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105 Cases of Macrocytosis- Etiologic Profile Reflecting Lifestyle Changes

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Introduction

Macrocytosis is encountered frequently during medical practice. Megaloblastic anemia (MA) due to Vitamin B12 or folate deficiency is the well known cause of macrocytosis. Pernicious anemia is a major cause of megaloblastosis in Western world where their diet supplies the necessary nutrients.[1] Nutritional megaloblastic anemia is very important in the Indian scenario.[2]However non megaloblastic macrocytosis also forms an important group which includes alcoholic liver disease, hemolytic anemias, leukemias etc. Kerala is a an Indian State where literacy rate is high. The rural urban divide is much less pronounced here and medical facilities are available even in the more remote areas. These lifestyle changes have influenced the disease spectrum of the state.

Macrocytosis defined as mean corpuscular volume(MCV) above 97 fl , [3] often precedes anemia and causes like alchoholism can cause macrocytosis without anemia. With increasing use of Electronic cell counters more cases are detected early and a new category –spurious macrocytosis has also come into being.

Materials and methods

This is a retrospective study. Macrocytosis was defined as MCV value more than 97 fl. Blood samples with MCV higher than 97 fl which were received in the Department of Pathology for peripheral smear examination were selected for this study spanning a period of two years, from April 2010 to end of March 2012. RBC indices were obtained using using 5 part electronic hematology cell counters which were regularly calibrated and maintained.

Case histories, physical examination findings and details of relevant investigations were retrieved from Medical Records Section. There were 137 cases of macrocytosis. Those cases for which no further details were available were excluded and 105 cases selected.

Retrospective studies have certain inherent problems. We found that cases of megaloblastic anemia suspected to be of nutritional origin were empirically given both vitamin B12 and folate. Only in very few cases were assays done. Response to treatment was taken as confirmatory evidence of deficiency. Financial constraints of the patients made this a more practical solution than the costly assays and determining the exact type of deficiency.

All 105 cases of macrocytosis were categorized into 4 groups.

Group A : Non megaloblastic macrocytosis.
Group B : Megaloblastic anemia- nutritional
Group C : Megaloblastic anemia- non nutritional
Group D : Spurious macrocytosis.

The various etiologies in each group were determined. The hemoglobin(Hb) values ,MCV, Mean Corpuscular hemoglobin(MCH),Mean corpuscular Hemoglobin Concentration(MCHC), and Red cell Distribution Width(RDW) were analyzed statistically.

Results

There were 139 cases of macrocytosis among the samples sent for peripheral smear examination in the time period chosen. The 105 cases chosen were grouped into four categories (table 1). This made nonmegaloblastic macrocytosis the most prevalent group constituting 58% of the total. Spurious macrocytosis was the least common category (11.4%).

Table 1: Categories of macrocytosis

A	Nonmegaloblastic macrocytosis	61	58%
B	Nutritional megaloblasic anemia	16	15.2%
C	Non Nutritional megaloblasic anemia	16	15.2%
D	Spurious macrocytosis	12	11.4%

The various causes of nonmegaloblastic macrocytosis (group A) were alcoholic and non alcoholic liver disease, acute leukemia, lymphoma, hemolysis, aplastic anemia, chronic obstructive lung disease(COPD), hypothyroidism,chronic kidney disease patients on hemodialysis, myelodysplastic syndrome(MDS), bone marrow involvement by colon carcinoma. (table 2). Among the 5 cases of aplastic anemia 2 were children with Fanconi anemia.

Table 2 : Causes of group A

Causes	Number of cases
Alcoholic liver disease	17
Acute leukemia/lymphoma	16
Hemolytic anemia	11
Aplastic anemia	5
COPD	4
Hypothyroidism	2
MDS	2
Nonalcoholic cirrhosis	2
CKD	1
Bone marrow with metastatic carcinoma	1

There were 16 cases each of nutritional(group B) and nonnutritional (group C) megaloblastic anemias. Nutritional megaloblastic anemia could not be sub classified due to reasons previously mentioned. The most common non nutritional cause was drug induced megaloblastosis. The drugs implicated included sodium valproate, methotrexate, hydroxyurea, and 5 fluorouracil (table 3)

Table 3: Causes of group C

Causes	Number of cases
drugs	8
Exfoliative dermatitis and psoriasis	5
Inflammatory bowel disease	2
bowel resection	1

In 12 cases, hemogram showed macrocytosis which were not evident in the blood smears. They were classed as spurious macrocytosis (Table 4).

