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"STUDY OF CELL COUNTER DETECTED MACROCYTOSIS IN TERTIARY CARE HOSPITAL"

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ABSTRACT

Background:
Macrocytosis is considered when mean corpuscular volume is more than 96fl. When a cell counter gives high MCV, clinician considers it as megaloblastic anemia. However, macrocytosis does not mean only megaloblastic anemia and it may be seen in absence of anemia. So, evaluating macrocytosis gives a clue about other conditions.

Aims and Objectives:
To study all cases of cell counter suggested macrocytosis with following specific objectives.
(1) To evaluate proportion of macrocytosis.
(2) To classify megaloblastic and non megaloblastic macrocytosis and to evaluate the causes of non-megaloblastic macrocytosis.
(3) To assess the range of macrocytosis in different conditions.

Materials and methods:
After EC approval, a prospective hospital based cross sectional study on macrocytosis was done from 1st October 2020 to 31st January 2021.

Key words: Macrocytosis, mean corpuscular volume, Megaloblastic macrocytosis, Non megaloblastic macrocytosis, cell counter detected macrocytosis.

INTRODUCTION

MACROCYTOSIS

- Macrocytosis is considered when mean corpuscular volume (MCV) is more than 96fl[1] and its prevalence ranges from 1.7% to 3.6%.
- There are numerous causes of macrocytosis, including physiological causes like in newborn, infants and pregnant females as well as pathological causes like megaloblastic anaemia, myelodysplasia, hypothyroidism, liver disease, hemolysis, hemorrhage, chronic obstructive pulmonary disease and iatrogenic conditions like alcohol abuse and medication side effects.
- When a cell counter gives high MCV, clinicians and pathologist usually consider it as megaloblastic anemia. However, macrocytosis may be seen in absence of anemia. So evaluating macrocytosis gives a clue about other conditions.
- Proportion of macrocytosis in the hospital of this study was not known. Hence this study was undertaken to

Aim was conducted on studying all cases of cell counter suggested macrocytosis with specific objectives of evaluating proportion of macrocytosis, classifying megaloblastic and non megaloblastic macrocytosis and evaluating the causes of non-megaloblastic macrocytosis and assessing the range of macrocytosis in different conditions.

MATERIAL AND METHOD

After Institutional Review Board, a prospective hospital based cross sectional study on macrocytosis was started from 1st October 2020 to 31st January 2021.

Inclusion:

- All sequential indoor CBCs with MCV more than 96 fl were evaluated for further study.

Exclusion:

- Those cases of macrocytosis in which detailed history was not available and whose sample was not being available for further testing for reticulocyte count and peripheral smear examination.
- Pregnant women.

Samples of EDTA anticoagulated blood collected from wards were run in Nihon automated cell counter and entire CBC were recorded for the samples with high MCV >96fl. Megaloblastic and non megaloblastic conditions were evaluated with the help of clinical history, blood indices, reticulocyte count and peripheral smear examination.

- Samples with HB <12 gm% in females and <13gm% in males were referred as anemic.
- Peripheral smears were prepared to study the morphology of the RBC's and classify as microcytic, normocytic and macrocytic.
- Reticulocyte count was done by manual method using supravital
- Demographic details like age, sex, history of patient were retrieved from the test request forms and further questioning.
- Proportion was calculated by percentage.

RESULT

A total number of 23108 samples of CBCs were evaluated during the period of 1st October 2020 to 31st January 2021. Out of which 350 CBCs had MCV >96 fl, these were evaluated further. So, in present study the prevalence of macrocytosis was 1.51%. Of these 350cases, 29% cases had macrocytosis but no anemia. All cases with macro-ovalocytosis, hypersegmented neutrophils and relevant clinical history of vitamin B12 and folate deficiency were considered as megaloblastic. 89% cases of high MCV were non megaloblastic. Only 11% cases had megaloblastic picture on peripheral smear.

Table R1: Causes of macrocytosis and different level of anemia

CAUSES	%	Hb >12gm%	Hb 7-12gm%	Hb <7gm%
Drug Related(123)	35%	88	31	04
Liver Diseases(125)	35.7%	45	74	06
Vitamin B12 Deficiency(28)	8%	00	12	16
Folate Deficiency(3)	0.8%	00	02	01
Dimorphic Anemia(3)	0.8%	00	02	01
Hemolytic Anemia(2)	0.5%	00	01	01
Diabetes(33)	9.4%	20	11	02
Hypothyroidism(9)	2.5%	07	02	00
Copd(8)	2.3%	07	01	00
Atrophic Gastritis(2)	0.5%	00	02	00
Others(Includingckd,RTA)(17)	4.8%	09	08	00

Table R2: Classification of conditions according to lineage association of cytopenia

Conditions	One Lineage Cytopenia			Two Lineage Cytopenia			Pancytopenia Cytopenia
	RBC	WBC	PLT	RBC& WBC	RBC &PC	WBC &PC	RBC, WBC & PC
Drug induced	62	02	01	11	05	01	03
Liver disease	46	00	02	04	34	01	11
Vitamin B12 deficiency	12	01	00	02	11	00	03
Folate deficiency	01	00	00	00	02	00	00
Dimorphic anemia	02	00	00	00	01	00	00
Hemolytic Anemia	00	00	02	00	00	00	01
Diabetes	16	00	02	00	01	00	01
Hypothyroidism	03	00	00	00	01	00	00
COPD	03	00	00	00	00	00	00
Atrophic gastritis	01	00	00	00	00	00	00
Other	12	00	00	01	02	00	01
Total	**156**	**03**	**07**	**18**	**57**	**02**	**20**

