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SPECTRUM OF MACROCYTIC ANEMIA IN ADULT POPULATION: CLINICAL EXPERIENCE FROM A TERTIARY CARE CENTRE.

General Medicine

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ABSTRACT

PURPOSE: Macrocytic anemia is a state with mean corpuscular volume (MCV) more than 100fL. Various disease initially may present as macrocytosis. Thus, a detailed evaluation is required in every case of macrocytic anemia.

MATERIAL AND METHODS: This study was conducted on 500 patients of macrocytic anemia at Pt. B. D. Sharma PGIMS, Rohtak. Patients with any chronic medical illness were excluded.

RESULTS: Majority of cases belonged to age group of 15-29 years of age with male preponderance. Pancytopenia was the most common hematological presentation. Megaloblastic anemia accounts for macrocytosis in 90% of the patients with MCV 110fL or more. Vitamin B12 was deficient in 84.5% cases with megaloblastic anemia. Non-megaloblastic causes include liver disease, aplastic anemia etc.

CONCLUSION: This study concluded that megaloblastic anemia is the most common cause of macrocytic anemia and likelihood of megaloblastic cause increases with MCV of >110fL.

KEYWORDS

Macrocytic Anemia, Megaloblastic, Pancytopenia

INTRODUCTION:

Macrocytosis is a common finding seen in 1.7–3.6% of patients seeking medical care.[1,2] Macrocytic anemia refers to a condition in which erythrocytes are larger than normal with an increase in mean corpuscular volume (MCV) more than 100 fL.[3] It can be classified into megaloblastic anemia and non-megaloblastic macrocytic anemia. Causes of megaloblastic anemia include vitamin B12 deficiency, folic acid deficiency, inherited disorders of DNA synthesis and drugs/toxin induced disorder of DNA synthesis. Non-megaloblastic causes include conditions causing reticulocytosis, liver disorders, alcoholism, bone marrow disorders and hypothyroidism. Spurious macrocytosis may result from paraproteinemia, marked leucocytosis, hyperglycemia and cold agglutinins causing false elevation of MCV.[4,5]

Macrocytosis serves as an important marker of various disease. It appears before evidence of any clinical or hematological manifestation of disease.[6] Macrocytosis is evident in 40% to 96% of alcoholics, many of whom have no anemia and can act as marker to identify high risk persons for screening of esophageal carcinoma and gastric carcinoma associated with alcohol abuse.[7,8] Macrocytic anemia refractory to treatment are usually initial manifestation of primary bone marrow disease like myelodyaplastic syndrome, leukemia or aplastic anemia. Mood disorders and psychosis has been reported among the patients with macrocytosis and usually suggests an underlying disease.[9] Various drugs may also cause raised MCV and can be used as a surrogate marker for adherence to treatment.[10,11] As macrocytic anemia can result from various treatable conditions, evaluation of its clinical and etiological profile can provide early diagnosis and timely initiation of treatment. Hence, this study has been planned.

MATERIAL AND METHODS:

This was prospective observational study conducted at Pt. B. D. Sharma PGIMS, Rohtak. 13,820 adult patients suffering from anemia attending OPD or admitted in medicine ward were screened for macrocytosis. Five hundred patients with the diagnosis of macrocytic anemia according to inclusion criteria were included in the study. Inclusion criteria were adults with 15-59 years of age of both genders, anemia with a hemoglobin of less than 13g/dl in male, less than 12g/dl in non-pregnant female, less than 11g/dl in pregnant female and mean red blood corpuscular volume (MCV) >100fL.[3,12] Adults with microcytic or normocytic anemia and those who were already a diagnosed case of any chronic medical illness like diabetes, hypertension, chronic kidney disease etc. were excluded. Anemia was further classified into mild anemia (hemoglobin 11– 12.9 g/dl in males and 11- 11.9 g/dl in females), moderate anemia (haemoglobin between 8.0– 10.9 g/dl) and severe anemia (haemoglobin below 8.0 g/dl).[12] This study was duly approved by the ethical committee and the post graduate board of studies of the institution. The purpose of the study was explained to the patients, their caregivers and informed consent was taken.

After enrolment all patients were subjected to detailed history, general physical and systemic examination. Following Routine hematological investigations were carried out in every case of macrocytic anemia: complete blood count, erythrocyte sedimentation rate, kidney function test, liver function test, vitamin B12 levels and folic acid levels by chemiluminescence, urine complete examination, chest X-RAY and ultrasonography of abdomen. Additional investigations were done as indicated for detection of underlying cause. Bone marrow aspiration and biopsy was done in patients who were non-responsive to treatment, low reticulocyte production index and peripheral smear showing abnormal cells. Other tests included thyroid profile, upper gastrointestinal endoscopy, PT/INR, osmotic fragility test, coomb's test (both direct and indirect), G6PD levels, serum LDH, serum haptoglobin, Anti-nuclear antibody (ANA) by immunofluorescence (IFA), CD55,59 by flow cytometry, computed tomography abdomen and fibroscan as indicated.

