

REVIEW

Cough and asthma

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Asthma is usually viewed as a disease in which the airways narrow excessively in response to various stimuli and there is variable airflow obstruction. While variable airflow obstruction and airway hyper-responsiveness is the dominant phenotype in many patients, there are others where fixed airflow obstruction, recurrent exacerbations, bronchitis or dry cough predominate. Furthermore, these features can be present, to a greater or lesser extent, in the same patient at different times.

Cough-variant asthma is one asthma phenotype that is particularly well recognized. Variant asthma, later cough-variant asthma, was originally described by Glauser in 1972 [1] and subsequently by Corrao et al. [2], who showed that the cough was responsive to bronchodilator therapy, implying that the cough is caused by bronchoconstriction. However, there are other potential mechanisms involved in the genesis of cough in asthma, including bronchitis secondary to eosinophilic airway inflammation [3] and heightened cough reflex sensitivity [4]. The latter appears to be a feature of cough-variant asthma, but is not always seen in classical asthma [5, 6].

Cough-variant asthma is a common cause of isolated cough, accounting for around 30% of cough referrals to cough clinics [7, 8]. Typically, the cough is dry or minimally productive, and it may occur nocturnally, after exercise or allergen exposure, although there are often no clinical clues. Cough-variant asthma is particularly well recognized in children, although there is some evidence of over-diagnosis [9].

The presence of other corticosteroid-responsive cough syndromes that do not strictly meet the criteria for diagnosis of asthma have muddled the diagnostic water. Eosinophilic bronchitis is another common cause of cough [7], which presents as an isolated chronic cough and is characterized by eosinophilic airway inflammation associated with increased Th2 cytokine expression [10], in the absence of airway hyper-responsiveness or variable airflow obstruction. Atopic cough has been defined as an isolated chronic cough, no variable airflow obstruction or airway hyper-responsiveness, and one or more objective indications of atopy as defined by blood or sputum eosinophilia, elevated total or specific IgE, or positive skin tests [8]. The main distinguishing features are summarized in Table 1. Whether eosinophilic bronchitis and atopic cough represent distinct clinical entities is unclear, although

the presence of bronchoalveolar lavage (BAL) eosinophilia in eosinophilic bronchitis, but not atopic cough, suggests that they might be. The presence of these corticosteroid-responsive cough syndromes emphasizes the importance of the assessment of airway inflammation or, if this is not available, a trial of corticosteroids, in all patients with chronic cough, irrespective of tests of variable airflow obstruction and airway hyper-responsiveness.

Longitudinal studies have demonstrated that up to one-third of patients who present with cough-variant asthma later develop the typical wheezing of classical asthma [2, 8, 11, 12]. In contrast, the development of wheezing or airway hyper-responsiveness is extremely uncommon in eosinophilic bronchitis [13] or in atopic cough [8]. Although there are no longitudinal studies of decline in lung function specifically in cough-variant asthma, subepithelial layer thickness, thought to be a pathological measure of airway remodelling, has been demonstrated to be increased in cough-variant asthma, although not to the same degree as in classical asthma [14]. This implies that airway remodelling and accelerated decline in lung function may occur in cough-variant asthma in the same way as it occurs in classical asthma. There is less information on the long-term prognosis in eosinophilic bronchitis and atopic cough, although the development of fixed airflow obstruction in a patient has been reported [15], and a significant number of patients with chronic obstructive pulmonary disease and patients with fixed airflow obstruction not due to smoking have sputum eosinophilia [16, 17].

As is usual in classical asthma, cough-variant asthma responds to treatment with inhaled bronchodilators [2] and corticosteroids [18]. Leukotriene receptor antagonists have also been demonstrated to be effective in reducing cough in this condition [19]. High-dose antihistamines have been demonstrated to reduce cough dramatically in seasonal asthma [20], but have not been specifically investigated in cough-variant asthma. Eosinophilic bronchitis and atopic cough are both characteristically resistant to treatment with inhaled bronchodilators, but respond to inhaled steroids [21], and atopic cough improves with antihistamines [22].

