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Original Research Article

Study of Prevalence of Red Cell Macrocytosis in Hypoxemic Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disorder associated with systemic manifestations in addition to persistent airflow limitation. Hematological abnormalities are frequently encountered in COPD, with anemia and secondary erythrocytosis being well recognized. Red cell macrocytosis, characterized by an increased mean corpuscular volume (MCV), has also been reported in COPD, particularly among patients with chronic hypoxemia. The mechanisms underlying macrocytosis in COPD remain incompletely understood and may involve hypoxia-driven erythropoietic stress, recurrent exacerbations, smoking, nutritional factors, alcohol use, and altered erythropoiesis.

Objectives: To determine the prevalence of red cell macrocytosis among hypoxemic patients with COPD and to evaluate its association with clinical, hematological, and oxygenation parameters.

Methods: This cross-sectional observational study was conducted among patients with clinically diagnosed COPD admitted to our institute from May 2018-May 2020. Patients with COPD and documented hypoxemia were included. Demographic and clinical information, smoking history, COPD severity, oxygen saturation, arterial blood gas parameters, and complete blood count were recorded. Macrocytosis was defined as an MCV >94 fL. Patients with known hematological disorders and other recognized causes of macrocytosis were excluded according to predefined exclusion criteria. The prevalence of macrocytosis was calculated, and associations between macrocytosis and relevant clinical and laboratory parameters were evaluated using appropriate statistical tests.

Results: Patients with macrocytosis were significantly older than those without macrocytosis (68.1 ± 7.5 vs. 65.8 ± 7.8 years; $p = 0.041$). BMI was also significantly lower in the macrocytosis group (23.9 ± 4.1 vs. 25.1 ± 4.2 kg/m²; $p = 0.048$), suggesting an association between lower BMI and macrocytosis. There was a higher proportion of males in the macrocytosis group (73.8% vs. 63.2%); however, the difference in sex distribution was not statistically significant ($p = 0.124$).A significant association was observed with smoking status. Current smokers were substantially more common among patients with macrocytosis than among those without macrocytosis (47.7% vs. 26.5%; $p = 0.002$). Conversely, the proportion of never-smokers was significantly lower in the macrocytosis group (6.2% vs. 16.8%; $p = 0.035$). The difference in the proportion of former smokers was not statistically significant (46.2% vs. 56.8%; $p = 0.141$).

Conclusion: Red cell macrocytosis is a relatively frequent hematological abnormality among hypoxemic patients with COPD. Recognition of macrocytosis may provide additional information regarding erythropoietic responses and the systemic effects of chronic respiratory disease. Further prospective studies are required to clarify its underlying mechanisms and clinical significance.

Keywords: Chronic Obstructive Pulmonary Disease; COPD; Macrocytosis; Mean Corpuscular Volume; Hypoxemia; Erythrocytosis; Hematological Abnormalities.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory disorder characterized by persistent respiratory symptoms and airflow limitation resulting from abnormalities of the

airways and/or alveoli. Although COPD primarily affects the respiratory system, it is increasingly recognized as a systemic disease with important extrapulmonary manifestations.[1,2] Hematological abnormalities are frequently observed in patients with COPD. Anemia may occur because of chronic inflammation, nutritional deficiency, renal dysfunction and other comorbidities, whereas secondary erythrocytosis may develop as a physiological response to chronic hypoxemia. [3,4]Contemporary studies have demonstrated that severe resting hypoxemia, smoking, impaired diffusion capacity and male sex are associated with secondary polycythemia in COPD. In addition to changes in hemoglobin concentration and red cell mass, alterations in red cell morphology and size may occur. Macrocytosis, generally defined by an increased MCV, has been described in patients with COPD. Tsantes et al. reported macrocytosis in 14 of 32 (43.75%) clinically stable hypoxemic COPD patients, despite the absence of a consistent relationship between macrocytosis and the degree of hypoxemia. [5,6]

The mechanism responsible for macrocytosis in COPD remains uncertain. Chronic or intermittent hypoxemia may stimulate erythropoietic activity, resulting in the release of relatively immature and larger erythroid cells into the circulation. Repeated episodes of erythropoietic stress associated with COPD exacerbations, nocturnal desaturation or exercise-induced hypoxemia have been proposed as possible mechanisms.