The results were analysed by calculating percentages, the mean values, standard deviation and chi-square test. Proportions were compared using chi-square test and significance. IBM SPSS statistics version 23 was used to conduct all statistical analyses. A p-value of less than 0.05 was considered statistically significant.

RESULTS:

Mean age of study population was 36 ± 13.36 years. Bimodal distribution of age with maximum number of cases belonging to age group of 15-29 years of age, followed by 50-59 years of age group was observed. There was male preponderance with male to female ratio of 1.85:1.

Majority of our study population was vegetarian. 80.28% of the patients with megaloblastic anemia were vegetarian with either vitamin B12 deficiency, folate deficiency or both deficiencies. 78.33% of the total cases with vitamin B12 deficiency were vegetarian.

The most common presenting symptom of the study population was generalized weakness followed by shortness of breath, jaundice, loss of appetite, bleeding manifestations, fever, weight loss and others. Bleeding manifestations were most common presenting complaint with liver disease (78.57%) followed by aplastic anemia (75%). 9.85 % cases with megaloblastic anemia presented with bleeding manifestation. Jaundice was most common presenting feature of hemolytic anemia and liver disease where it was present in all the cases while it was present in 29.57% cases with megaloblastic anemia. On clinical examination pallor was universal finding followed by icterus.

5.63% and 1.41% cases of megaloblastic anemia had hepatomegaly and splenomegaly, respectively. Non-megaloblastic causes had hepatomegaly and splenomegaly in 37.93% and 34.48%, respectively. (Table-1)

TABLE 1: Clinical Spectrum Of Macrocytic Anemia In Study Population

Clinical spectrum of macrocytic anmeia	Number of cases (n=500)
Generalized weakness	410
Loss of appetite	175
Shortness of breath	205
Bleeding manifestations	125
Jaundice	185
Fever	30
Weight loss	20
Pallor	500
Hepatomegaly	75
Splenomegaly	55
Pedal edema	50
Abdominal distention	45
Lymphadenopathy	5

Mean haemoglobin in our study population was 5.02 ±2.02 g/dl. Most of the patients had severe anemia at presentation with 89% patients having haemoglobin less than 8g/dl. Anemia was mild in 4% and moderate in 7% of cases. 94.36% and 75.865% of the patients with megaloblastic anemia and non-megaloblastic anemia, respectively presented with severe anemia. All the patients diagnosed with aplastic anemia had severe anemia at presentation. While mild anemia was present only in cases with liver disease and hypothyroidism. Pancytopenia was the most common hematological presentation (62%) in our study population. 82.25% were diagnosed to have megaloblastic anemia and 17.74% were having non-megaloblastic cause of anemia.

Reticulocyte production index (RPI) was normal in majority of patients & was increased in only 10 cases. Five of them had positive coomb's test, high LDH and positive of ANA by IFA. Another five patients had deficient CD55 and CD59 on flow cytometry and diagnosed to have paroxysmal nocturnal hemoglobinuria. Low RPI was seen in 40 cases who also had pancytopenia. Bone marrow biopsy was performed in them, which suggested aplastic anemia. Bone marrow examination was performed in 70 cases. 40 of them had aplastic anemia, 10 cases were reported as myelodysplastic syndrome and five biopsies showed chronic lymphocytic leukemia. Five cases had heptosplenomegaly with pancytopenia, raised ESR, positive Mantoux test, biopsy confirmed the presence of granulomatous inflammation which was clinically suggestive of disseminated tuberculosis. Erythroid hyperplasia was present in ten cases, in whom later on after performing CECT abdomen, chronic liver disease with portal hypertension was diagnosed.

