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Original Research Article

Tropical sprue in megaloblastic anemia

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ABSTRACT

Background: The causes of megaloblastic anemia may vary in different geographical regions. The aim of the present study is to evaluate the utilization of bone marrow examination and upper gastrointestinal endoscopy (UGIE) in megaloblastic anemia.
Methods: This was a cross-sectional descriptive study done on 50 patients (age ≥15years) of macrocytic anemia after applying inclusion and exclusion criteria. A bone marrow aspiration with biopsy and an UGIE with duodenal biopsy were performed in consented patients with evidence of megaloblastic anemia in the peripheral smear or Vitamin B12 deficiency or folate deficiency or both.
Results: Out of 50 cases, 38 patients had pure Vitamin B12 deficiency, 2 patients had pure folate deficiency and 5 patients had combined deficiency. Among 43 patients with vitamin B12 deficiency, only four (9.3%) were vegetarians and remaining 39 (90.7%) were having non-vegetarian diet. Bone marrow study was done in 29 patients (out of 50) and all of them were found to have megaloblastic erythropoiesis in the bone marrow. Thirty three out of 50 consented for UGIE and duodenal biopsy. Out of 33, 17 patients (51.5%) had features of tropical sprue in biopsy.
Conclusions: We found a high prevalence of tropical sprue in megaloblastic anemia due to Vitamin B12 and/or folate deficiency. We recommend that UGIE with deep duodenal biopsy should be considered in all patients with megaloblastic anemia to rule out tropical sprue in India.

Keywords: Bone marrow study, Duodenal biopsy, Megaloblastic anemia, Tropical sprue, Upper gastrointestinal endoscopy

INTRODUCTION

Megaloblastic anemia is characterized by macrocytic anemia and abnormally large erythrocyte precursor cells (megaloblasts) in the bone marrow. Disorders that affect the synthesis of DNA in the precursors of erythrocytes in the bone marrow lead to megaloblastic anemia. Vitamin B12 and folate deficiencies are the most common causes of megaloblastic anemia.

The causes of megaloblastic anemia may vary in different geographical areas. Pernicious anemia is a major cause of megaloblastic anemia in western countries, but nutritional deficiencies and malabsorption could be the leading cause of megaloblastic anemia in India.[1] Studies have shown that vitamin B12 deficiency is more common in vegetarians.[2,3]

The main cause of folate deficiency is less intake of green leafy vegetables and legumes. There have been hardly any studies on the role of bone marrow and upper gastrointestinal endoscopy (UGIE) in the evaluation of megaloblastic anemia. The objective of the present study is to evaluate the utilization of bone marrow examination and UGIE in megaloblastic anemia.

METHODS

This was a cross-sectional descriptive study carried over a period of 12 months from July 2013 to June 2014 on 50 patients (age ≥15years) of macrocytic anemia treated in a tertiary care hospital of South India. Macrocytic anemia was identified when:

- A mean red blood corpuscular volume >95 fL
- Anemia with hemoglobin of
  a) <13 g/dL in male
  b) <12 g/dL in female.

Inclusion criteria

Patients above the age of 15 years with macrocytic anemia.

Exclusion criteria

Patients with liver disease, chronic kidney disease, hypothyroidism, hemolytic anemia, hemorrhagic disease, post splenectomy and pregnant patients.

The history was taken in detail; a complete and thorough physical examination was carried out in all patients. Detailed information was sought on alcohol consumption, drug intake, thyroid disorder and other comorbid illness. All patients were investigated with a hemogram that included estimation of hemoglobin level, red cell indices (MCV, MCH and MCHC), red cell distribution width, total leucocyte count, differential leucocyte count, platelet count, reticulocyte count, and peripheral smear examination.

All patients were subjected to fasting serum Vitamin B12, fasting serum folic acid, serum TSH, creatinine, liver function test and lactate dehydrogenase. A bone marrow aspiration with biopsy and an UGIE with deep duodenal biopsy were performed in patients with evidence of megaloblastic anemia in the peripheral smear or Vitamin B12 deficiency or folate deficiency or both, who gave consent for the same.

Statistical analysis

The data were analyzed using Microsoft Excel 2010 and Statistical Package for Social Science (SPSS) Version 19.0. Continuous variables were expressed as mean/SD and categorical variables were expressed as percentage. Independent student T test and Anova tests were used as described below. A predictive value of less than 0.05 was taken as statistically significant.

RESULTS

In current study population of fifty patients presenting with macrocytic anemia, 34 were male comprising about 68% and 16 were female comprising about 32%. The mean age of male and female were 53.15±15.89 and 54.37±16.58 respectively. Majority of the population belong to the age group above 40 years, both in males and females. Six patients in this study group were vegetarians. Five patients gave history of consuming alcohol. Three patients gave history of drug exposure and were on phenytoin/ sodium valproate.