One question of particular interest is to what extent the different clinical manifestations of asthma are related to differences in the underlying immunopathology. We have recently highlighted the importance of mast cell airway smooth muscle myositis in the generation of airway hyper-responsiveness and variable airflow obstruction [23] and that of eosinophilic airway inflammation in severe asthma exacerbations [24]. In eosinophilic bronchitis, improvement in cough with inhaled corticosteroid treatment is closely related to treatment-induced reduction in sputum eosinophil

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Table 1. Summary of the features of asthma, cough-variant asthma and eosinophilic bronchitis

	Airway hyper-responsiveness	Eosinophilic airway inflammation	BAL eosinophilia	Response to bronchodilator	Response to inhaled steroids	Atopy
Classical asthma	+	+/-	+	+	+	+/-
Cough-variant asthma	+	+/-	+	+	+	+/-
Eosinophilic bronchitis	-	+	+	-	+	+/-
Atopic cough	-	+/-	-	-	+	+

Symbols refer to typical cases: (+) present, (-) absent and (+/-) may be present or absent. BAL, bronchoalveolar lavage.

count [21], suggesting a direct causal association between eosinophilic airway inflammation and cough. However, other mechanisms may be important. One intriguing observation is that of increased sputum PGD₂ and histamine concentrations [25] and increased bronchial brushing mast cell numbers [26] in eosinophilic bronchitis compared with classical asthma. The view that mast cell mediator release is important in the genesis of cough is supported by the efficacy of antihistamines in cough associated with asthma [20] and atopic cough [22]. We have recently found that sputum PGD₂ and histamine concentrations are also high in patients with cough-variant asthma [27], suggesting that, in contrast to typical asthma, in cough-variant asthma superficial mast cells are important. Thus, it may be that mast cells localizing in the superficial structures, perhaps adjacent to sensory nerve endings, are particularly important in the genesis of heightened cough

reflex sensitivity and cough in cough-variant asthma and eosinophilic bronchitis (Fig. 1).

Further careful immunopathological studies of the different asthma phenotypes are required to investigate fully the possibility that different clinical patterns of disease are related to differences in pathology. The possibility that these aspects respond differently to available treatment should also be investigated. Such work can only increase our understanding of complex pathophysiological mechanisms operating in the asthmatic airway and may lead to a more rational use of treatment.

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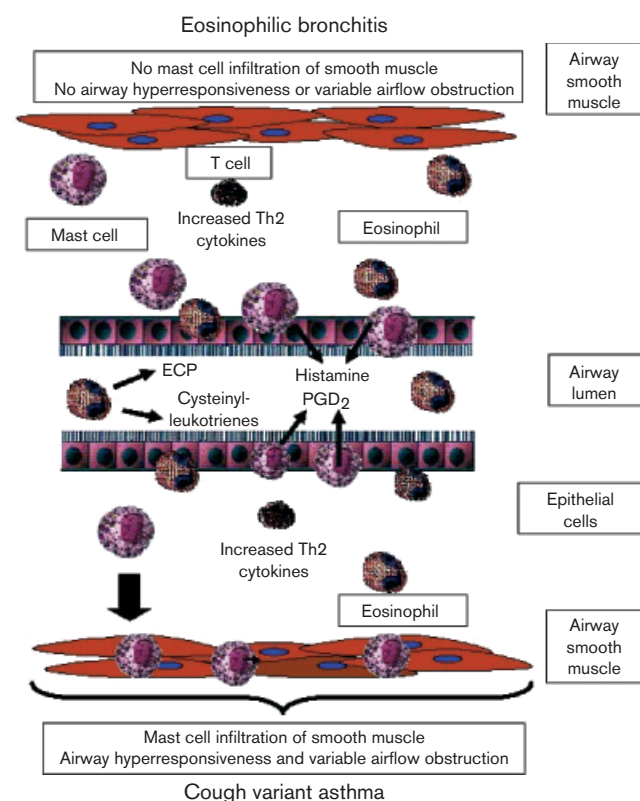


Fig. 1. Schematic diagram of airway inflammation in cough-variant asthma and eosinophilic bronchitis.

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