are often treated as cases of PUO, leading to wastage of precious time as well as money.

As per the modified Petersdorf criteria, PUO is defined as:

1. A temperature exceeding 38.3°C (101°F);
2. Duration of the fever of more than 3 weeks; and
3. Evaluation of three outpatient visits or 3 days in hospital

Our patient satisfied all the above criteria of PUO and her fever improved after 48 hrs of initiation of parenteral Vitamin B12 therapy.

Though the association of fever with Vitamin B12 deficiency has been well documented in past and appears to be causal4-7, it is still not on the list enumerating causes of PUO.

One of the hypothesis suggests that Vitamin B12 deficiency anemia, being characterized by hypercellular marrow and ineffective hematopoiesis, there is premature destruction of hematopoietic precursors possibly releasing intracellular substances, which may function as systemic pyrogens5.

The dramatic response to Vitamin B 12 supplementation (within 24 to 72 hours) strongly supports the above hypothesis.

Alternatively, it has been hypothesized that defective oxygenation at the thermoregulatory center of hypothalamus might be the cause of pyrexia, but the lack of correlation between neurological manifestation and pyrexia in megaloblastic anemia does not support this theory.5

Conclusion

Although the reason is unclear, the association of fever with Vitamin B12 deficiency anemia remains a well-documented phenomenon. Further studies on bone marrow microenvironment and role of cytokine signalling in these cases may help in discovering the cause in future.

It might be concluded that, as there appears to be a causal relationship between fever and Vitamin B12 deficiency, measurement of B12 and folate levels may be advised in all patients presenting with fever without any obvious cause.

The correct identification of B12/folate deficiency being the cause of fever (after all other causes have been ruled out), would help in adequate and timely management of the patient and avoid unnecessary use of antibiotics

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