

EDITORIAL

Clinical & Experimental Allergy

Airway eosinophilia in occupational asthma

This editorial discusses the findings of the paper in this issue by Malo et al. [8] pp. 497–504.

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Standardized non-invasive methods for assessing airway inflammation are increasingly used in the investigation of inflammatory respiratory diseases. Monitoring airway inflammation by the analysis of cells in induced sputum or by the fraction of nitric oxide in exhaled air (FeNO) has been proposed in the diagnosis and the management of asthma. Eosinophilic inflammation was detected in approximately 75% of asthmatics in a study not biased by corticosteroid treatment [1]. The presence of sputum eosinophilia, or its surrogate elevated FeNO, predicts a better response to corticosteroids compared with sputum neutrophilia [2, 3]. There is evidence that a management strategy of asthma aimed at normalizing the sputum eosinophil count is associated with significantly fewer exacerbations than the standard clinical care. In the studies reporting these findings, this benefit was not obtained at the expense of increased therapy in the intervention groups [4]. The hypothesis that eosinophils in the airway may predict asthma exacerbation is consistent with the results of the SOCS trial [5]. This study demonstrated that an increase in sputum eosinophils counts in the 2 weeks after discontinuation of inhaled corticosteroids has high sensitivity (90%) for asthma deterioration occurring over the subsequent 14 weeks. Taken together, these findings suggest that the assessment of airway inflammation may be helpful for targeting corticosteroid treatment at those individuals who would most benefit from it. Moreover, analysis of induced sputum identified phenotypes of severe asthma with prominent eosinophilic inflammation, which can benefit from treatment with mepolizumab, a monoclonal antibody against IL-5. Mepolizumab reduced the number of blood and sputum eosinophils and allowed prednisone sparing or reduction in asthma exacerbations [6, 7].

In this issue of *Clinical and Experimental Allergy*, Malo et al. [8] address the question of whether the assessment of airway inflammation is useful in the investigation of occupational asthma (OA). OA can be regarded as an adult-onset asthma due to a known agent, specific to the workplace. Although OA occurs in susceptible individuals, the exposure to the occupational agent is a necessary factor for the development of the disease. The demonstration of a causal role of the occupational agent is essential in the diagnosis of OA. The most reliable way to do this is to reproduce the disease upon specific inhalation challenges. This procedure exposes workers with suspected OA to suspected causing agents in a controlled setting to demonstrate a direct relationship between exposure to an occupational agent and asthma. Specific inhalation challenges have several limitations. They are performed in only a few centres having specialized facilities and expertise, and they require a remarkable amount of time and resources. A suspected workplace agent must to be identified. Finally, only workers with preserved lung function in whom the disease is relatively stable can undergo specific inhalation challenges because exposure to an occupational agent to which the worker is sensitized, albeit under controlled low concentrations, may induce a severe asthma attack.

The investigation of Malo et al. [8] aimed to detect whether the combination of bronchial responsiveness (BR) to methacholine and the profile of inflammatory cells in induced sputum was predictive of OA. Retrospective analysis of 519 subjects who underwent specific inhalation challenges in the investigation of OA was performed. The study included 129 subjects with OA, 187 subjects with non-OA and 203 without asthma. Whether responsiveness to methacholine and levels of inflammatory cells in induced sputum before the specific inhalation challenge were associated with the presence of OA, was examined by a bivariate analysis. Sputum eosinophilia and/or responsiveness to methacholine exhibited poor predictive values, both negative and positive, in distinguishing OA from non-OA. Although, the study failed to detect a predictor of a positive response to specific inhalation challenge, there are other important findings.

Firstly, the results confirm the concept that OA has not only clinical and functional features similar to non-OA,

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but it also has similar pathological characteristics. This is relevant because OA encompasses asthma induced by an IgE mechanism (proteins and few chemicals), and asthma (usually caused by reactive chemicals) for which an immunological mechanism is strongly suspected, but antigen-specific IgE cannot be identified. These similarities are also found between allergic asthma and intrinsic, or non-allergic, asthma, which is characterized by a progressive loss of lung function beginning later in life in the absence of atopy.

