

Identifying Subtypes of Paucigranulocytic Asthma: Now There Are 3



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Over the last 20 years, considerable progress in identifying subtypes of chronic airway inflammation in asthma has contributed to the development of new anti-inflammatory antibody therapies. Approximately 50% of adults with asthma have type 2 (T2) inflammation with airway eosinophilia, which in many individuals is associated with a good therapeutic response to corticosteroids and biologics targeting T2 cytokines.¹ Non-T2 inflammation, defined as an absence of markers of T2-high inflammation, is associated with neutrophilic or paucigranulocytic airway inflammation, corticosteroid insensitivity, and a poor response to current biological therapies.² Factors implicated in neutrophilic inflammation include airway dysbiosis, corticosteroid treatment, and environmental exposure to cigarette smoke and atmospheric pollutants. Much less is known about the role of paucigranulocytic inflammation in asthma, defined as a lack of increased sputum eosinophils and neutrophils.³ Paucigranulocytic inflammation is one of the commonest inflammatory phenotypes, with prevalence rates ranging from 30% to 50% among adolescents and adults with asthma,³⁻⁶ and with lower rates in severe asthma.^{5,6} In some studies, paucigranulocytic inflammation is associated with better lung function and less airway hyperresponsiveness compared with eosinophilic asthma.⁶ The mechanisms underlying paucigranulocytic asthma are unclear, but could be due to asthma in remission, corticosteroid-induced suppression of airway eosinophilia, corticosteroid-insensitive airway inflammation involving nerves, smooth muscle, or other cells, and tissue remodeling.^{6,7} In the absence of identifiable targetable inflammatory pathways, treatment is largely symptomatic. Whether paucigranulocytic asthma is a homogeneous or heterogeneous condition has not been previously reported.

In the current issue of *The Journal of Allergy and Clinical Immunology: In Practice*, Deng et al⁸ report the results of a study that used hierarchical cluster analysis of 10 demographic and clinical variables to identify subtypes of paucigranulocytic inflammation in 145 Chinese adults with asthma. Of the asthma population screened, approximately half had paucigranulocytic inflammation, and, within this phenotype, 3 clusters were identified. Cluster 1, termed “mild paucigranulocytic asthma,”

was the largest, comprising 76% of the study population. Cluster 2, termed “paucigranulocytic asthma with psychological dysfunction and rhinoconjunctivitis and other allergic diseases,” accounted for 14% of the patients. Cluster 3, termed “smoking-associated paucigranulocytic asthma,” accounted for 10% of the patients. In a separate population of 115 patients with paucigranulocytic asthma recruited from the same institution in China, decision tree analysis with 2 variables—psychological dysfunction and smoking pack year history—gave a 97% accuracy in cluster classification. Major strengths of the study are the methodology used to perform cluster analysis and the new finding of heterogeneity in paucigranulocytic asthma.

The “mild paucigranulocytic asthma” subtype (cluster 1) included mainly females (72%) and never smokers (86%) and had better spirometric lung function than the “smoking-associated” paucigranulocytic cluster. The clinical features of this mild subtype resemble those reported in previous studies of paucigranulocytic airway inflammation, including good lung function.⁶ All participants in the cluster 2 subtype were considered to have psychological dysfunction, defined as a Hospital Anxiety and Depression Scale score of 8 or more on the anxiety subscale or the depression subscale, and 80% had a history of rhinoconjunctivitis and other allergic diseases. Unfortunately, the study does not provide a breakdown of the numbers of patients with either anxiety or depression. The finding that anxiety and depression was strongly associated with one subtype of paucigranulocytic inflammation (cluster 2) is unexpected because both anxiety and depression occur in a wide range of people with asthma. Interestingly, among adults with asthma participating in the US National Health and Nutrition Examination Survey, anxiety and depression were linked to noneosinophilic asthma, although data on the influence of paucigranulocytic inflammation or its subtypes were not reported.⁹ The “smoking-associated paucigranulocytic asthma” subtype (cluster 3) were older, had later onset of asthma, and greater airflow obstruction, and fewer had a history of allergic diseases than clusters 1 and 2. All patients were male and had a high pack year history, and 47% were current smokers. Over 12-month follow-up, cluster 3 participants had an increased number of severe exacerbations, emergency room visits, and admissions to hospital with asthma compared with cluster 1. Current smoking is a well-recognized risk factor for poor asthma control and corticosteroid insensitivity,¹⁰ but previous reports had not identified an association between smoking status and paucigranulocytic subtypes.^{4,6} Clinical features of cluster 3 participants, such as late-onset asthma, short duration of disease, heavy smoking history, and chronic airflow obstruction, suggest that some individuals had asthma-chronic obstructive pulmonary disease overlap. However, the prevalence of asthma-chronic obstructive pulmonary disease overlap among the 3 clusters was only 12% and did not differ between clusters.

