

# “Smear doesn’t Lie”- Diagnosis of Pediatric Megaloblastic Anemia Revisited”

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## ABSTRACT

**Introduction:** Nutritional anemias are the commonest cause of anemia in children. Atypical presentation at unusual age may create confusion clinically and may cause delay in diagnosis.

**Case report:** We hereby discuss one such case of megaloblastic anemia in infant with unusual features and brief discussion about lab diagnosis of megaloblastic anemia.

**Conclusion:** Good peripheral smear examination showing classical findings with low reticulocyte count supported by biochemical tests like serum cobalamin and folic acid level clinch the diagnosis.

**Keywords:** Megaloblastic, Reticulocyte, Cobalamin

## INTRODUCTION

Nutritional anemias are the commonest cause of anemia in children. Atypical presentation at unusual age may create confusion clinically and may cause delay in diagnosis. We hereby discuss one such case of megaloblastic anemia in infant with unusual features and brief discussion about lab diagnosis of megaloblastic anemia.

## CASE REPORT

6 months old female child born out of non-consanguineous marriage presented to emergency department with complaints of frequent vomiting since 1 month of age, which was non billous and non-projectile. She was exclusively breast fed till date.

On examination child was pale with spleen of 3 cm below coastal margin & liver of 4cm and audible hemic murmur. There was developmental delay with absence of knuckle pigmentation, koilonychia, and hemolytic facies. Possibility of hemolytic anemia most likely thalassemia was kept.

Her Complete blood count showed anemia with Hb 6 g/dl, leucocyte count-  $5.6 \times 10^3 / \mu\text{l}$  & platelet count-  $164 \times 10^3 / \mu\text{l}$ . MCV was 95.0 fl, MCH- 34.6 pg & MCHC 36.4g/dl. Peripheral smear showed Macrocytic normochromic RBC with anisopoikilocytosis. Tear drop cells, macro ovalocytes, Cabot’s ring and fine basophilic stippling was noticed. There was neutropenia with few hypersegmented forms. Platelets were adequate. No abnormal cells were seen. (Figure 1a & b). Peripheral smear showed features suggestive of megaloblastic anemia.

Her liver & kidney function tests were within normal limits. LDH was markedly elevated 1871 U/L. Serum B12 was reduced with values of <50 pg/ml. She was indeed having severe megaloblastic anemia. We decided to avoid invasive bone marrow examination and rather wait to look for response

to therapeutic trial with multivitamin therapy. It answered one of our questions but raised more doubts. We hereby discuss unusual features of this common clinical entity with review of diagnostic tools for megaloblastic anemia.

Megaloblastic anemia (MA) occurs due to non-availability of vitamin B12 or folic acid for nucleic acid synthesis. Nuclear maturation lags behind cytoplasmic growth leading to megaloblast and ineffective erythropoiesis in bone marrow manifesting as macrocytic anemia & neurological dysfunction.

Though more common in old age & pregnancy, MA contributed to 20% of all pediatric nutritional anemia cases in Turkish study & 38% in Indian study with mean age of 18 to 24 months.<sup>1,2</sup> Stores of newborn are sufficient for initial few months with daily requirement of only 0.4 mcg as compared to 2.4 mcg in adults leading to this age of presentation. In our case child was symptomatic since 1 month of age. On reviewing literature case reports describing early onset megaloblastic anemia were found due to occult B12 deficiency in mothers or they may harbor subclinical pernicious anemia.<sup>3</sup> In our case mother had normal Hb & RBC indices with reduced serum B12 (151 pg/ml).

Presentation may be very non specific in children as progressive lethargy, apathy, irritability and developmental delay with gross motor dysfunction which contributes to feeding difficulties. In our case child presented with vomiting since 1 month of age. Possibility of surgical cause of vomiting was excluded with imaging. Resolution of symptom after therapeutic trial with vitamin B12 & folic acid favored it to be manifestation of MA rather than cause. In MA complete blood count shows macrocytic RBC indices which may precede development of anemia. MCV may not be >100fl but higher than patients normal baseline value. This may be accompanied by pancytopenia in severely deficient cases. In such cases false alarm of conditions like

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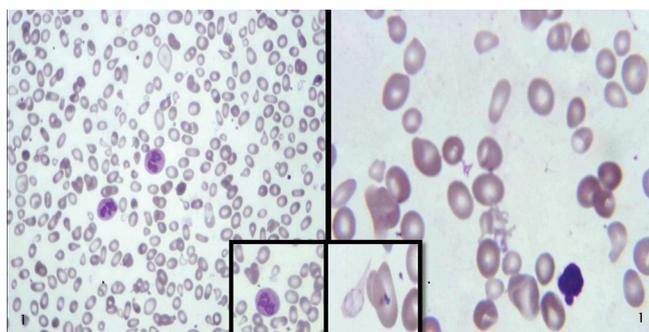
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Sr. No.	Test	Advantage	Disadvantage
1.	Total serum B12	Easily available	-Affected by inactive B12 component -Threshold to decide deficiency is ambiguous
2.	Holo TC	Better predictor of B12 deficiency	Costly, lack of standardisation
3.	Homocysteine	Both HCY and MMA are indicator of functional deficiency and also better marker to look for response to therapy	HCY is not specific for B12 deficiency
4.	Methyl malonic acid	specific for B12 deficiency	