Mean MCV in our study was 109.08 ± 6.92 fL. 60% of the cases had MCV value 100-109fL. 58.33% of them had megaloblastic anemia and 41.66% had non-megaloblastic anemia. MCV value 110fL or more was found in 40% of the cases. Out of them megaloblastic anemia was the cause of macrocytosis in 90% of the cases. This difference was statistically significant with p-value of 0.0001. (Table-2)

TABLE 2: Relation Of Mcv With Type Of Macrocytic Anemia

Type of anemia MCV (fL)	Megaloblastic anemia	Non-megaloblastic anemia	Uncorrected chi-square value 58.44	p-value 0.0001
100.1-109	175	125		
110 or more	180	20		

Most common cause of macrocytic anemia was found as megaloblastic anemia. 71% had megaloblastic anemia while 29% cases were due to non-megaloblastic causes. Among megaloblastic anemia, 42.25% had vitamin B12 deficiency, 15.49% had folate deficiency and 42.25% had both vitamin B12 and folate deficiency. Vitamin B12 was deficient in 84.5% cases with megaloblastic anemia resulting in most common cause of megaloblastic anemia.

Among non-megaloblastic causes of macrocytic anemia, most common cause was found to be liver disease which was present in 48.27% of non-megaloblastic anemia followed by aplastic anemia in 27.58%. Hemolytic anemia was present in ten cases, myelodysplastic syndrome in ten cases, chronic lymphocytic leukemia in five case, disseminated tuberculosis in five cases and hypothyroidism in five cases.

DISCUSSION:

Macrocytic anaemia is one of the preventable and treatable causes of anemia. The causes of macrocytosis varies in different populations studied. The etiology and demographic profile varies among various western and Indian studies. Savage et al. in their study from western world have reported drug therapy and alcohol abuse as the most frequent causes and Vitamin B12/folate deficiency as uncommon cause.[13] Similarly some studies have also reported bone marrow disorders as the most frequent cause.[14] In contrast, study conducted by Unnikrishnan et al. from India have reported megaloblastic anemia as most common cause followed by bone marrow disorders and liver disease.[15] Similarly, in our study, the most common cause of macrocytic anemia was found as megaloblastic anemia with vitamin B12 deficiency being the commonest cause followed by liver disease and primary bone marrow disorders. This difference may be attributed to the vegetarian diet pattern in this region of India. Majority of our study population had vegetarian diet. 80.28% of the patients with megaloblastic anemia were vegetarian with either vitamin B12 deficiency, folate deficiency or both deficiencies.

Patients with anemia usually seek medical attention because of decreased work or exercise tolerance, shortness of breath, palpitations, or other signs of cardiorespiratory adjustments to anemia. The clinical manifestations of anemia depend upon the degree of anemia whether mild, moderate or severe and the capacity of the cardiovascular and pulmonary systems to compensate for the anemia. The most common presenting symptom was generalized weakness followed by shortness of breath, jaundice, loss of appetite, bleeding manifestations, fever and weight loss. Other symptom included abdominal pain, abdominal distention, pedal edema and constipation. Similar results were found in other studies.[15,16]

Bleeding was present in 25% of the study population. It may result from low platelet count due to bone marrow involvement causing dypoiesis of different cell lines or coagulation abnormality as seen in liver diseases. It was similar to findings with study by Unnikrishnan et al. where bleeding was there in 26.1% cases of macrocytic anemia.15 Patients with macrocytic anemia can also present with jaundice as a result of liver disease, ineffective erythropoiesis or hemolysis. In this study, it was a common presenting feature of liver disease and hemolytic anemia.

Megaloblastic anemia usually develops gradually, and the degree of anemia is often severe when first detected. Majority of the patients had severe anemia with mean haemoglobin of 5.02 ±2.02 g/dl at presentation. This may occur because most of the patients consult a tertiary care centre when there is cardio-pulmonary compromise. 94.36% of the patients with megaloblastic anemia had severe anemia. If the anemia is associated with thrombocytopenia or abnormalities in white blood cell numbers or the presence of abnormal leukocytes, consideration must be given to the possibility of bone marrow failure due to aplastic anemia, leukemia, or other malignant marrow disease. Leukopoiesis and megakaryopoiesis may be disturbed in megaloblastic anemia causing anemia with thrombocytopenia or leukopenia. Alternatively, pancytopenia can be secondary to peripheral destruction or sequestration of cells as in hypersplenism. Pancytopenia was the most common hematological presentation in this study and most of them had megaloblastic anemia. Khunger et at. and various studies have reported megaloblastic anemia as most common cause of pancytopenia.[17-19]

The mechanisms underlying the formation of macrocytes are complex and diverse. In Vitamin B12/folate deficiencies, there is DNA synthesis defect involving nuclear maturation. Macrocytosis in alcoholism is related to the direct toxic effect of alcohol on the red cell membrane.5 In myelodysplastic syndrome, macrocytosis results from the dysplastic changes in the erythroid precursors and in hepatobiliary disease and hypothyroidism, there is deposition of excess lipids on the red cell membrane, which results in raised MCV.[20]

The present study concluded that macrocytic anemia can result from various conditions which are commonly encountered in general

practice. Macrocytosis needs to be evaluated even in the absence of anemia, as it may be the first clue to an underlying pathology. The most common cause of macrocytic anemia was found to be megaloblastic anemia with majority of them having vitamin B12 deficiency. As shown in this study macrocytosis may be the presenting feature of deadly illnesses such as aplastic anemia, leukemia and myelodysplastic syndrome thus, detailed evaluation is required in every case for early diagnosis and treatment. The present study also reported that the likelihood of megaloblastic cause of macrocytic anemia was higher in the presence of MCV more than 110fL.

