Original Article

Evaluation of Macrocytic Anemia in a tertiary care hospital in Kanchipuram, Tamil Nadu, India

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Abstract

Introduction: Macrocytosis is used to describe large erythrocytes with a Mean Corpuscular Volume(MCV) of >101fl. There are a number of causes with characteristic haematological, biochemical and bone marrow findings which lead to macrocytic anemia.

Materials and Methods: We conducted an observational study of 62 cases in the Hematology Laboratory, at a tertiary care hospital in Kanchipuram with the aim to identify and evaluate macrocytic anemia and the underlying causes in routine hemograms and peripheral blood smears and correlate with the accompanying haematological features along with biochemical and bone marrow studies done in selected cases.

Results: Out of 62 cases received during the study period, Alcoholic Liver Disease emerged as the most common underlying cause (21 cases), followed by Hypothyroidism (16 cases) , Non-Alcoholic Liver Disease (11 cases), Vitamin B12 deficiency (9 cases) and drug-related causes (5 cases). Macrocytes were overall the most common peripheral blood smear finding accompanied by macro-ovalocytes and hypersegmented neutrophils in cases of Vitamin B12 deficiency.

Conclusions: Macrocytic anemia is commonly seen in alcoholic as well as several non-alcoholic cases, which should be fairly evaluated for further treatment and prevention.

Keywords: Macrocytic anemia, Mean corpuscular volume(MCV), Alcoholism, Peripheral blood smear.

Introduction

Macrocytosis is used to describe large erythrocytes with a Mean corpuscular volume of >101fl (Normal adult range : 80-101fl).[1] It is a common physiological finding in newborns, infants and pregnancy. Sometimes, it may also be present without the evidence of symptomatic anemia.[2,5]

The most common causes include alcoholism, vitamin B12 deficiency, hypothyroidism, non-alcoholic liver disease, drug intake,etc. Our study was done to find out the most common etiology out of these and correlate with the accompanying haematological and biochemical features.

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Materials and methods

The study was conducted after approval of the Institutional Ethics Committee(65/Path/IEC/2021) for a period of 11 months, starting from June 2021 till April 2022, in the hematology laboratory at a tertiary care hospital in Kanchipuram. A total of 62 cases with MCV >101fl and evidence of anemia were included in this study. Newborns, infants, pregnant females and cases where there were no evident etiologies were excluded from the study. A complete clinical history including drug history was taken for all cases and haematological parameters like complete blood count and RBC indices were taken from the Erba Mannheim 5 part hematology analyser while peripheral blood smears were done using Leishmann staining. Serum B12 and folate assays were done in cases (n=9) in which the peripheral blood smear showed macro-ovalocytes and hypersegmented neutrophils while bone marrow studies were carried out in 4 such cases as the remaining 5 cases resulted in dry tap. Liver function tests (21 cases of Alcoholic Liver Disease and 11 cases of Non-Alcoholic Liver Disease) and Serum TSH studies (16 cases of Hypothyroidism) were done where clinically relevant histories or already known diagnoses were elicited. These biochemical parameters were obtained from patients' case sheets.

The following values were taken as our operational definitions: [1,12,14]

1. Macrocytosis - MCV > 101 fl
2. Anemia: Male - Hb < 13g/dl

   Female – Hb < 12g/dl
3. Hypothyroidism – Serum TSH > 5.0 mIU/ l (1st time diagnosis)

Serum TSH >2.5mIU/l (known cases undergoing treatment)

4. Deranged LFT - i) Total Bilirubin > 1.0 mg/dl

   ii) Direct Bilirubin > 0.2 mg/dl

   iii) Aspartate transaminase (AST/SGOT) > 40 IU/l

   iv) Alanine transaminase (ALT/SGPT) > 33 IU/l

   v) Alkaline phosphatase > 120 mg/dl

   vi) Total Protein < 6.0 g/dl

   vii) Albumin < 3.5g/dl
5. Serum B12 deficiency < 180 ng/l
6. Serum folate deficiency < 3 µg/l

The various data collected were entered in the IBM SPSS software, Version22 , tested for statistical significance using the Independent T-test and P- value < 0.05 were considered as significant.

Results

The study group comprised of 46 males and 16 females in the age range of 26-82 years with the most commonly affected age group being 34-52 years. The most common underlying cause of macrocytosis was Alcoholic Liver Disease , as seen in 21 (34%) cases where all the patients were males in the age group of 34-71 years with the mean age being 47 years. It was followed by Hypothyroidism seen in 16 (26%) cases, out of which 13 were females in the age group of 26-61 years (mean age = 37 years) and 3 were males in the age group of 43-61 years (mean age = 52 years). The third most common cause was Non-Alcoholic Liver Disease seen in 11 (18%) cases, out of which 10 were males in the age group of 40-78 years (mean age = 58 years) and 1 was female (age = 76 years). It was followed by 9 (14%) cases of Vitamin B12 deficiency, where 8 were males in the age group of 41-82 years (mean age = 60 years) and 1 was female (age= 43years).