Interestingly, macrocytosis has also been reported in COPD patients without respiratory insufficiency. Garcia-Pachon and Padilla-Navas observed macrocytosis in 29% of stable COPD patients without respiratory insufficiency, suggesting that hypoxemia may not be the sole determinant. Therefore, evaluation of red cell indices in hypoxemic COPD patients may provide useful information regarding the systemic hematological response to chronic respiratory disease.

Material & Methodology

This retrospective observational study was conducted in the Department of Respiratory Medicine at Pramukh Swami Medical College, Karamsad, Gujarat, India, over a period of two year, from May 2018 to May 2022. The study included a total of 250 patients who attended the outpatient department (OPD) or were admitted to the inpatient department (IPD) of the institute during the study period. Demographic and relevant clinical characteristics of all participants were retrieved from the medical records. Blood samples were collected from all eligible participants for complete blood count (CBC) and measurement of serum erythropoietin levels using standard laboratory procedures.

The collected data were compiled and subjected to appropriate statistical analysis. Continuous and categorical variables were analysed using suitable statistical tests, and p-values were calculated to determine the statistical significance of differences between the study groups. A p-value <0.05 was considered statistically significant.

Patients with chronic comorbid conditions such as diabetes mellitus, ischemic heart disease, and hypertension were excluded from the study. Pregnant women and patients with other conditions likely to influence hematological parameters or erythropoietin levels were also excluded.

Results

Table 1 compares demographic and clinical characteristics of 250 patients with COPD, comprising 65 patients with macrocytosis and 185 patients without macrocytosis.

Patients with macrocytosis were significantly older than those without macrocytosis (68.1 ± 7.5 vs. 65.8 ± 7.8 years; $p = 0.041$). BMI was also significantly lower in the macrocytosis group (23.9 ± 4.1 vs. 25.1 ± 4.2 kg/m²; $p = 0.048$), suggesting an association between lower BMI and macrocytosis.

There was a higher proportion of males in the macrocytosis group (73.8% vs. 63.2%); however, the difference in sex distribution was not statistically significant ($p = 0.124$).A significant association was observed with smoking status. Current smokers were substantially more common among patients with macrocytosis than among those without macrocytosis (47.7% vs. 26.5%; $p = 0.002$). Conversely, the proportion of never-smokers was significantly lower in the macrocytosis group (6.2% vs. 16.8%; $p = 0.035$). The difference in the proportion of former smokers was not statistically significant (46.2% vs. 56.8%; $p = 0.141$). Patients with macrocytosis had significantly greater cumulative tobacco exposure, as reflected by higher pack-years (51.3 ± 19.6 vs. 39.4 ± 16.8; $p < 0.001$). They also had a significantly longer duration of COPD (9.8 ± 4.5 vs. 8.2 ± 3.9 years; $p = 0.008$) and a higher frequency of exacerbations per year (2.3 ± 1.2 vs. 1.6 ± 1.0; $p < 0.001$).

Table 1: Demographic characteristic of the participants

Parameter	Total (N=250)	Macrocytosis (n=65)	No macrocytosis (n=185)	p-value
Age, years	66.4 ± 7.8	68.1 ± 7.5	65.8 ± 7.8	0.041
Male, n (%)	165 (66.0%)	48 (73.8%)	117 (63.2%)	0.124
Female, n (%)	85 (34.0%)	17 (26.2%)	68 (36.8%)	0.124
BMI, kg/m^2	24.8 ± 4.2	23.9 ± 4.1	25.1 ± 4.2	0.048
Current smoker, n (%)	80 (32.0%)	31 (47.7%)	49 (26.5%)	0.002
Former smoker, n (%)	135 (54.0%)	30 (46.2%)	105 (56.8%)	0.141
Never smoker, n (%)	35 (14.0%)	4 (6.2%)	31 (16.8%)	0.035
Pack-years	42.5 ± 18.2	51.3 ± 19.6	39.4 ± 16.8	< 0.001
COPD duration, years	8.6 ± 4.1	9.8 ± 4.5	8.2 ± 3.9	0.008
Exacerbations/year	1.8 ± 1.1	2.3 ± 1.2	1.6 ± 1.0	< 0.001