Table 4: Causes of group D

Causes	Number of cases
Multiple myeoma	8
hyperglycemia	4

The Hb values and red blood cell(RBC) indices were analyzed (Table 5). Anova test was done to analyse the significance of RBC indices and haemoglobin levels in the four groups. There were significant variations in Hb (0.019),MCV(0.000) and MCH(0.000) among the four groups. No significant variations were noted in MCHC and RDW.

Table 5 : Hemoglobin and RBC indices of the four groups

Group	No.of cases	Mean+/_SD Hb	Mean+/_SD MCV	Mean+/_SD MCH	Mean+/_SD MCHC	Mean+/_SD RDW
A	61	7.76+/_2.89	104.08+/_6.98	33.47+/_3.47	32.11+/_2.25	19.49+/_15.66
B	16	6.63+/_1.86	113.7+/_8.11	37.91+/_3.72	33.47+/_2.12	21.15+/_5.22
C	16	9.62+/_2.12	102.51+/_5.14	33.22+/_2.71	32.38+/_1.95	16.1+/_2.62
D	12	7.62+/_3.07	101.1+/_4.81	31.4+/_3.78	31.05+/_3.44	16.06+/_2.77

* SD -standard deviation

The mean Hb value was highest in non nutritional megaloblastosis (group C) and lowest in nutritional megaloblastosis (group B). MCV was highest in group B (nutritional megaloblastic anemia) and least in group D (spurious macrocytosis) . MCH was highest in group B and lowest in Group D. MCH values were within the normal range in groups A, C and D.

We found that nutritional megaloblastic anemia showed lowest Hb, and highest MCV and MCH values

MCHC does not show much deviation between the groups. The mean MCHC values in all four groups fall within normal range. RDW is increased above normal range in all the four groups . Mean RDW is highest in nutritional megoloblastic anemia(Group B) and lowest in spurious macrocytosis(Group D). (Table 5)

Discussion

With increasing use of electronic hematology cell counters macrocytosis is often encountered. Various etiological factors contribute to the development of macrocytosis. The patient may or may not be anemic.

Causes of macrocytosis include megaloblastic anemia which may be due to nutritional deficiency of vitamin B12 and folate or due to non nutritional causes like antifolate therapy .Other causes are non megaloblastic macrocytosis and spurious macrocytosis.

The most frequent category encountered in this study is non megaloblastic macrocytosis(group A). Alcoholic liver disease was the most common cause . The mechanism of raised MCV is uncertain. In liver disease, the volume may increase due to excessive lipid deposition on red cell membrane and it is especially prominent in liver disease due to alcohol. [1] Other studies have suggested the role of tissue folate deficiency as a causative factor . [4] Early B12 deficiency and alcoholism show uniform macrocytes as compared to the macro ovalocytes in full fledged megaloblastic anemia. [5]

Acute leukemias accounts for a considerable chunk of group A. There were also 2 cases of MDS. The reasons for macrocytosis in these disorders is not well understood.

Hemolytic anemias very often show increased MCV due to marrow response and reticuocytosis. Interestingly in chronic hemolytic conditions, there can be excess utilization of folate which leads to megaloblastic marrow picture. [6],[7]

Aplastic anemia is also a cause for macrocytosis. Among the 5 cases in the present series, 2 were pediatric patients with Fanconi anemia. Both cases showed evidence of myelodysplasia in the bone marrow.

COPD also can cause macrocytosis but is usually mild. COPD patients develop frequent erythropoietic stress leading to release of young red cells with high MCV into the peripheral blood. No correlation is established between red cell size and severity of hypoxemia. [8]Hypothyroidism is another condition which causes macrocytosis but high MCV values above 110fl is rare. The 2 cases in our series had MCV of 98 and 100 fl.

Anemia is common in chronic kidney disease. Usually this is normocytic normochromic anemia but many patients show macrocytosis. Incidence of macrocytosis was more in hemodialysed patients in one series, suggesting loss of water soluble B12 and folate during hemodialysis . [9] Proposed causes of macrocytosis in dialysis patients include B12 and folate loss and dialysis induced change in red cell volume. [10]

Megaloblastic anemia is one of the most important causes of macrocytosis. The term megaloblast was first coined by Ehlrich to designate the abnormal erythroid precursors found in the bonemarrow of patients with pernicious anemia. Megaloblasts are large with abnormal "sieve"like chromatin. This is a morphological expression of abnormal DNA synthesis. Most often MA is due to deficiency of vitamin B12, folate or both. Other causes include inherited or drug induced disorders of DNA synthesis and malabsorption. Gastric intrinsic factor (IF) is necessary for the absorption of vitamin B12. Pernicious anemia is a disorder where there is severe lack of IF resulting in vitamin B12 deficiency and hence MA.