The least common cause was due to drug intake seen in 5 cases (8%), where 4 were males in the age group of 56-82 years (mean age= 62years) and 1 was female (age= 45 years). (Table 1)

All the cases were found to be anaemic, irrespective of the underlying cause, with mean haemoglobin being 10.2 g/dl in alcoholic cases and 9.3 g/dl in non-alcoholic category which included all the aforementioned etiological entities except alcoholism (P-value = 0.01). (Table 2)

For Mean Corpuscular Volume (MCV), the mean value was 108 fl in alcoholic cases and 105 fl in non- alcoholic category (P-value = 0.04). (Table 2)

The peripheral blood smear findings showed macrocytes in all the cases (Fig.1), along with few characteristic findings of macro-ovalocytes and hypersegmented neutrophils in cases of B12 deficiency.(Fig.2 & 3)

Serum TSH was found to be high in 9 cases of hypothyroidism,which included patients being diagnosed 1st time and already known cases undergoing treatment, ranging from 3.2 – 12 mIU/l (mean TSH = 7.2 mIU/l) whereas it was found in the therapeutic range(0.5-2.5mIU/l)[12] for remaining 7 cases, ranging from 0.5-2.0mIU/l (mean TSH = 0.9mIU/l). (Table 3)

Liver function tests were deranged in all 21 cases of alcoholic liver disease and 9 out of 11 cases of non-alcoholic liver disease. The remaining 2 patients showed corrected liver functions with treatment. (Table 4)

B12 levels were found to be low in all the 9 cases, ranging from 141- 179ng/l (mean = 160ng/l). Folate levels were found to be normal in all such cases, ranging from 5-12µg/l (mean = 9.0µg/l). Bone marrow studies were done in 4 out of 9 cases which showed megaloblastic changes like megaloblasts with sieve-like chromatin, features of dyserythropoeisis and giant metamyelocytes. (Fig.4, 5 & 6)

Table 1: Distribution of causes of macrocytosis with anemia

Underlying Cause	Cases	Percentage
Alcoholic liver disease	21	34%
Hypothyroidism	16	26%
Non-Alcoholic Liver disease	11	18%
Vitamin B12 deficiency	09	14%
Drug-related	05	8%
Total	**62**	**100%**

Table 2: Mean hematological profile in macrocytic anemia due to Alcoholic liver disease and non-alcoholic causes

Parameter	Alcoholic liver disease category (21 cases)	Non-alcoholic category (41 cases)
Haemoglobin (g/dl)	10.2 (9.5-11.3)	9.3 (6.7-11.2)
MCV (fl)	108 (103-127)	105 (105-108)
MCH (pg)	30.8 (25-31)	30.4 (29-32)
RBC count (mill./cu.mm)	3.17 (2.98-3.41)	3.10 (1.45-3.26)
RDW-CV (%)	14.3 (13.7-15.2)	14.7 (12.9-15.8)
Total WBC count(cells/cu.mm)	8,600 (7,200-12,000)	5,100 (3,000-9,600)
Platelet count (lakhs/cu.mm)	2.6 (84,000 – 3.2)	1.9 (78,000-2.6)
Peripheral blood smear	Predominantly, macrocytes	Predominantly macrocytes, along with few macro-ovalocytes and hypersegmented neutrophils in B12 deficiency

Table 3. Serum TSH profile in patients with Hypothyroidism (1st time diagnosis and known cases undergoing treatment)

S.no.	Age (in years)	Sex	Serum TSH (mIU/l)
1.	36	Female	3.2
2.	61	Female	0.9
3.	52	Male	1.0
4.	45	Female	0.5
5.	61	Male	7.1
6.	36	Female	2.0
7.	43	Male	0.6
8.	27	Female	6.4
9.	49	Female	12
10.	32	Female	10
11.	28	Female	12
12.	35	Female(diagnosed 1st time)	4.1
13.	38	Female	0.7
14.	36	Female	0.6
15.	26	Female(diagnosed 1st time)	5.1
16.	34	Female	5.1

Table 4. Mean Liver Function Test profile in Alcoholic Liver Disease and Non-Alcoholic Liver Disease cases

