Eosinophilic Bronchitis without Asthma

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Introduction

The passage of eosinophil leukocytes through the vascular lumen into tissues occurs in several complex phases, including rolling, activation, firm adhesion and transendothelial migration [1]. Eosinophil leukocytes, as a defensive element of mucosal surfaces, respond not only to antigens but to parasites, chemicals and trauma. They can accumulate either for repairing or for destroying the bronchial epithelium [2]. In 1989, Gibson and colleagues [3] described a group of non-smoking patients with a corticosteroid-responsive chronic cough who had sputum evidence of an eosinophilic bronchitis but normal spirometry, no evidence of airway hyperresponsiveness, and normal peak expiratory flow variability. The condition has subsequently been recognized as an important cause of chronic coughs, being present in 10–15% of patients referred for specialist investigation [4, 5].

Clinical Features of Eosinophilic Bronchitis

Eosinophilic bronchitis without asthma (EBWA) was defined as a cough lasting longer than 2 months, a sputum eosinophil count >3%, forced expiratory volume in 1 s (FEV1) >80% predicted, FEV1/forced vital capacity >70%, within a single day peak flow amplitude as a percentage of mean of <20% with twice daily measurements over 2 weeks and methacholine PC20 >16 mg/ml [5]. Patients with EBWA typically have a cough productive of scanty sputum in the morning, in keeping with a bronchitic component to their cough [4]. These subjects were...
predominantly middle-aged, non-atopic and non-smokers [5], perhaps reflecting a selection bias since primary care physicians are likely to attribute a chronic cough in smokers to chronic bronchitis [6].

A positive correlation between the steroid-induced change in cough reflex sensitivity and the sputum eosinophil count has been reported [7]. This finding suggests that heightened cough reflex sensitivity contributes to the cough in EBWA and that eosinophilic airway inflammation is causally associated with increased cough reflex sensitivity. However, Park and colleagues [8] have shown that asymptomatic sputum eosinophilia (≥3%) reappeared between the 4th and 24th month of follow-up in 10 patients of the ‘non-recurrent’ EBWA group. This indicates that eosinophilic airway inflammation is not always related to cough development in eosinophilic bronchitis.

There are a number of similarities between the condition described by Fujimura and colleagues [9] known as ‘atopic cough’ and EBWA. Both present with a corticosteroid-responsive cough, a sputum eosinophilia, normal spirometry, normal airway responsiveness, and increased capsaicin cough sensitivity [7]. Atopy appears to be more common in atopic coughs and the cough is usually dry, whereas the cough in EBWA is occasionally productive of tenacious sputum. In atopic coughs, the inflammation is confined to the upper airway with biopsy evidence of tracheobronchitis without eosinophilia present in the bronchoalveolar lavage [4]. Fujimura and colleagues [9] also reported that eosinophilic inflammation of the trachea and central bronchi, but not the peripheral airways, may be pathological characteristics of atopic coughs. In contrast, a similar degree of bronchoalveolar lavage eosinophilia in patients with EBWA has been shown compared with subjects with asthma [10].

**Diagnosis**

Making a positive diagnosis of EBWA requires assessment of airway inflammation in the lower respiratory tract, ideally using induced sputum analysis, after other causes of cough have been excluded by clinical, radiological and physiological assessment (spirometry and methacholine challenge test) [11]. The procedure of sputum induction involves patients inhaling increasing concentrations of hypertonic saline solutions (3, 4 and 5%) in sequence for 7 min each via a nebulizer after premedication with a short-acting bronchodilator. It has been reported that there is no significant difference in total and differential cell counts between spontaneous and induced sputum [12]. In induced sputum, the proportions of eosinophils were <1.5%, neutrophils 14.3–64.4%, macrophages 33.0–86.1%, lymphocytes <2.7%, and bronchial epithelial cells 0–4.4%, respectively [13, 14]. Airway inflammation should ideally be measured by induced sputum analysis, but, if this is unavailable or unsuccessful, exhaled nitric oxide should be considered before lavage, although bronchial lavage fluid obtained at bronchoscopy provides information similar to that obtained from induced sputum.

**Etiology and Pathogenesis**

The etiology of EBWA can be associated with exposure to an occupational sensitizer or to a common inhaled antigen. Potential occupational dust exposure has been reported in 44% of 52 patients described by Berry and colleagues [5]. Chloramine [15], bucillamine [16], isocyanate, flour, mushroom spores, natural rubber latex, acrylates, epoxy resin hardener [17], welding fumes and formaldehyde [18] have been reported to cause eosinophilic bronchitis.

It has been speculated that airway inflammation in patients with EBWA is confined to the upper airway because upper airway symptoms are common in these patients. However, EBWA is not typically associated with a nasal eosinophilia or upper airway hyperresponsiveness [7]. This observation supported a predominant lower airway inflammation.

The major pathological feature in EBWA is eosinophilic airway inflammation, like asthma [19]. An increase in the sputum eosinophil count occurring well before the exacerbation of asthma has been reported [20]. Table 1 shows the pathogenetic differences and similarities of the 2 conditions. Morphometric and cellular analyses revealed no differences in basement membrane thickness and in the numbers of eosinophils, T lymphocytes expressing Th2-type cytokines (IL-4, IL-5), chemokine receptors (CCR3, CCR5, CCR6, CXCR3) and activation markers such as CD25 [21]. Both conditions were associated with increased levels of cysteinyl leukotrienes and eosinophilic cationic protein [22], and they have a similar degree of IL-5 and granulocyte-macrophage colony-stimulating factor gene expression in bronchoalveolar fluid cells [10].