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Conflicts of interest: The author declares no relevant conflicts of interest.

Received for publication January 21, 2021; accepted for publication January 22, 2021.

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J Allergy Clin Immunol Pract 2021;9:2356-7. 2213-2198

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<https://doi.org/10.1016/j.jaip.2021.01.021>

The stability of sputum inflammatory differential cell counts was monitored in 175 patients over 4 weeks. Paucigranulocytic inflammation remained stable in 70% of patients, with less variability than other inflammatory phenotypes. Nevertheless, 24% of the paucigranulocytic group changed to neutrophilic inflammation, and 47% of the neutrophilic and 43% of the eosinophilic groups changed to paucigranulocytic inflammation. Paucigranulocytic clusters were unaltered in 70% (cluster 1), 75% (cluster 2), and 56% (cluster 3) of cases. Previous data on the stability of sputum phenotypes over time are conflicting.² Collectively, these findings highlight the importance of assessing the long-term stability of paucigranulocytic inflammation and its subtypes in future studies.

Although of considerable interest, the study by Deng et al⁸ has some potential limitations. First, participants were recruited from a single center in China, and the results may not be generalizable to other sites in China or to asthma populations in other countries. For example, obesity did not differ between paucigranulocytic clusters, but only a small proportion of participants had a high body mass index and studies are warranted in populations with a higher proportion of obese individuals. Second, it is not clear whether participants were exposed to low-molecular-weight occupational agents, which are associated with inflammatory phenotypes including paucigranulocytic inflammation. Third, a small number of individuals were included in clusters 2 and 3, which limits the strength of evidence provided by the data. Finally, because the asthma control questionnaire scores of the participants was low, the cluster analysis results may differ from those of more symptomatic patients. Alternatively, the low asthma control questionnaire score may reflect better symptom control in paucigranulocytic asthma.

What are the implications of the study by Deng et al⁸ for the management of paucigranulocytic asthma? The identification of subtypes of paucigranulocytic asthma indicates the need to address treatable traits, such as management strategies for anxiety and depression (cluster 2) and behavior and drug therapies to support smoking cessation for current smokers (cluster 3). Whether the response to corticosteroids or other current therapies differs in subtypes of paucigranulocytic inflammation remains to be investigated. Up to one-quarter of the patients with paucigranulocytic inflammation had severe asthma (Global

Initiative for Asthma steps 4/5),⁸ indicating an unmet need for improved therapies for this group. Bronchial thermoplasty targets airway structures, such as smooth muscle and epithelial cells, but its value for treating paucigranulocytic asthma or its subtypes is not known.

In conclusion, the study by Deng et al⁸ has for the first time identified subtypes of paucigranulocytic asthma and provided a stimulus for research into mechanisms and effective management strategies for this phenotype. Future studies should investigate whether the heterogeneity of paucigranulocytic asthma differs in different countries and in urban and rural populations, and what effect factors such as race, body mass index, exposure to environmental pollution, and smoking status have on paucigranulocytic subtypes. Establishing whether clinical subtypes of paucigranulocytic asthma are associated with specific endotypes may contribute to the development of novel targeted therapies.

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