Parameter	Alcoholic Liver Disease (21 cases)	Non- Alcoholic Liver Disease (9 out of 11 cases)
Total Bilirubin	3.3 (1.0 – 12.2)	2.0 (1.0- 3.5)
Direct Bilirubin	0.4 (0.4 – 1.0)	0.4 (0.3 – 0.5)
AST/SGOT	52 (45 – 78)	42 (42 - 50)
ALT/SGPT	38 (35 - 81)	35 (35 – 61)
Alkaline phosphatase	134 (122- 156)	128 (125 – 155)
Total Protein	5.8 (5.0 – 5.9)	5.9 (5.0-5.9)
Albumin	3.0(2.9 – 3.3)	3.2 (3.0-3.4)

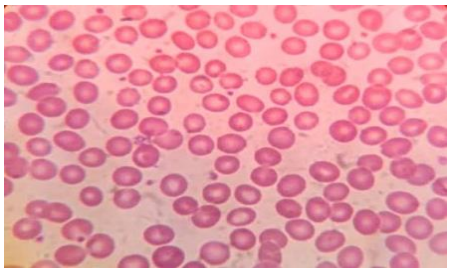

Fig.1. Peripheral blood smear showing macrocytes (arrow) in a case of macrocytic anemia in alcoholic liver disease

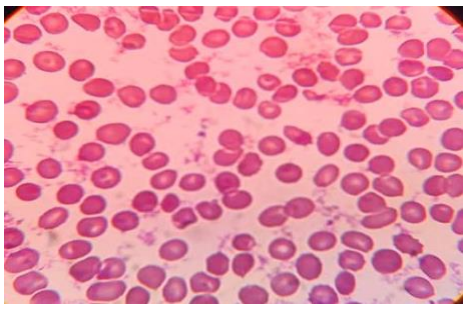

Fig.2. Peripheral blood smear showing macrocytes and macro-ovalocytes (arrow) in a case of macrocytic anemia due to Vitamin B12 deficiency

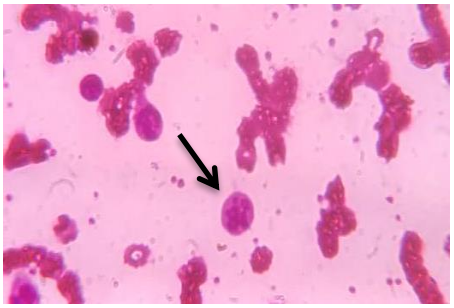

Fig.3. Peripheral blood smear showing hypersegmented neutrophil (arrow) in a case of macrocytic anemia due to Vitamin B12 deficiency

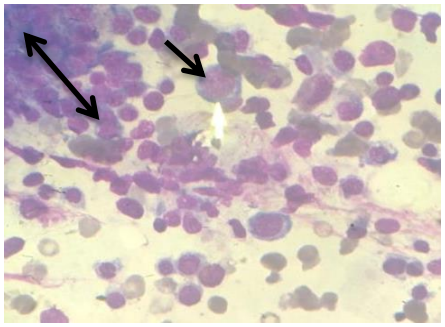

Fig.4. Bone marrow aspirate from a macrocytic anemia due to Vitamin B12 deficiency showing erythroid hyperplasia(double arrow) and megaloblasts with sieve-like chromatin (single arrow)

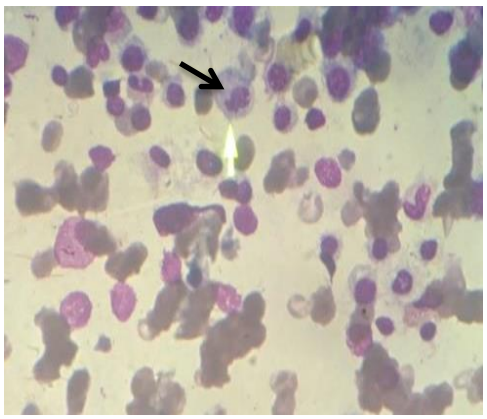

Fig.5. Bone marrow aspirate in Vitamin B12 deficiency showing features of dyserythropoeisis (arrow)

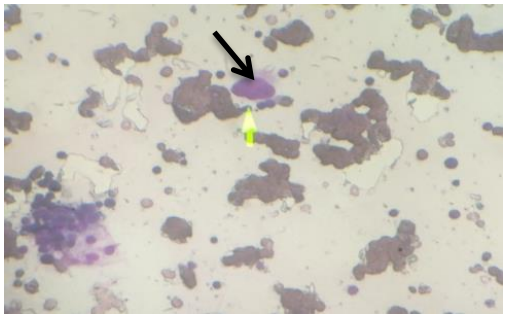

Fig.6. Bone marrow aspirate in Vitamin B12 deficiency showing a giant metamyelocyte (arrow)

