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CLINICAL & BASIC RESEARCH

Elevated Peripheral Blood Eosinophils during Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Prevalence and clinical significance

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abstract: ***Objectives:*** This study aimed to evaluate the prevalence and clinical significance of elevated peripheral blood eosinophil (PBE) counts in hospitalised patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in Oman. An elevated PBE count during AECOPD is a potential predictor of treatment responsiveness and future exacerbation risk. ***Methods:*** This single-centre retrospective study included all patients with AECOPD who were admitted to Sultan Qaboos University Hospital, Muscat, Oman, between January 2017 and July 2019. The patients were classified as having eosinophilic or non-eosinophilic AECOPD based on blood eosinophil counts. An elevated eosinophil count was defined as a blood eosinophil count >0.3 × 10^9 cells/L on admission. The length of hospital stay, use of oral and inhaled steroids, number of readmissions in a year and use of mechanical ventilation on admission were compared between the eosinophilic and non-eosinophilic AECOPD groups. ***Results:*** Of the 102 patients included in the study, 42.2% had eosinophilic AECOPD. The eosinophilic AECOPD group had a reduced length of hospital stay (P = 0.02) but an increased risk of readmission in a year (P = 0.04). Most patients in both groups were treated with inhaled and oral steroids. The need for mechanical ventilation did not differ between the groups. ***Conclusion:*** Eosinophilia is highly prevalent in patients with AECOPD and is associated with a reduced length of hospital stay but an increased risk of readmission in a year. It can be used as a surrogate marker to predict the health outcomes of patients with AECOPD and select treatment options.

Keywords: Chronic Obstructive Pulmonary Disease; Eosinophils; Steroids; Length of Stay; Hospital Readmission; Oman.

Advances in Knowledge

- *Eosinophilia is highly prevalent in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD).*
- *Eosinophilic exacerbation of COPD is associated with a reduced length of hospital stay but an increased risk of readmission in a year.*

Application to Patient Care

- *Peripheral blood eosinophil (PBE) count can be used as a surrogate marker to predict treatment response.*
- *PBE count can be used to guide the treatment choices for patients with chronic obstructive pulmonary disease.*

Chronic obstructive pulmonary disease (COPD) is characterised by irreversible airflow limitation. Patients with COPD suffer from exacerbation, reduced quality of life and increased morbidity and mortality.[1–3]

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is mainly associated with neutrophilic inflammation; however, predominant eosinophilic airway inflammation has been reported in a subset of patients with COPD.[4–6] Up to 40% of patients with COPD have an eosinophilic phenotype of COPD, defined as peripheral blood eosinophil (PBE) counts ≥2%.[4] Several studies have demonstrated that patients with elevated PBE counts are at an increased risk of frequent exacerbations but show a good response to steroid therapy.[1,4] Evidence suggests that circulating eosinophils can be recruited to the lungs and can increase inflammation by the actions of cytokines, immunoregulatory cells and other proinflammatory mediators.[7] Accordingly, PBE count has been suggested to be useful as a surrogate marker to direct the use of oral steroid therapy in patients with AECOPD and as a predictor of future exacerbation and disease stability.[6] The data assessing the role of PBE on mortality outcomes are inconsistent.[8,9] Overall, the role of PBEs in the clinical manifestation of COPD remains highly debatable.[10,11] No prior study has been conducted in the Middle East to assess the prevalence and clinical significance of eosinophilia during AECOPD. The present study aimed to evaluate the prevalence and clinical significance of elevated PBE counts in hospitalised patients with AECOPD.

Methods

This retrospective cohort study was conducted between January 2017 and July 2019 at Sultan Qaboos University Hospital (SQUH), Muscat, Oman, a

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Table 1: Characteristics, treatment options and outcomes of patients with eosinophilic and non-eosinophilic chronic obstructive pulmonary disease exacerbation admitted to a tertiary care hospital in Muscat, Oman (N = 102)