REFERENCES

1. Davidson RJL, Hamilton PJ. High mean red cell volume: its incidence and signifi cance in routine haematology. J Clin Pathol 1978;31:493–8
2. Breedveld FC, Bieger R, van Wermeskerken RK. The clinical significance of macrocytosis. Acta Med Scand 1981;209(4):319-22.
3. Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis; Clin Med Res 2006;4:236-41.
4. Hattersley PG, Gerard PW, Caggiano V, Nash DR. Erroneous values on the Model S Coulter Counter due to high titer cold autoagglutinins. Am J Clin Pathol 1971;55:442-6.
5. Kaferle J, Strzoda CE. Evaluation of macrocytosis. Am Fam Phys 2009;79:203-8.
6. Hall CA. Vitamin B12 deficiency and early rise in mean corpuscular volume. JAMA 1981;245(11):1144–6.
7. Yokoyama A, Yokoyama T, Muramatsu T, Omori T, Matsushita S, Higuchi S et al. Macrocytosis, a new predictor for esophageal squamous cell carcinoma in Japanese men. Carcinogenesis 2003;24:1773–8.
8. Ransing RS, Patil S, Pevekar K, Mishra K, Patil B. Unrecognized Prevalence of Macrocytosis among the Patients with First Episode of Psychosis and Depression. Indian J Psychol Med 2018;40(1):68–73.
9. Papadakis KA. Mean corpuscular volume: a simple and inexpensive way to monitor azathioprine/6-mercaptopurine treatment in patients with inflammatory bowel disease? Evidence-Based Gastroenterology 2004;5:22-3.
10. Steele RH, Keogh GL, Quin J, Fernando SL, Stojkova V. Mean cell volume (MCV) changes in HIV-positive patients taking nucleoside reverse transcriptase inhibitors (NRTIs): a surrogate marker for adherence. Int J STD AIDS 2002;13:748-54.
11. Yokoyama A, Yokoyama T, Omori T, Matsushita S, Mizukami T, Takahashi H et al. Helicobacter pylori, chronic atrophic gastritis, inactive aldehyde dehydrogenase-2, macrocytosis and multiple upper aerodigestive tract cancers and the risk for gastric cancer in alcoholic Japanese men. J Gastroenterol Hepatol 2007;22(2):210-7.
12. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011.
13. Savage DG, Ogundipe A, Allen RH, Stabler SP, Lindenbaum J. Etiology and diagnostic evaluation of macrocytosis. Am J Med Sci 2000; 319(6):343–52.
14. Takahashi, N, Kameoka, J, Takahashi, N, Tamai, Y, Murai, K, Honma R et al. Causes of macrocytic anemia among 628 patients: mean corpuscular volumes of 114 and 130 fL as critical markers for categorization. Int J Hematol 2016;104(3):344-57.
15. Unnikrishnan V, Dutta TK, Badhe BA, Bobby Z, Panigrahi AK. Clinico-aetiologic profile of macrocytic anemias with special reference to megaloblastic anemia Indian J Hematol Blood Transfus 2008;24:155-65.
16. Kannan A, Tilak V, Rai M, Gupta V. Evaluation of clinical, biochemical and hematological parameters in macrocytic anemia. Int J Res Med Sci 2016;4(7):2670-8.
17. Khunger JM, Arulselvi S, Sharma U, Ranga S, Talib VH. Pancytopenia a clinicohaematological study of 200 cases. Indian J Pathol Microbiol 2002;45:375-9.
18. Ishtiaq O, Baqai HZ, Anwer F, Hussain N. Patterns of pancytopenia patients in a general medical ward and a proposed diagnostic approach. J Ayub Med Coll Abbottabad 2004;16:8-13.
19. Kumar R, Kalra SP, Kumar H, Anand AC, Madan H. Pancytopenia a six year study. J Assoc Physicians India 2001;49:1078-81.
20. Mason KD, Szer J. Investigating patients with macrocytosis. Med Today 2005; 6(12):35–9.