

Lessons from Occupational Eosinophilic Bronchitis



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Among patients who have a chronic cough, nonasthmatic eosinophilic bronchitis (NAEB) has been recognized for more than 20 years to be a cause in a subset of patients. An early study that included induced sputum in the diagnostic algorithm of chronic cough reported eosinophilic bronchitis in 13% of patients attending a cough clinic,¹ and 30% of those who had sputum induction. NAEB represents 1 of the top 4 common causes of chronic dry cough.^{1,2}

In contrast, although there are many occupational causes of chronic cough,³ an occupational cause for eosinophilic bronchitis has only been recognized on the basis of single case reports before the current report by Wisniewska et al⁴ in the current issue.⁴ As the authors review in a supplement to their current article, a total of 13 well-documented subjects have been previously reported.⁴ Thus, there has been no earlier well-documented case series of occupational eosinophilic bronchitis (OEB), and the relative frequency and features of this entity have been unclear. The lack of general availability of induced sputum cytology as a diagnostic test has likely contributed to a lack of data on this condition and lack of recognition of it.

The study in this issue of the journal reports findings from a cohort of 573 subjects from 6 tertiary referral centers in different European countries, in which specific inhalation challenges were performed to investigate work-related asthma symptoms. Induced sputum cytology was routinely performed before and after specific challenge. On the basis of a 3% increase in induced sputum eosinophils after exposure to a specific workplace sensitizer but lack of change in spirometry or airway responsiveness, the authors confirmed a diagnosis of OEB in 33 subjects (14% of all those with a positive specific occupational challenge test and 6% of the whole cohort). These 33 individuals with OEB comprised 13% of subjects who, without the addition of the induced sputum testing, would have been considered to have a negative specific inhalation challenge and therefore would likely have been advised to continue their same work. They also likely would have had any workers' compensation claim rejected. In contrast, confirmation of this diagnosis can lead to appropriate changes at work to avoid further exposure to the causative

sensitizer for the affected workers, and potentially can improve or reduce progression of symptoms and airway disease. This also may reduce risk for coworkers. The causative agents included both high- and low-molecular weight sensitizers, similar to previous case reports, with diisocyanates and flour being the most common, similar to the causes in those with occupational asthma.

Because, the definitive test for OEB, induced sputum cytology testing, is not widely available, it is likely that this diagnosis is easily missed in clinical practice. Suspicion may be raised from a history of isolated cough with normal pulmonary function and methacholine challenge: the study in this issue⁴ indicates that the patients with OEB were more likely to have an isolated cough as their symptom compared both to those with confirmed occupational asthma and those in the study who had challenge-negative work-related symptoms (likely including work-exacerbated asthma). However, an isolated cough is neither sensitive nor specific, present in only 21% of the patients with OEB, and most also had other symptoms. When there is a lack of objective asthma or airway hyperresponsiveness and absence of other identified causes of symptoms, an improvement in symptoms with a therapeutic trial of inhaled steroids could add support to the diagnosis when induced sputum cytology is not available; this has been included in suggested algorithms for chronic cough to help identify nonoccupational eosinophilic bronchitis.^{5,6} However, an objective diagnosis, when possible, is preferred for clinical management and also for a fair workers' compensation decision.

When sputum eosinophils can be assessed, the timing of the test in relation to exposure can be important. The mean time away from the last exposure to the work sensitizer before the specific challenge in this cohort was 6 months, and only 30% of those with confirmed OEB had a prechallenge sputum eosinophil count of more than 3%.⁴ This illustrates that, analogous to airway responsiveness tests for occupational asthma, the test for sputum eosinophils should be performed shortly after exposure to the work sensitizer with repeat for comparison away from exposure.

Unfortunately, blood eosinophil counts do not substitute for sputum eosinophils for this diagnosis as demonstrated in this study.⁴ A role of fractional exhaled nitric oxide (FENO) measures has been considered as a possible surrogate for sputum eosinophils, but the role of this test and other noninvasive markers in the diagnosis of NAEB has been less clear and is an area for which there is a need for further research.⁷ In the study of Wisniewska et al,⁴ FENO before and after challenge was measured in a subset of patients. In those with OEB, the post-challenge mean FENO (24 parts per billion [ppb]; interquartile range, 16-50) was higher than in those who had a negative specific challenge, but mean increases postchallenge were significantly less than in those with occupational asthma. The

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sensitivity and specificity of different cutoff values for the postchallenge increase in FENO showed that a cutoff of more than 14-ppb increase in FENO postchallenge had a positive predictive value of 70% for OEB and a negative predictive value of 86% (sensitivity 33%, specificity 96%), whereas for a cutoff of more than 8 ppb, these predictive values were 50% and 87%, respectively (sensitivity 43%, specificity 90%). Therefore, although not highly sensitive, there may be benefit from the use of FENO when induced sputum cytology is not available or for the minority of patients who are unable to produce a sputum sample with induction.

In addition to limited availability of induced sputum, mainly related to the technical time required for sample processing for cytology, there is a limitation related to infection control during respiratory pandemics such as coronavirus disease 2019. Point-of-care tests for eosinophilic markers in sputum, such as a bioactive paper-based ELISA for eosinophil proteins such as eosinophil peroxidase, have been suggested.⁸ Potentially, in the future these might greatly enhance the recognition of NAEB and eosinophilic asthma. The present study adds another rationale for research to provide a simple and effective test for airway eosinophilic inflammation.

Management of OEB comprises avoidance of exposure to the causative workplace sensitizer and use of pharmacologic agents. The study in this issue of the journal did not address the management and outcome of these patients.⁴ A recent ACCP Consensus Statement⁷ included recommendations on the management of cough due to NAEB, based on a systematic review of the literature. The authors identified very few published therapeutic trials and provided a weak recommendation to use inhaled steroids as the first-line treatment, followed, if needed, by a step-up in dosage and/or a therapeutic trial of a leukotriene inhibitor.

The study in this issue of the journal demonstrated that patients with OEB had a shorter duration of symptoms at work before diagnosis compared with those who had occupational asthma,⁴ and it has been suggested that NAEB may represent an early

manifestation of asthma, before development of airway hyper-responsiveness. However a follow-up study over a mean of 3 years showed that only 9% developed findings of asthma.⁹ Similarly, a study by Lai et al¹⁰ among 234 patients with NAEB found that over the course of follow-up for a year, only 5.7% developed mild asthma and there was no progressive decline in spirometric variables, whereas the majority had continuing symptoms from NAEB. It is hoped that the authors of the important study in this issue will be able to follow-up and add to their cohort of patients with OEB to clarify responses to environmental modification and determine longer-term outcomes.

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