Discussion

Different study groups have different causes of macrocytic anemia depending upon the age distribution, environmental factors, nutritional status, addiction history and other predisposing risk factors. In an independent study done by Saeed et al.[4] in Aligarh, Uttar Pradesh, India, the most common etiology for macrocytosis was found to be Vitamin B12 deficiency (60%). This study was similar to the one done by Unnikrishnan et al,[18] where megaloblastic anemia was given special reference as a etiology for macrocytic anemia. However, our study results (34%), were found to be similar to the study done by Keenan et al.[7] where alcoholism was the leading cause of macrocytic anemia (36%). In an another independent study done by Berad et al,[19] macrocytic anemia was seen in 25 out of 75 cases (33%), which included severe alcoholics who consumed more than 80-90 mg of alcohol or more than 11 drinks per day. Our study results could be attributed to a similar factor as the rate of consumption of alcohol was seen to be quite significant in our study area.The mechanism of macrocytosis in alcoholic liver disease is not exactly clear but few studies have postulated the following theories:

Alcoholism causes direct toxicity to the bone marrow.[3] In such cases, there is a relatively increased production of structurally abnormal erythroid precursors, one of which is the development of large vacuoles in the pronormoblasts. These do not get the adequate time to mature and eventually get released into the circulation as functionally immature cells. Another mechanism suggested is that alcoholics frequently have defective red blood cells that are destroyed prematurely, possibly resulting in anemia.[3] Alcoholism can also exacerbate an already present Vitamin B12 and folate deficiency by interfering with the absorption and aggravating the abnormal nutritional status. However, these effects are all dose-dependent as many of these effects start disappearing within 2-4 months of abstinence.[3]

In our study, apart from alcoholism, hypothyroidism(26%) was also found to be linked to macrocytic anemia, which was similar to the case report presented by Sims.[17] In another study of anemia in primary hypothyroidism done by Patel et al,[20] frequency of macrocytic anemia in overt hypothyroid and subclinical hypothyroid patients were 23% and 28% respectively (P- value =0.113).In hypothyroidism, macrocytosis is a physiological adaptation to the slower basal metabolic rate , decreased tissue oxygen requirements and to the deficient thyroid hormones which are involved in regulation of haemoglobin synthesis.[10] Thyroid hormones also stimulate synthesis of erythropoietin, and thus a deficiency can lead to anemia.

In our third most common etiological entity called non-alcoholic liver disease (18%), there is an increased lipid deposition on the membrane of the RBCs, which causes increased surface area and leads to macrocytosis.[9,11] Added to this, there may be associated nutritional deficits in such patients, such as B12 and folate deficiency which

contribute towards the anemia. A study done on red blood cell status in alcoholic and non-alcoholic liver disease by Maruyama et al [21] showed that macrocytic anemia was a common finding in both alcoholics and patients of non-alcoholic liver disease.

Other than the causes aforementioned, one of the very common cause for macrocytic anemia is B12 deficiency which causes a maturation defect in the normal erythropoiesis.[5] The haemoglobin synthesis may continue normally but there is a lag in nuclear division, which results in larger RBCs. In these cases, bone marrow aspirates almost always show an increase in the erythroid lineage along with characteristic megaloblastic changes as already discussed before.

Drug intake (37%) was found to be the most common cause in the study done by Savage et al.[8] Metformin, anti-convulsants, anti-retroviral drugs, sulfamethoxazole, trimethoprim are some of the common drugs causing macrocytosis.[2,5] In our study, 5 cases (8%), who were known diabetics were found to have a history of drug intake, in which the drug prescribed commonly to all of them was Metformin, a biguanide used in Diabetes mellitus Type II. The exact causal relationship is unknown however, it has been postulated that prolonged Metformin therapy induces Vitamin B12 deficiency and subsequent macrocytic anemia in diabetic patients.[22]

Conclusion

With the advent of routine haematological investigations, peripheral blood smears and availability of bone marrow studies , it has become very easy to identify macrocytic anemia in the population. To prevent future complications and other associated co-morbidities, it is imperative that a close follow-up is done since the time of diagnosis and a thorough evaluation for all the possible etiologies would help in drawing up a treatment plan so as to restrict the pathogenesis in the early stages itself. A simple method of abstinence alone can reverse

the symptoms and rectify the blood picture in cases of macrocytic anemia due to alcoholism. Similarly, a proper nutritious diet, with inclusion of both plant and animal based products, legumes and pulses that are rich in Vitamin B12 and folic acid should be able to control further deterioration of the symptoms, if not reverse it totally. In the remaining etiological factors, a proper screening, work-up, early diagnosis, aggressive treatment and supplementation for patients of hypothyroidism and non-alcoholic liver disease can be given in order to stop the worsening of symptoms and the haematological profile. Likewise, macrocytosis-causing drugs can be switched to better alternatives after calculating the risk-benefit ratios and patient compliance.

Therefore, in many patients with known etiologies, routine blood testing can be very useful in identification, assessment and follow-up of treatment strategies for macrocytic anemia.

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