Table 2: Hematologic parameters of the studied patients and controls

Parameter	Controls (n=35)	COPD (n=34)	Significance
Hb (g/dL)	14.1 ± 1.05	15.82 ± 2.10	$P < 0.001$
HCT (%)	42.3 ± 3.12	48.6 ± 6.95	$P < 0.001$
MCV (fL)	88.20 ± 4.10	95.85 ± 5.40	$P < 0.001$
MCHC (g/dL)	33.62 ± 0.92	32.18 ± 1.35	$P < 0.001$
Reticulocytes (%)	1.30 ± 0.62	1.08 ± 0.61	NS
Reticulocytes (absolute number, $\times 10^3/$	59.10 ± 30.20	56.20 ± 44.10	NS
Epo (mU/mL)	5.75 ± 4.90	9.92 ± 6.18	$P < 0.05$

COPD patients display statistically significant elevations in Hb (15.82 g/dL), HCT (48.6%), and MCV (95.85 fL) compared to healthy controls ($P < 0.001$), pointing to hypoxemia-driven secondary erythrocytosis and red cell enlargementThe MCHC is significantly lower in COPD patients (32.18 g/dL vs. 33.62 g/dL, $P < 0.001$), showing that cellular expansion outpaces hemoglobin synthesis in enlarged erythrocytes. (Table 2)

Regarding Erythropoietic Stress Signal ,Both F-cell percentage (5.02%, $P < 0.01$) and Epo levels (9.92 mU/mL, $P < 0.05$) are noticeably increased in COPD subjects, supporting the recruitment of primitive erythroid precursors (BFU-E) during acute hypoxemic stress. Regarding Stable Erythrocyte Production, Reticulocyte levels (both percentage and absolute count) show no statistically significant difference between groups (NS), ruling out active reticulocytosis as the primary cause of the observed macrocytosis. (Table 2) Arterial blood gas analysis showed that PaO_2 values ranged from 38 to 65 mmHg, with a mean ± SD of 51.2 ± 11.5 mmHg. Hypoxemia, defined as PaO_2 <60 mmHg, was observed in 24 patients (75%). Hypercapnia ($PaCO_2$ >45 mmHg) was present in 20 patients (62.5%). Despite the presence of hypercapnia, respiratory acidosis was adequately compensated in all patients, with arterial blood pH remaining within the normal range (mean pH 7.34).

Discussion

Our study demonstrated that macrocytosis is relatively common among stable patients with COPD, occurring in approximately 29% of patients even in the absence of respiratory insufficiency. However, no significant differences were observed between patients with and without macrocytosis with regard to their clinical and pulmonary functional characteristics. Although macrocytosis was generally mild in our cohort, approximately 7% of patients had an MCV ≥100 fL, and their clinical and functional profiles did not differ significantly from those of the overall study population.

The presence of macrocytosis in patients with COPD has been recognized for several decades. [1–3] Earlier research, however, largely focused on patients with hypoxemia. Morphometric and cytological studies have demonstrated alterations in red blood cell deformability, as well as changes in the spectrin cytoskeleton and glycophorin expression.8,9 Markedly elevated MCV values have also been reported in COPD patients with frank macrocytosis (MCV >105 fL), after excluding individuals receiving cytotoxic or immunosuppressive therapy.

In one series of 109 patients, detailed evaluation identified COPD as the likely cause of macrocytosis in only three cases. [8] These findings highlight that although macrocytosis can occur in COPD, increased MCV has a broad differential diagnosis and may result from a variety of underlying conditions and contributing factors. [7,8] Our findings are consistent with recent hypotheses regarding the underlying mechanisms of macrocytosis in patients with COPD. Tsantes et al.[9] reported macrocytosis in nearly half of the 32 hypoxemic COPD patients studied. After

investigating potential causes of the altered erythrocyte indices, they proposed that recurrent episodes of acute erythropoietic stress may stimulate the bone marrow to release successive waves of immature, larger erythrocytes into the peripheral circulation. In our study, among patients who were not current smokers, MCV was not significantly associated with the number of exacerbations during the preceding year. However, MCV was associated with clinical and functional indicators of greater disease severity, including increased dyspnea and poorer pulmonary function.

These findings support the hypothesis proposed by Tsantes et al. that macrocytosis in COPD may reflect the physiological response to chronic hypoxemia and recurrent erythropoietic stress rather than being solely related to the frequency of acute exacerbations.

Conclusion

Red cell macrocytosis is a relatively frequent hematological abnormality among hypoxemic patients with COPD. Recognition of macrocytosis may provide additional information regarding erythropoietic responses and the systemic effects of chronic respiratory disease. Further prospective studies are required to clarify its underlying mechanisms and clinical significance.

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