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# Eosinophilic Bronchial Disorders Presenting Chronic Cough; Atopic Cough, Cough Variant Asthma and Non-Asthmatic Eosinophilic Bronchitis

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## Abstract

Chronic persistent non-productive cough is troublesome, whereas productive cough is physiologic and acts to remove abnormal secretions and foreign bodies from the lower respiratory tract. Atopic cough is a new clinical entity for bronchodilator-resistant non-productive cough associated with generalized atopy. Pathological characteristics of atopic cough included trachea bronchitis without Broncho Alveolar Lavage (BAL) eosinophilia, and the physiological characteristics included hypersensitivity of the cough reflex without bronchial hyper reactivity. Patients with atopic cough have eosinophilia of the nebulized hypertonic saline-induced sputum but normal spirometry findings and no variability of Peak Expiratory Flow (PEF). These features of atopic cough are distinct from those of cough variant asthma, since these patients have mild bronchial hyper reactivity and eosinophilic inflammation of the central and peripheral airways and their cough is responsive to bronchodilator treatment. Moreover cough-variant asthma is a precursor of typical asthma, while atopic cough is not, because nearly 30% of patients with cough-variant asthma eventually develop typical asthma but patients with atopic cough do not. Although nearly 60% of patients with atopic cough can be successfully treated with histamine H1-receptor antagonists, but other still require additional corticosteroid therapy because bronchoscopic study indicate that bronchial eosinophilic inflammation is more severe in the H1-receptor antagonist-resistant group.

Further investigations are required for the clinical entity of eosinophilic bronchitis without asthma, since it seems to resemble to atopic cough and there seems to be considerable overlap of these two clinical entities.

**Keywords** Chronic cough; Atopic cough; Cough variant asthma; Eosinophilic bronchitis

## Abbreviations

BAL: Broncho Alveolar Lavage; BHR: Bronchial Hyperreactivity; FEV: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; GSEM: Geometric Standard Error of the Mean; IgE: Immunoglobulin E; IL: Interleukin; NO: Nitric Oxide; PC20: Provocative Concentration of Methacholine Producing a 20% Decrease in FEV1; PEF: Peak Expiratory Flow

## Introduction

Cough is one of the most frequently encountered symptoms in general practice and the respiratory clinic. We revealed that the prevalence of cough among the general population is 10.2% in a large-scale cohort study [1]. In the US, nearly 30 millions of people seek medical evaluation of cough at outpatient clinics every year, and up to 38% of a pulmonologist's outpatient practice is accounted for by persistently troublesome chronic cough [2,3]. It has been known that cough, especially chronic cough, can profoundly and adversely affect the quality of patient's lives and social activities. Therefore it is important to understand the mechanisms of chronic cough for accurate diagnosis and adequate treatment.

Chronic cough has been defined as "cough lasting longer than 8 weeks as the only symptom and whose cause is not apparent by physiological examination and routine testing such as chest X-ray and spirometry" [4]. Accumulating evidences indicate that eosinophilic bronchial disorders including atopic cough, cough variant asthma and eosinophilic bronchitis are common causes of chronic cough [5-9]. But diagnosis of these eosinophilic bronchial disorders remains difficult because considerable overlaps may be exist in these clinical entities. For the reason that different causes of cough have different treatments, accurate diagnosis of the cause of cough is required for each physician.

## Atopic cough

Atopic cough is a relatively new clinical entity whose pathogenesis has been investigated since first being reported in 1989 by Fujimura and their colleagues [10-17]. This entity was proposed because the existence of a bronchodilator-resistant non-productive cough associated atopy and characterized by the eosinophilic tracheobronchitis without Broncho Alveolar Lavage (BAL) eosinophilia, cough hypersensitivity without Bronchial Hyper Responsiveness (BHR) [14]. The term "atopic predisposition" does not mean production of Immunoglobrin E (IgE) antibodies in the more narrow sense, and was signified a predisposition to past, present, or future development of an allergic disorder [10-17].

As clinical features a non-productive scratchy cough in the throat including larynx and trachea is the only symptom. Patients complain that sputum is sticking in their throat. Though all ages of patients seem to be affected, the incidence is higher in women, especially middle-age women. Cough can be induced by many triggers including cold air, warm air, talking on the phone, passive smoking, exercise and perfumes. Coughing is most frequent at bedtime, followed by late at night to early morning, upon awakening and early morning [18]. As mentioned about atopic predisposition, previous medical and family histories are often positive for atopic disorders other than patients with bronchial asthma. Serum total IgE, specific IgE antibodies and the number of peripheral eosinophil counts suggesting an atopic predisposition may be present, but using these alone for screening purposes may be generally not useful [19].