Characteristic	n (%)			*P* value
	Total	Normal eosinophil count (n = 59)	High eosinophil count (n = 43)	
Mean age in years ± SD	72.9 ± 10.9	73.0 ± 12.3	72.4 ± 8.8	0.17
Male	81 (79.4)	50 (84.8)	31 (72.1)	0.10
Smoking	95 (93.1)	56 (94.9)	39 (90.7)	0.40
Median eosinophil count on admission in cells × 10^9/L (IQR)	0.3 (0.0–0.6)	0.1 (0–0.2)	0.6 (0.5–1.2)	<0.001
Mean FEV1 in % ± SD	43.8 ± 17.8	44.3 ± 17.2	43.1 ± 18.7	0.52
Treatment				
Oral steroids	94 (92.2)	55 (93.2)	39 (90.7)	0.72
Inhaled steroids	80 (78.4)	44 (74.6)	36 (83.7)	0.33
Need for mechanical ventilation	47 (46.1)	30 (50.9)	17 (39.5)	0.32
Outcome				
Median length of hospital stay in days (IQR)	4 (3–7)	5 (4–7)	4 (6–3)	0.02
Median eosinophil count on discharge in cells × 10^9/L (IQR)	0.1 (0.0–0.3)	0.1 (0–0.3)	0.2 (0.0–0.5)	0.43
Median readmission in a year (IQR)	0 (0–2)	0 (0–1)	1 (0–3)	0.04

**Mean ± standard deviation. †number of patients (%). ‡median (IQR). §Forced expiratory volume in one second.*

500-bed multi-speciality tertiary hospital providing health care for Muscat and Al-Batinah governorates' residents. It is also considered a major referral centre for many specialities that provide high-quality care for patients referred from the entire country of Oman.[12]

All patients with AECOPD admitted to SQUH during the study period were included in the study. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria was used to ascertain COPD diagnosis for all included patients.[13] Additionally, when there was more than one lung function test, the study considered the most recent lung function test before the index hospitalisation. The data were collected from electronic patient records using a standardised electronic data collection sheet. The patients were classified as having eosinophilic or non-eosinophilic AECOPD based on their blood eosinophil counts. An elevated eosinophil count was defined as a blood eosinophil count greater than 0.3 × 10^9 cells/L at the time of admission. Furthermore, the length of hospital stay, use of oral and inhaled steroids, number of readmissions in a year and use of mechanical ventilation on admission were compared between the eosinophilic and non-eosinophilic AECOPD groups.

Categorical variables were reported as numbers and percentages, while continuous variables were expressed as means ± standard deviations for normally distributed data and as medians and interquartile ranges for non-normally distributed data. Continuous variables between the groups were compared using Student's t-test for normally distributed data and Wilcoxon's rank-sum test for non-normally distributed data. Fisher's exact test was used to assess the association between categorical variables (given the small sample size). A two-sided *P* value <0.05 was considered statistically significant. Statistical calculations were performed using Stata, Version 16.1 (StataCorp., College Station, Texas, USA).

The study was approved by the Medical Research Ethics Committee of the College of Medicine and Health Sciences of Sultan Qaboos University (SQU-EC/037/19 MREC).

Results

A search of the hospital database revealed 128 patients with AECOPD who were hospitalised during the study period. Overall, 23 patients were found to be asthmatic, while three patients were lost to follow-up. Thus, 102 patients were included in the study. The mean age of the patients was 72.9 ± 10.9 years, and 79.4% of the patients were male. A total of 93.1% of the patients had a history of smoking (current or ex-smoker). Both groups exhibited a severely reduced forced expiratory volume in one second (FEV1; 43.8 ± 17.8%). In total, 42.2% of the patients had eosinophilic AECOPD. Patients with non-eosinophilic AECOPD stayed in the hospital for a longer duration than those with eosinophilic AECOPD (*P* = 0.02). Patients with eosinophilic AECOPD had a significantly higher

number of readmissions in a year than those with non-eosinophilic AECOPD (P = 0.04). Most patients in both groups received systemic steroids (92.2%) and were on inhaled steroids (78.4%) before admission. There was no significant difference in the need for mechanical ventilation between the groups (P = 0.32). Moreover, the eosinophil counts just before discharge did not differ significantly between the groups (P = 0.43) [Table 1].

Discussion

To the best of the authors' knowledge, the present study is the first to assess the prevalence and clinical significance of eosinophilia in hospitalised COPD patients in the Middle East, where a majority of the patients are of Arab ethnicity. The study findings indicate that patients with eosinophilic AECOPD had a reduced length of hospital stay but were at an increased risk of readmission in a year.