Secondly, the work of Malo et al. [8] contributes to clarifying the controversy over the type of airway inflammation in OA due to reactive chemicals, because neutrophilic airway inflammation has been reported after exposure to isocyanates [9, 10]. The analysis of the data indicates that sputum neutrophils are not a feature of OA. This observation is based on the largest sample of occupational asthmatics ever participating in this type of investigation, including those involving induced sputum. Neutrophilia in OA may be due to interfering factors unrelated to the pathophysiology of the disease. Treatment with corticosteroids may blunt eosinophil influx, endotoxin contamination may favour sputum neutrophilia, and relatively high levels of exposure to reactive chemicals may produce irritant effects.

Thirdly, a subgroup of subjects with definite OA, having no functional characteristics of asthma before specific inhalation challenge, but exhibiting sputum eosinophilia, was identified. These subjects represented 12.4% of the cases of OA. In these subjects, who presented normal responsiveness to methacholine and were not treated with inhaled corticosteroids, the presence of sputum eosinophils $> 3\%$ gave a positive predictive value of 85% for OA. The interpretation of these findings is that some occupational asthmatics may improve rapidly after cessation of exposure (median 76 days in this cohort) and that eosinophilic inflammation is more persistent than bronchial hyperresponsiveness. Complete recovery is reported in 30–50% of the cases of OA [11]. It is certainly unsatisfactory that more than 50% of patients with OA continue to suffer from a disease, which they would have avoided had they not been exposed to it at work and which is associated with negative socio-economic and health consequences. Nonetheless, the rate of recovery from OA is remarkably higher than that from adult-onset non-OA, even if the two types of asthma exhibit no substantial differences in symptoms, lung function and airway pathology. Epidemiological data from the European Community Respiratory Health Survey I and II indicate that

the percentage of adult asthmatics in remission (no symptoms, no exacerbations, and no asthma medications in the preceding year) at the end of a 9-year follow-up is 11.9% [12]. An important factor for the outcome of OA is that exposure to the causing agent can be completely avoided, unlike in the majority of cases of non-OA.

A consequence of the finding that occupational and non-OA are indistinguishable by functional and pathological criteria is that specific inhalation challenge remains the most important tool for diagnosis of OA. Identification of the cause of OA has medical, legal, and socio-economic consequences. The early detection of workers with established disease, and their subsequent removal from exposure, is the most effective way to prevent progression to moderate or severe disease with its associated morbidity and disability. Failure to diagnose may well result in a worker's continued exposure to the asthma-provoking agent with all the medical consequences that implies. A diagnosis of OA also has significant social and financial consequences. Leaving the job on a physician's advice implies retraining for a new occupation or retirement with financial compensation. Correct identification of an occupational cause of asthma tells the worker what alternative job can be performed safely. On the other hand, if it is excluded that a disease had an occupational cause, leaving the job will not be necessary. In addition, an individual diagnosis of OA represents a potential sentinel event calling for a careful evaluation of the workplace to identify and prevent new cases of OA.

Earlier studies have shown that the magnitude of asthmatic reaction to an inhaled allergen is dependant upon both skin sensitivity to the allergen and non-specific BR [13]. This relationship could be useful in predicting and avoiding excessive bronchoconstriction when specific inhalation challenges are used for diagnosing OA. Unfortunately, inhalation challenges are mainly used when the suspected cause of OA is a reactive chemical, and immunological tests to demonstrate allergic sensitivity are often unavailable. In a study of allergic asthma, sputum eosinophilia was one of the major determinants of the magnitude of late asthmatic reactions elicited by allergen challenge [14]. If this were true for OA, measurement of airway eosinophilia could be used instead of allergen sensitivity to predict the magnitude of the response to an occupational agent. Studies appropriately designed to reveal whether a baseline degree of allergic inflammation and functional findings is related to the severity of the asthmatic reaction to occupational agents could be useful.

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