Physiological and pathological findings have been investigated by Fujimura M and their co-workers [10-19]. They revealed that airway reversibility with bronchodilators is the same as in normal controls and implied that the tonus of bronchial smooth muscle is normal [12]. Bronchial responsiveness to inhaled methacholine and diurnal variations in Peak Expiratory Flow (PEF) are also within normal limits [12]. Cough reflex sensitivity to inhaled capsaicin is increased but becomes normal with treatment and improvement in cough [10]. About 80-90% patients with atopic cough have increased eosinophils in induced sputum, but the number of eosinophils is less than in cough-variant asthma and asthma [13]. Bronchoscopic investigations revealed that most patients have eosinophilic infiltration in the tracheal or bronchial sub mucosal tissue [14,15], however the extent of infiltration is mild compared with cough-variant asthma and asthma [20]. Analysis of BAL fluid also shows the absence of eosinophila [14,15]. Exhaled Nitric Oxide (NO), a biomarker of eosinophilic inflammation of lower airways, in patients of atopic cough were significantly lower than those in patients with cough variant asthma and bronchial asthma [20]. These findings indicate that in atopic cough, eosinophilic inflammation does not involve the peripheral airways, a finding quite different than in cough-variant asthma [21].

The diagnosis of atopic cough was made according to the following criteria proposed by the Japanese Cough Research Society: Table 1 shows patient selection criteria for atopic cough in a clinical study, and table 2 shows simplified diagnostic criteria for use in general clinical settings [4]. Accurate diagnosis of atopic cough is important because cough variant asthma is a precursor of asthma but that atopic cough is not [11]. About 30% of patients with cough variant asthma will eventually develop asthma within a few years when they do not treated with anti-inflammatory agents, however, asthma does not occur in patients with atopic cough [6]. But nearly 50% of patients will have a recurrent cough within 4 years, if treatment is discontinued once cough improves [6]. Longitudinal decline in pulmonary function is similar to that in healthy individuals [16]. Development to chronic obstructive pulmonary disease has not been reported.

We have to mention about the treatment of atopic cough, because bronchodilators including a leukotriene receptor antagonist are ineffective [22]. Histamine H1 antagonists are effective, but its efficacy rate is about 60% [15,23]. Therefore additional administration of Th2-cytokine inhibitor or steroid is often required [17]. Bronchial biopsy shows more intense eosinophilic infiltration in severe cases of atopic cough [15]. Administration of 20-30 mg/day of oral steroids for 1-2 weeks, as in cough-variant asthma and asthma, can provide relief of cough, if inhaled steroids are ineffective.

| | |
|---|---|
| 1 | Dry cough for at least 8 weeks without wheezing or dyspnoea |
| 2 | One or more findings suggesting an atopic predisposition† or induced sputum eosinophilia |
| 3 | No airway reversibility‡ |
| 4 | Normal airway responsiveness |
| 5 | Increased cough sensitivity |
| 6 | No response to bronchodilator therapy |
| 7 | No abnormal findings on CXR |
| 8 | Normal pulmonary function |

Table 1: Diagnostic criteria for atopic cough (must fulfil all criteria 1–8)

†Findings suggesting an atopic predisposition:

(i) Current or past history an allergic disorder other than asthma;

(ii) Peripheral blood eosinophilia;

(iii) Increased serum total IgE;

(iv)Positive for specific IgE; and

(v) Positive allergen intradermal test

‡

Less than 10% increase in FEV1 with adequate dose of a bronchodilator

Helpful findings:

(i) Presence of eosinophils in tracheobronchial biopsy specimens;

(ii) Absence of eosinophils in BAL fluid; and

(iii) Relief of cough with histamine H1 antagonists and/or steroids.

| | |
|---|---|
| 1 | Dry cough for at least 3 weeks without wheezing or dyspnoea |
| 2 | No response to bronchodilator therapy |
| 3 | One or more findings suggesting an atopic predisposition† or induced sputum eosinophilia |
| 4 | Relief of cough with histamine H1 antagonists and/or steroids |