The major symptom at presentation was fatigability (58%, n=29), 16% (n=8) presented with chronic diarrhea and 26% (n=13) with other symptoms like short pyrexia etc. No patient had bleeding tendencies or features of nervous system involvement.

On clinical examination, pallor was noticed in all patients in various degrees from mild to severe. Icterus was seen in 10 patients, hyperpigmentation of the knuckles in 7 patients. Organomegaly was noticed in 2 patients, among them one had hepato-splenomegaly and one had splenomegaly.

Out of 50 cases, 38 patients had low Vitamin B12, 5 patients had low levels of both folate and Vitamin B12 and 2 patients had low folate level alone. Vitamin B12 and folate levels were normal in the remaining five patients (Table1). Among 43 patients with Vitamin B12 deficiency, only four (9.3%) were vegetarians and remaining 39 (90.7%) were having non- vegetarian diet.

Table 1: Vitamin B12 and folate status in the study group.

Vitamin status	n=50	Percentage (%)
Pure vitamin B12 deficiency	38	76
Pure folate deficiency	2	4
Combined deficiency	5	10
Both normal	5	10

Table 2 shows hematological parameters of our patients. Out of 50 patients, 24 patients presented with anemia alone, 6 patients with bicytopenia (low hemoglobin and low platelets) and the remaining 20 patients with pancytopenia.

Table 2: Hematological parameters.

Hematological parameter	Mean ± SD
Hemoglobin (g%)	7.1 ± 2.5
MCV (fL)	115.1 ± 10.3
Red cell distribution width	22.71 ± 6.2
Total WBC count	4775 ± 2643
Platelet count	123686 ± 100097

Table 3: Comparison of severity of anemia with macrocytosis.

Hemoglobin (g%)	MCV(fL) Mean ± SD	n =50	P value
< 6	113.56 ± 7.83	18	>0.05
> 6	115.96 ± 11.39	32	

Study found no statistical significance (p=0.4) between the severity of anemia and the degree of macrocytosis, when the values of MCV were compared with the degree of anemia using independent student T test (Table 3). There was no statistical significance (p=>0.5) between the mean of MCV and levels of serum Vitamin B12 using Anova test (Table 4).

Table 4: Comparison of serum Vitamin B12 level and MCV.

Vitamin B12 level (pg/mL)	n=50	MCV (fL) Mean ± SD	P value
< 100	n = 28	116.69±10.89	>0.05
101-190	n = 15	112.20±6.83	
> 190	n = 7	114.92±12.50	

Out of 24 patients with anemia, 21 had low serum Vitamin B12 and 16 of 20 patients with pancytopenia had low serum Vitamin B12. All 6 patients with bicytopenia had low serum Vitamin B12. When the various levels of low serum Vitamin B12 were compared with presentation of patient with anemia, bicytopenia or pancytopenia using Anova test there was no significance (p=>0.5) (Table 5).

Table 5: Comparison of serum Vitamin B12 level and hematological presentation.

Presentation	n=50	Vitamin B-12 level (pg/mL) Mean ± SD	P value
Pancytopenia	20	64.37±31.41	>0.05
Bicytopenia	6	76.83±33.36	
Anemia	24	98.24±44.88	

The peripheral smear examination showed neutrophilic hyper segmentation and / or macro-ovalocytosis in 25 patients suggesting megaloblastic erythropoiesis. These patients and another four (Vitamin B12/folate/or both deficient) who gave consent were subjected to a bone marrow examination. Among 50 patients, bone marrow examination was done in 29 and all of them were found to have megaloblastic erythropoiesis in the bone marrow.

Thirty three out of 50 consented for UGIE and deep duodenal biopsy. Twenty-six of them showed duodenal finding of either scalloped duodenal folds or folded duodenal margins. Others showed features of erosive gastritis, atrophic gastritis or antral gastritis. One had external gastric impression and the other had gastric polyp (Table 6).

Among twenty-six patients who had abnormal duodenal features in endoscopy, fifteen showed features suggestive of tropical sprue in duodenal biopsy (Table 6). Two patients who had normal duodenal findings also had features of tropical sprue in biopsy. Hence 17 patients out of 33 (51.5%), who gave consent for endoscopy and biopsy had tropical sprue. Among 17 patients with tropical sprue, 15 had low Vitamin B12 level, one had both low vitamin B12 and folate levels and one had both normal.

Table 6: Upper gastrointestinal endoscopy and duodenal biopsy findings.