Table R3: Peripheral smear findings in cell counter detected macrocytosis

P/S FINDINGS (n= Number of cases)	%
Macrocytic normochromic (200)	57
Macrocytic hypochromic (132)	38
Normocytic + Macrocytic hypochromic (32)	9
Microcytic + Macrocytic hypochromic (25)	7
Macrocytic hyperchromic (9)	2.5
Normocytic normochromic (3)	0.8
Macro ovalocytes (74)	11
Target cells (79)	22.5
Hyper segmented neutrophils (10)	2.8
Eosinophilia (71)	20

Table R4: Conditions and grade of increased in MCV values

Conditions	96-99 (borderline)	100-104 (mild)	105-114 (moderate)	115-124 (severe)	≥125 (markedly severe)
Drug related	40	71	22	10	02
Alcoholic liver disease	39	53	05	01	-
Alcoholic cirrhosis	01	04	05	-	-
Chronic liver disease	07	06	-	-	-
Vitamin B12 deficiency	06	16	04	-	-
Folate deficiency	-	01	02	-	-

Dimorphic anemia	02	01		-	-
Hemolytic Anemia	-	01		01	-
Diabetes	06	21	04	02	-
Hypothyroidism	04	03	02		-
COPD	03	05			-
Pancytopenia	-	-	01	01	-
Atrophic gastritis	-	-	02		-

DISCUSSION

Alcoholism, Vit B12 deficiency disorders and drug induced macrocytosis are most common causes of macrocytosis. In study of P. Veda alcoholism out numbers B12 deficiency cases, whereas in studies of Saeed megaloblastosis out numbers alcoholism. However, in Savage and present studies liver diseases and drug induced macrocytosis are the most common causes. Most of our macrocytosis cases with liver diseases were due to alcoholism.

Macrocytosis without anemia has been observed in 60% patients, in study of Aslinia F et al and Colon-Otero et al. However, in present study, 29% cases presented without anemia. This could be due to high numbers of cases receiving ART in the study.

Anticonvulsants, sulfasalazine, antiretroviral drugs, folate antagonists, metformin, chemotherapeutics agents, pyrimethamine, sulfamethoxazole and trimethoprim are some of the known drugs causing macrocytosis. Most patients with HIV, being treated with reverse transcriptase inhibitors display macrocytosis without anemia. The antiretrovial drugs are mainly causing high MCV and MCH. So, in these patients, macrocytosis is considered as useful marker indicating the patient's compliance in taking medications. Peripheral smear of patient taking anti-retroviral therapy shows round, uniformly distributed macrocytosis. These findings are also seen in patient taking antiepileptic drugs.

Mean RDW (23.5%) in megaloblastic cases was more than that in non-megaloblastic cases (16.8%) in Saeed et al study. In present study, mean RDW (18%) in megaloblastic cases was more than that in non-megaloblastic cases (14.8%). But the difference was not as much as seen in study of Saeed, again it is probably due to concurrent microcytosis.

Gupta et al. have compared the red cell parameters in macrocytosis of aplastic anemia and megaloblastic anemia and observed that RDW in megaloblastic anemia was significantly higher (21.4%) than the RDW in aplastic anemia (13.5%). An increased RDW has been reported in megaloblastic anemia, myelodysplastic syndromes, aplastic anemia and chemotherapy, Of which highest RDW may also be helpful in different causes of macrocytosis seen in megaloblastic anemia from aplastic anemia. In liver disease and aplastic anemia, RDW is normal or mildly increased. As stated by Mahmoud et al. unexplained macrocytosis in age >=75yrs might be a sign for myelodysplastic syndrome.

In Aslina F Study Macro-ovalocytes, hypersegmented neutrophils were seen in Megaloblastic disorders and Round macrocytes in alcoholism, round target cells were seen in Liver disease like hepatitis, obstructive jaundice. In GF Reidler study target cells, macrocytes in cirrhosis, thrombocytopenia was seen in Chronic liver disease and Cirrhosis. In the present study these features were also observed in most cases of alcoholism and predominantly round, uniform macrocytes and target cells are observed in 22.5% liver diseases cases.

Peripheral smear of COPD patients show macrocytosis induced by hypoxemia and eosinophilia in B.J.O Neil et al. study. In present study presence of macrocytosis and eosinophilia (3 out of 7) were seen in peripheral smear of COPD cases.

Although in most countries normal MCV reference range is taken as 80-100 fl. Most general practitioners in Australia like to investigate the patients with MCV above 96 fl. In study of Stella E et al, out of 268, 205 MCV between 96-99.9 fl. In present study 110 out of 350 samples had MCV were between 96-99.9 fl and their peripheral smear examination showed macrocytosis. So they can be investigated earlier if cut off value of MCV is kept at 95fl specially to rule at early megaloblastic anemia before numbness, memory trouble, fatigue, peripheral neuropathy and other CNS symptoms set in.

It has been seen that Macrocytosis should be evaluated even in the absence of anemia, as it may be the first clue to an underlying pathology. As seen in discussion above detailed medical history including alcohol and drug intake, evaluation of red cell parameters and peripheral smear assist in arriving at a provisional diagnosis in directing further management. Hence in resource limited settings, combined evaluation of MCV along with other CBC features, peripheral smear and reticulocyte count are very helpful in deciding further management.

CONCLUSION

(1) Proportion of macrocytosis was 1.5% in present study.
(2) 90% cases of macrocytosis were non megaloblastic conditions and included drug related, liver diseases, diabetes, hypothyroidism, COPD, atrophic gastritis. 29% cases had association of macrocytosis without anemia.
(3) Highest MCV value obtained was 127fl. Most cases of MCV >120fl were seen with drug related macrocytosis. Megaloblastic anemia did not show severe degree of macrocytosis probably due to co-existing iron deficiency anemia in the population. Border line (96-99) macrocytosis was associated with COPD, hypothyroidism and liver diseases.

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