Table 2: Simplified diagnostic criteria for atopic cough (must fulfil all criteria 1–4)

†Findings suggesting an atopic predisposition:

(i) Current or past history of an allergic disorder than asthma;

(ii) Peripheral blood eosinophilia;

(iii) Increased serum total IgE;

(iv)Positive for specific IgE; and

(v) Positive intradermal allergen test

## Cough variant asthma

Cough variant asthma is a variant form of asthma presenting cough as the sole presenting symptom, reported by Corrao and their colleagues [24]. Clinical features included a chronic non-productive

cough without wheezing or dyspnoea, near normal pulmonary function but increased airway responsiveness, relief of the cough after bronchodilator therapy. This subtype of asthma is recognized as a common cause of chronic cough [8,25-27], and more frequent in women [10,11,21].

There is usually no or little sputum production. Coughing is most frequent at bedtime, late at night and in the early morning. Upper respiratory infection, cold air, exercise, cigarette smoke and rainy weather are known as exacerbating factors of this disorder. Though cough is the sole presenting symptom, in about 30% of adult patients, wheezing will eventually develop with a transition to classic asthma within a few years when they do not treated with anti-inflammatory agents [6].

Involvement of atopy in cough variant asthma was implicated because seasonal variation is common in this disorder. For example, exacerbations in autumn imply sensitization to house dust mite allergens [28]. Elevated total and specific IgE levels of 7 common aeroallergens support the atopic features of cough variant asthma, but we must mention about these values are lower than that of classical asthma [28].

Pulmonary function tests for patients with cough variant asthma show slightly, but statistically lower values of PEF or Forced Expiratory Volume in One Second (FEV1) than healthy subjects or those with post-infectious cough [21]. Mild diurnal changes of PEF and decreases in PEF with worsening of cough are observed, but to a lesser degree than that observed in classical asthma [29]. Improvement of cough with bronchodilators suggests that bronchoconstriction may be the cause of cough variant asthma. Bronchial hyper responsiveness in cough variant asthma is similar to or milder than that of classical asthma [10,11,24]. Reversibility of FEV1 with bronchodilators is also smaller in patients with cough variant asthma than those in classical asthma. Cough receptor sensitivity, assessed by inhaled capsaicin, is increased in most non-productive cough. But it may or may not be sensitive in cough variant asthma as compared with healthy subjects, therefore, it remains obscure [10,30-32].

Eosinophils are increased in sputum, BAL fluid and bronchial mucosal tissue, and the magnitude of increase correlates with with severity of cough variant asthma [13,21,33]. As for the biopsied specimens of central airway mucosa and the BAL fluid findings from peripheral airways and lung parencima, the degree of eosinophilia is similar between classic asthma and cough variant asthma, indicationg no difference in the site of eosinophilic inflammation [21]. Also similar to classical asthma, structural airway remodeling changes are present, thus early anti-inflammatory treatment is recommended for this disorder [34,35]. This may be a consequence of long-term mechanical stimulation due to coughing [35]. In addition, increased inflammatory mediators such as histamine, prostaglandin D2, prostaglandin E2 and cysteinyl-leukotrienes, increased expression of substance P, and decreased pH of airway lining fluid may play a role in the development of cough [26,36,37].

Though cough variant asthma is characterized by bronchial hyper reactivity and responsiveness to bronchodilators, only the presence of bronchial hyper reactivity is not diagnostic [38]. Since bronchodilators such as β2-agonists and theophillines are not effective in chronic cough except for cough variant asthma, improvement of cough with this treatment is the essential diagnostic feature of this disorder as shown by the double-blined controlled study [38]. Based on these findings, responsiveness to bronchodilators is considered to be the important diagnostic feature of cough variant asthma [4]. Table 3 shows patient selection criteria for clinical studies, and table 4 shows simplified diagnostic criteria for use in general clinical practice. Sputum eosinophilia suggests a diagnosis of cough variant asthma [13,33]. However, this finding is also present in atopic cough and eosinophilic bronchitis [13,33]. Elevated exhaled NO levels may be useful for the differential diagnosis [20].