Endoscopy findings	n =33
Scalloped duodenal folds / flattened duodenal margins	26
Erosive gastritis	2
Atrophic gastritis	2
Antral gastritis	1
Others	2
Duodenal biopsy findings	**n =33**
Tropical sprue	17
Intraepithelial lymphocytosis	2
Non-specific	3
Brunner's gland hyperplasia	3
Peptic duodenitis	1
No specific pathology	7

DISCUSSION

Megaloblastic anemia has variable etiological factors. In current study population 76% had Vitamin B12 deficiency, 10% had deficiency of both Vitamin B12 and folate and 4% had pure folate deficiency. Our findings were consistent with a study by Khanduri and Sharma, who have reported Vitamin B12 deficiency to be 65% in 120 patients of megaloblastic anemia, combined Vitamin B12 and folate deficiency in 12% and folate deficiency in 6% .[4] A similar high prevalence of Vitamin B12 deficiency was reported by Sarode et al, in 102 cases (76%) of nutritional megaloblastic anaemia.[5] In contrast to this finding, Haq et al, found that folic acid deficiency was the commonest cause (62.5%) of megaloblastic anemia in her patients.[6]

The predominant symptoms in this study were fatigability (58%) and chronic diarrhea (16%). No patient presented with bleeding manifestation or had neurological symptoms. Unnikrishnan et al, found 91.7% of their patients presenting with fatigability, but in contrast to present study, 36.7% had bleeding manifestation and 10% presented with neurological symptoms.[7] In another study by Haq et al, in a population of 80 patients, 84% had fatigability and 27.5% had bleeding tendency.[6] Bleeding manifestations in thrombocytopenia due to Vitamin B12 or folate deficiency are typically mild and this may be the reason why no patient presented with bleeding tendency in the study.

In the present study, clinical examination revealed pallor in 100%, icterus in 20%, skin hyperpigmentation in 14% and organomegaly in 4%. Haq et al, found pallor in 84% and splenomegaly in 48%.[6] In a study by Unnikrishnan et al, 35% had jaundice, 31.7% had splenomegaly, 28.3% had hepatomegaly and 23.3% had skin changes.[7] Thus

when compared to the above studies we found lesser percentage of patients with organomegaly and skin changes.

Among 43 patients with Vitamin B12 deficiency, only four (9.3%) were vegetarians and remaining 39 (90.7%) were having non-vegetarian diet. 39 out of 44 (88.6%) non-vegetarians had Vitamin B12 deficiency in present study group. In concordance with present study, Unnikrishnan et al, and Iqbal et al, also reported a higher proportion of non-vegetarians having megaloblastic anemia and Vitamin B12 deficiency.[7,8] In contrast to our finding, Liggy et al and Kankonkar et al, showed Vitamin B12 deficiency higher in vegetarians than non-vegetarian. But the study cohort was different, Liggy et al, included all the patients and not only anemic patients, Kankonkar studied B12 deficiency in different diseases.[9,10] In current study 40% of patients had pancytopenia. Other studies have also found that megaloblastic anemia can present with pancytopenia.[5,11]

Bone marrow study was done in 29 out of 50 patients by us. All patients had megaloblastic erythropoiesis in the bone marrow. Khanduri and Sharma have suggested that bone marrow study should be done in selected patients when myelodysplasia is a differential diagnosis.[4] We also agree with them that bone marrow examination need not be done in all patients initially with megaloblastic anemia or Vitamin B12/folate deficiency, as it did not contribute to identifying a different etiology. In present study population of 50 patients, 33 (66%) underwent endoscopy and biopsy. 17 patients out of 33 (51.5%) had tropical sprue (TS). Among 17 patients with TS, 15 had low Vitamin B12 level, one had both low Vitamin B12 and folate levels and one had both normal.

An interesting observation in this study was that tropical sprue was more prevalent in megaloblastic anemia due to Vitamin B12 and/or folate deficiency. This may be because of endemic nature of TS in India. We found that Vitamin B12 deficiency was more in non-vegetarians and this may be due to underlying TS associated malabsorption.

TS is a malabsorption syndrome of unknown etiology or due to a probable persistent infection. TS cause malabsorption of folic acid and Vitamin B12 leading to megaloblastic anemia. A study done in West India in 1968 has reported that majority of patients with TS have Vitamin B12 deficiency.[12] After extensive literature search, we could not find many studies of endoscopic biopsy in megaloblastic anemia. There are few studies in malabsorption syndrome. Dutta et al. in a south Indian study and Ranjan et al. in a north Indian study found that TS was the commonest cause of malabsorption syndrome.[13,14]

There are a few limitations to current study. The sample size was small and we could not do complete work up for megaloblastic anemia and malabsorption due to cost factor.

CONCLUSION

To conclude, we found a high prevalence of TS in megaloblastic anemia due to Vitamin B12 and/or folate deficiency. We observed in thisstudy that being a non-vegetarian does not protect against Vitamin B12 deficiency, hence we recommend that all patients with megaloblastic anemia (including vegetarians) in India should be subjected to UGIE with deep duodenal biopsy to rule out TS, as the prevalence is high and treatment is different.

Study also found that bone marrow study did not yield added information and hence need not be considered in all patients with megaloblastic anemia or Vitamin B12/folate deficiency at the time of presentation, unless clinically indicated. We need larger and more studies to confirm our finding.

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