The prevalence of eosinophilic AECOPD ranged from 10–37% in previous studies.[14–16] These differences in the prevalence of eosinophilia during AECOPD could be explained by the difference in patients' ethnicity, use of corticosteroids before admission and difference in cut-off values used to define eosinophilia.[1,17–19] When defining eosinophilic COPD, the most commonly used cut-off value is 2%, which corresponds to 150 cells/μL.[1] However, the absolute eosinophil count might be more accurate because the white blood cell count can differ significantly for various reasons. In the present study, a cut-off value greater than 300 cells/μL was used to define eosinophilic AECOPD and this has been validated in previous studies.[1,7,17,20,21] The prevalence of eosinophilic AECOPD in the current cohort was 42.2%, which is higher than most of the previously reported values. This higher prevalence of eosinophilic AECOPD could be related to the high prevalence of smoking in this cohort.

In patients with COPD and under certain circumstances, PBEs are recruited to the lungs, prompting cascades of inflammatory responses, including secretion of chemokines, cytokines and cytotoxic granular products.[22] Most patients in both groups were treated with inhaled and oral steroids; however, patients with elevated PBE counts showed a better response, as evidenced by a reduced length of hospital stay (P = 0.02). This could be explained by the anti-inflammatory role of corticosteroids in patients with eosinophilic AECOPD. Notably, the study's finding regarding the reduced length of hospital stay for eosinophilic AECOPD patients is in line with previous studies.[17,23]

About 40% of patients with eosinophilic AECOPD required mechanical ventilation compared to 50.9% of patients with non-eosinophilic AECOPD. This disparity may be attributed to the poor response of non-eosinophilic AECOPD to corticosteroids. Furthermore, studies have demonstrated that non-eosinophilic AECOPD is strongly associated with infections and worse outcomes, which may be explained by the higher need for mechanical ventilation.[22]

No significant differences in age, gender, FEV1 and smoking status between the groups were found in this study. Additionally, just before discharge from the hospital, the eosinophil count did not differ significantly between the eosinophilic and non-eosinophilic AECOPD patients. This finding could be attributed to the high percentage of patients who were treated with steroids in both groups. Moreover, this finding may provide insight into using oral and inhaled steroids in patients with AECOPD based on the eosinophil count and, thus, help avoid risks associated with the indiscriminate use of steroids in such patients.[24] Additionally, no difference in the need for mechanical ventilation between the groups was noted (P = 0.32).

Furthermore, in the present study, the mortality outcome was not assessed because of the small sample size; however, studies have suggested that eosinophilic AECOPD is associated with a lower inpatient mortality rate, but the data are conflicting.[8,9,23] Conversely, patients with eosinophilic AECOPD had an increased number of readmissions in a year (P = 0.04), which is in line with previous findings.[18,23]

It is noteworthy that, to the best of the authors' knowledge, this study was the first to assess the prevalence of eosinophilia in patients of Arab ethnicity. Ultimately, the results confirmed that eosinophil count could be used as a surrogate marker to predict the treatment response and risk of readmission in inpatients with AECOPD. This finding supports the 2020 GOLD recommendation regarding the role of PBE in guiding the treatment choice for patients with COPD.[10]

The present study has several limitations. First, it was a single-centre retrospective study. Second, the inpatient mortality rate in the groups could not be assessed because of the small sample size. Third, the study included hospitalised patients with AECOPD; however, it did not include patients with mild and moderate exacerbations who were managed in the outpatient setting. Finally, potential confounders including heart failure, ischaemic heart disease and hypertension, were not considered.

Conclusion

Eosinophilia is highly prevalent in hospitalised patients with AECOPD. It is associated with a reduced length of hospital stay and an increased risk of readmission in a year. Additionally, the eosinophil count can be used as a surrogate marker to predict the health outcomes of patients with AECOPD and select treatment options, including corticosteroid use.

AUTHORS' CONTRIBUTION

MS, AA and JA contributed to the research design. MS collected the data. MS and AA analysed the data and handled manuscript writing. AA and JA revised the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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