Other investigations done in cases of MA apart from blood and bone marrow smears are serum cobalamine, serum and red cell folate assays. Serum cobalamine level when performed by a reliable assay is an early indicator of deficiency, falling to low values before macrocytosis, megaloblastic change or neuropathy develops. However other conditions like folate deficiency, pregnancy, multiple myeloma etc may occasionally cause low serum levels of cobalamine. Red cell folate levels are more reliable than serum levels as it is unaffected by recent diet changes . [11] Measurement of methyl malonic acid (MMA) and homocysteine levels often help in differentiating between vitamin B12 and folate deficiencies. Homocysteine levels are elevated in both while MMA is raised only in vitamin B12 deficiency. [12]

Many drugs can cause folate deficiency. Valproic acid which is an anticonvulsant, inhibits mitochondrial folate metabolism. Hydantoin can lead to low folate levels. Antifolates such as methotrexate inhibit folate binding to dihydrofolate reductase and this limits the availability of tetrahydrofolate which is important in DNA metabolism. Sulfasalazine interferes with folate absorption. Chemotherapeutic agents interfering with nucleoprotein synthesis like hydroxyurea and 5 flourouracil cause MA. [3] In the present study incidence of nutritional and non nutritional MA were equal.

A significant subcategory is spurious or false macrocytosis and is a byproduct of the electronic era. This forms a small group but awareness is important in the evaluation of patients. Severe hyperglycemia, leukocytosis, cold agglutinins and presence of a paraprotein as in multiple myeloma can lead to artifacts of electronic cell sizing. [3][12]Moreover partial occlusion of instrument aperture, leaving the blood sample at room temperature for several hours may also result in false elevations in MCV value. [12]Cold agglutinins make RBCs clump, making them appear larger to automatic cell counters. [13] Non Hodgkin Lymphomas may be associated with cold agglutinins resulting in spurious macrocytosis. [14] Weiss and Bessman reports two patients with warm autoimmune HA whose MCV values where spuriously high. Red cell size distribution histogram showed doublets and triplets of normal sized red cells similar to cases with cold agglutinins. Since this artifact increases the MCV slightly less than it reduces the red cell count, the hematocrit is falsely low and MCHC is falsely high. [14][15] Hyperglycemic blood is more concentrated and when it is diluted to measure the MCV, the cells swell causing a false macrocytosis. Increased turbidity of a sample with marked leukocytosis also can cause the instrument to overestimate the cell size. [6] Presence of paraproteins as in monoclonal gammopathy and multiple myeloma can actually cause macrocytosis , [16][17]but spurious increase in MCV can also occur. [18] In this study myeloma and hyperglycemia were the causes for this false elevation of MCV.

There were significant variations in Hb values, MCV and MCH among the four groups.

Our analysis showed alcoholic liver disease as the leading cause of macrocytosis, closely followed by nutritional megaloblastic anemia. A small proportion of spurious macrocytosis was also encountered. Another study done at Puducherry, India reported megaloblastic anemia as the most

common cause of macrocytosis . [2] This disparity may reflect the lifestyle changes in Kerala State where while the literacy rate is high, the alcohol consumption is highest among all Indian states. The government owned Kerala State Beverages Corporation holds monopoly over liquor sales in the state. It is one of the most profitable public sector units in Kerala. Taxes on alcohol is a major source of revenue for the Government . The amount in rupees contributed by the Corporation to the State Exchequer during the year 2000-01 by way of Sales tax, Excise Duty, License Fee etc was 1025.93 crores while during the year 2011-12 was 6352.56 crore! [19]

Conclusion

Causes of macrocytosis vary widely. Spurious macrocytosis is occasionally encountered with the popularity of electronic hematology cell counters. Increasing urbanization has changed the conventional etiologic patterns in a developing country like India. With one of the highest per capita consumption of alcohol in India, alcohol-related problems are on the rise in Kerala State. Alcoholism causes psychosocial and physical morbidity and the present study unveils one more facet of this social evil.

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