| | |
|---|---|
| 1 | Cough for at least 8 weeks without wheezing. No wheezing on auscultation of chest |
| 2 | No past history of asthma symptoms such as wheezing or dyspnoea |
| 3 | No history of upper respiratory infection within previous 8 weeks |
| 4 | Increased airway responsiveness† |
| 5 | Effective response to bronchodilator therapy‡ |
| 6 | No increase in cough sensitivity§ |
| 7 | No abnormal findings on CXR |

Table 3: Diagnostic criteria for cough-variant asthma (must meet all criteria 1–7)

†Reference values for increased airway responsiveness: Dmin <12.5 units, PC20-FEV1 <10 mg/dL with methacholine.‡ Evaluate response to bronchodilator therapy using oral or inhaled β2 agonists. Use of an objective parameter (e.g. VAS, symptom score) is preferable.§ Cough sensitivity is not increased in some reports and decreases with treatment in other reports, but in pure cough-variant asthma there is no increase. The issue of cough sensitivity is currently under review.

Some studies suggest that peripheral airway obstruction plays a role. In some cases, decreases in FEV1 and FEV1/FVC have been reported.

| | |
|---|---|
| 1 | Cough for at least 8 weeks (3 weeks) without wheezing. No wheezing on auscultation of chest |
| 2 | Effective response to bronchodilator therapy |

Table 4: Simplified diagnostic criteria for cough-variant asthma (must meet criteria 1 and 2)

Helpful findings: (i) sputum and peripheral blood eosinophilia (the former is especially useful); and (ii) increased airway responsiveness.

A subset of patients with cough-variant asthma develops wheezing with a progression to classic asthma. If inhaled steroids are not used, the rate of progression is reported 30 - 40% in adults [24,39]. Factors that may predict the development of classic asthma include bronchial hyperreactivity and maximal airway response to methacholine, sputum eosinophilia, sensitization to some allergens, and a failure in use of inhaled steroids [11,28,39-41].

After the establishment of diagnosis, treatment of cough variant asthma is essentially the same as in classical asthma [4]. As for patients with intermittent cough, bronchodilators such as short-acting inhaled β2 agonists or theophylline's may be used as needed. Inpatients with persistent cough, inhaled corticosteroids are the first line treatment because eosinopilic airway inflammation and remodeling as in classical asthma are present [21]. A long-acting β2 agonist, slow-release theophylline, or leukotriene receptor antagonist can be added, since early intervenient treatment may prevent the progression to classical asthma [11,35]. Alternative mono-therapy with leukotriene

receptor antagonist may be considered [42,43]. In patients with acute exacerbations of cough variant asthma, a short-term administration of oral corticosteroids may be added.

## Non-asthmatic eosinophilic bronchitis

Non-asthmatic eosinophilic bronchitis is also a new clinical entity originally termed "eosinophilic bronchitis without asthma" by Gibson and their colleagues [44]. Non-asthmatic eosinophilic bronchitis is pathologically similar to asthma with morning sputum and tissue eosinophilia, however, physiologically different from asthma since it lacks airway responsiveness [44]. It was not initially proposed as a distinct entity but aroused some controversy on the relation between eosinophilic airway inflammation and airway hyper responsiveness. Several studies have shown that it is a common cause of chronic cough [5-7]. Cough was originally described as productive, but many patients have non-productive cough. Atopic features may be involed since some patients have allergic rhinitis, peripheral eosinophilia and positive findings for specific IgE antigens [6,45].

Though bronchial responsiveness to inhaled methacholine in most cases is within normal limits, improvement in pulmonary function with inhaled β2 agonist observed in less than 12% of patients [45]. The value of diurnal variation in PEF is similar to that in cough variant asthma. Cough reflex sensitivity is increased but may normalize after treatment in association with the degree of cough [46].

Sputum eosinophilia defined as >2.5% or 3% is present in 100% of spontaneous or induced sputum samples in patients with non-asthmatic eosinophilic bronchitis [5,44]. The degree of eosinophilia is similar to that in stable classical asthma, however, less than in acute attacks [44,47]. Endobronchial biopsies revealed that eosinophilic infiltration in the intraepithelium and subepithelium mucosa; remodeling features such as subepithelial basement membrane thickening. The degree of this finding is similar to that in asthma [48-51]. Additionally, the degree of submucosal T lymphocyte, mast cells, and macrophage infiltration, BAL eosinophilia, elevation of exhaled nitric oxide levels are similar to those in asthma [48-51]. Lack of increase in microvascular permeability or interleukin (IL)-13 levels has also been reported [52,53].