**Table-1:** Summary of advantages and pit falls of various biochemical assay.



**Figure-1a:** Leishman giemsa stained peripheral smear showing anisopoikilocytosis with inset showing hypersegmented neutrophil (400X); **Figure-1b:** Leishman giemsa stained peripheral smear showing macrocytes and macro ovalocytes with inset showing cabot's ring (1000X)

aplastic anemia and inherited bone marrow failure may create concern in pediatric age group. In our case also patient had MCV of 95 fl with absolute neutropenia.

On peripheral smear macrocytic RBC with many macroovalocytes are seen with anisopoikilocytosis and tear drop cells. Hypersegmented neutrophils are earliest to come and persist till day 10 of therapy. Other features of ineffective erythropoiesis like cabots ring, Howell jolly body and basophilic stippling are seen. However, one should be aware of other possible causes of macrocytosis like liver disease, hypothyroidism, chemotherapy & antiretroviral agents. Similarly hyper segmented neutrophil may be seen in uremic patients and patients on hydroxyurea.

MA is a close mimic of hemolytic anemia due to ineffective erythropoiesis and hemolysis of RBCs with defective membrane.<sup>4</sup> Similar to our case features like Jaundice, high LDH and splenomegaly at young age adds to confusion with hemolytic anemia like thalassemia. However, simple test of corrected reticulocyte comes to rescue as its low in MA. In our case corrected reticulocyte count was 0.2%. Baseline reticulocyte count also helps us to monitor for response to therapeutic trial with vitamin B12 and folic acid.

Total serum B12 level measured includes both 20%-biologically active component holo transcobalamin (holo TC) and rest inactive component bound to haptocorrin. Hence total serum B12 lacks sensitivity and specificity to diagnose megaloblastic anemia. Holo TC seems to be better biomarker and predictor of megaloblastic anemia than total serum B12.<sup>5</sup> WHO suggests use of 200pg/ml as value of total serum B12 to discriminate between deficient versus non deficient sample. However, assay also lacks standardization

with ambiguity about lower cut off to report B12 deficiency. Vitamin B12 acts as co enzyme for conversion of methyl malonyl co A (MMA) to succinyl Co A and homocysteine (Hcy) to methionine. Hence these precursors namely MMA and Hcy are elevated during vitamin B12 deficiency and serves as biomarkers. Out of the two MMA is more specific for B12 deficiency. Cost of the test, lack of standardization and limited availability are the major disadvantages of these assay.

Considering this information serum B12 is still used widely to diagnose megaloblastic anemia. When found low with proper clinical and hematological parameters it supports the diagnosis of megaloblastic anemia. However, normal values do not exclude the diagnosis always. (table 1)

Bone marrow smears show classical features as erythroid hyperplasia with megaloblastic maturation. Myeloid series show giant myeloid forms. Megakaryocytes usually appear normal. Erythroid changes may revert back to normal within 12 hours of administration of therapeutic trial with multivitamin. However, bone marrow examination is not routinely needed in all cases. Response to therapeutic trial in form of rising reticulocyte and hemoglobin & normalization of LDH can be evaluated on day 8 to 10 of therapy.

Megaloblastic anemia should be treated with the intramuscular injection of cyanocobalamin 1 mg/day for 1 week, followed by 1 mg/wk for 1 month, and then 1 mg every 1 or 2 months.<sup>6</sup> Our patient showed reticulocyte count of 11% on day 10 of treatment with Hb of 8.8g/dl. She showed complete relief of clinical symptoms including vomiting and complete normalization of complete blood count on day 45 of therapy.

## CONCLUSION

This case made us re visit a very common entity-megaloblastic anemia in infants with new perspective. It can manifest at unusually young age of 1 month with non specific clinical features of vomiting and failure to thrive. Clinically mimics hemolytic anemia. Mothers CBC may be normal with subtle decrease in serum B12. Good peripheral smear examination showing classical findings with low reticulocyte count supported by biochemical tests like serum cobalamin and folic acid level clinched the diagnosis. Good follow up with monitoring for hematological response helped us to avoid invasive test like bone marrow in young child.

In children not responding to adequate vitamin therapy bone marrow examination and work up for rare hereditary causes

of megaloblastic anemia is required.

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