Non-asthmatic eosinophilic bronchitis is diagnosed as below (table 5); chronic cough in patients with no symptoms or objective evidence of variable airflow obstruction, normal airway hyper-responsiveness (provocative concentration of methacholine producing a 20% decrease in FEV1, (PC20) greater than 16 mg/ml) and sputum eosinophilia [5,54]. If sputum induction cannot be successful, measurement of exhaled nitric oxide may be useful as an alternative diagnostic tool [55].

When the onset of non-asthmatic eosinophilic bronchitis is related to inhaled allergen or an occupational exposure, avoidance strategy initially is recommended. Anti-inflammatory treatment is mainly in the form of inhaled corticosteroid, because antileukotriene and antihistaminic therapies have not yet been tried in this disorder [54]. Patients improve symptomatically and have a significant fall in sputum eosinophilia after inhaled corticosteroid therapy [45,46]. Capsaicin cough sensitivity, which was increased moderately before treatment, improved toward normal after treatment with budesonide, showing significant positive correlation between the treatment-induced change in cough sensitivity and eosinophil count [46]. These findings suggest that elevated cough sensitivity contributes to the cough in patients with this disorder and that eosinophilic airway inflammation is causally associated with the increased cough sensitivity. Oral corticosteroids are required to control symptoms and eosinophilic inflammation.

| | |
|---|---|
| 1 | A chronic cough in patients with no symptoms or objective evidence of variable airflow obstruction |
| 2 | Normal airway hyper-responsiveness (provocation concentration of methacholin e producing a 20% decrease in forced expiratory volume in 1 minute (FEV1), PC 20 greater than 16 mg/mL). |
| 3 | Sputum eosinophilia (An acceped upper cut-off level of greater than 3% nonsquamous sputum eosinophils) † |

Table 5: Diagnostic criteria for non-asthmatic eosinophilic bronchiis (must fulfil all criteria 1–3)

†This is outside the 90th percentile for normal patients (1.1%).

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In a 1-year observational study, 9% of patients with non-asthmatic eosinophilic bronchitis developed asthma and airway hyper responsiveness, 16% of those developed fixed airflow obstruction [56]. Another study has also revealed a more rapid decline of FEV1 in a subset of patients with recurrent disease than in non-recurrent disease [57]. A follow-up study of the original cases of Gibson et al. demonstrated the development of asthma in 1 of 9 subjects [44,58]. So patients with non-asthmatic eosinophilic bronchitis can develop classical asthma and chronic airway obstruction, like those with cough variant asthma and unlike those with atopic cough.

## Conclusions

Eosinophilic bronchial disorders presenting chronic cough is an important clinical entity, but considerable overlaps may exist in atopic cough, cough variant asthma and non-asthmatic eosinophilic bronchitis due to confusion or lack of consensus. Table 6 shows summary of pathophysiological findings in these disorders [4]. Eosinophilic bronchial disorders presenting chronic cough is an important clinical entity, but considerable overlaps may exist in atopic cough, cough variant asthma and non-asthmatic eosinophilic bronchitis due to confusion or lack of consensus.

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asthmatic eosinophilic bronchitis significantly overlaps with atopic cough, but some differences exist for example different prognosis to develop asthma and chronic airway obstruction, eosinophilia in BAL fluids and elevation of exhaled NO, suggesting overlaps with cough variant asthma. For the reason that different causes of cough need different treatments, further study for differential diagnosis of the eosinophilic bronchial disorders may be required.

| | Cough-variant asthma | Atopic cough | Eosinophilic bronchitis without asthma |
|---|---|---|---|
| Pathologic findings Eosinophilic inflammation | Central to peripheral airways | Central airway | Central airway peripheral airway |
| Physiologic findings | Slightly increased tonus of bronchial smooth muscle and bronchoconstriction due to mild airway hyperresponsiveness | Normal airway responsiveness Increased cough receptor sensitivity | Normal airway responsiveness Increased cough receptor sensitivity |
| Mechanism of cough | Mediated by bronchoconstriction | Due to increased cough receptor sensitivity | Probably due to increased cough receptor sensitivity |
| Presence of cough required for diagnosis | Yes | Yes | No |

Table 6: Summary of pathophysiological findings in cough-variant asthma, atopic cough and non-asthmatic eosinophilic bronchitis

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