The most important difference in cellular morphology between the 2 conditions is the localization and activation of mast cells. Mast cell numbers in bronchial brush-
ing samples were increased in patients with EBWA compared with those with asthma [10]. In contrast, mast cell infiltration in the smooth muscle is significantly higher in asthma patients than in either eosinophilic bronchitis patients or healthy control subjects [23]. The most striking functional differences compared with asthma are the absence of airway hyperresponsiveness and variable airflow obstruction in EBWA. A possible explanation is that the inflammatory cell infiltration in eosinophilic bronchitis is more localized to the epithelium so that mediators released by mast cells or other inflammatory cells reach airway smooth muscle in lower concentrations than in asthma. The increased chemokine concentrations of CXCL8 and CXCL10 can contribute to mast cell recruitment to the superficial airways in EBWA [24]. When compared with asthma, the sputum histamine and prostaglandin D\(_2\) (PGD\(_2\)) concentrations were only significantly elevated in subjects with EBWA [22]. The elevation of histamine in combination with PGD\(_2\) is highly suggestive of mast cell activation since basophils, which also produce histamine, do not produce PGD\(_2\) [25]. Thus, mast cell activation appears to be a feature of EBWA.

Airway smooth muscle mast cell numbers inversely correlated with airway responsiveness [26]. It has been reported that the infiltration of airway smooth muscle by mast cells that express IL-4 and IL-13 is a feature of asthma but not of EBWA [19, 23]. The sputum IL-13 concentration and IL-13 expression in the bronchial submucosa were higher in patients with mild asthma than in patients with EBWA [21]. It has also been identified that most of the cells in the bronchial submucosa that expressed IL-13 protein were eosinophils. The number of eosinophils in the submucosa was similar in asthma and eosinophilic bronchitis, suggesting that there is a difference in expression of IL-13 by eosinophils between these 2 conditions [27]. Interestingly, neutrophil numbers were increased in the submucosa in those with EBWA compared with mild asthmatics or controls. This finding may be due to raised sputum concentration of the neutrophil chemokine IL-8 in EBWA [20].

IL-4 and IL-13 increase the expression of vascular endothelial growth factor (VEGF) on airway smooth muscle [28]. VEGF increases microvascular permeability by inducing fenestration in endothelial cells so that plasma proteins can leak into the extravascular space, leading to mucosal edema and thereby narrow airway diameters, which could amplify the effect of airway smooth muscle contraction. Kanazawa et al. [29] reported that the production of VEGF and airway permeability were increased in asthmatics but not in patients with EBWA. However, Siddiqui et al. [30] found a similar increase in sputum VEGF concentrations in both subgroups.

### Table 1. The pathogenetic comparison of asthma and eosinophilic bronchitis

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<tr>
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<th>Eosinophilic Bronchitis</th>
<th>Asthma</th>
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<tbody>
<tr>
<td>Eosinophilic airway inflammation</td>
<td>100%</td>
<td>66–100%</td>
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<tr>
<td>Mast cells in the smooth muscle</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Sputum histamine and PGD(_2) concentrations</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>IL-13 expression in sputum</td>
<td>normal</td>
<td>++</td>
</tr>
<tr>
<td>Mast cell numbers in bronchial brushing samples</td>
<td>increased</td>
<td>increased</td>
</tr>
<tr>
<td>Numbers of eosinophils in sputum or submucosa</td>
<td>increased</td>
<td>increased</td>
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<tr>
<td>Eosinophilic cationic protein levels in sputum</td>
<td>increased</td>
<td>increased</td>
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<tr>
<td>Basement membrane thickness</td>
<td>increased</td>
<td>increased</td>
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<tr>
<td>T lymphocytes expressing Th2-type cytokines in bronchial lavage fluid</td>
<td>increased</td>
<td>increased</td>
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<td>Levels of cysteiny1 leukotrienes in sputum</td>
<td>increased</td>
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<td>IL-5 and GM-CSF gene expression in bronchoalveolar fluid cells</td>
<td>increased</td>
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<tr>
<td>Sputum VEGF concentrations</td>
<td>increased</td>
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<td><strong>GM-CSF = Granulocyte-macrophage colony-stimulating factor.</strong></td>
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### Treatment

Patients improve symptomatically and have a significant fall in their sputum eosinophil count following treatment with inhaled corticosteroids [7]. The suggested dose is generally budesonide 400 μg twice daily or the equivalent dose of fluticasone [4, 8]. It also remains unclear whether therapy should be discontinued when symptoms
resolve. In spite of therapy, sputum eosinophilia can recur between 4 and 24 months of therapy [8]. Very occasionally, treatment with oral corticosteroids is required to control symptoms and eosinophilic inflammation [26]. A predominant small airway inflammatory reaction offers a possible explanation for the poor response to inhaled corticosteroids. On the other hand, the heterogeneous response to inhaled steroids suggests that different pathogenetic pathways may be responsible for the disease.

**Prognosis**

Hancox and colleagues [31] reviewed 9 patients with EBWA at 5–10 years after diagnosis and reported that 1 subject acquired clinical symptoms of mild asthma, but this was not proven objectively using lung function testing. In contrast, a larger series consisting of 32 patients suggested that EBWA is rarely self-limiting. Asthma, with typical symptoms and airway hyperresponsiveness, developed in 3 patients (9%). Five patients (16%) developed fixed airflow obstruction, and 21 patients (66%) had persistent symptoms and/or ongoing airway inflammation. Only 1 patient had complete resolution of symptoms and no sputum eosinophilia while not receiving corticosteroid therapy [5]. It is not clear whether EBWA is a precursor of asthma but, if so, recognition of this condition may permit effective treatment and reduction in the rising prevalence of asthma [19].

Park and colleagues [8] reported that about half of the EBWA patients developed recurrent sputum eosinophilia during the follow-up period. They also showed that recurrent episodes of EBWA are associated with the development of airflow obstruction and airway hyperresponsiveness. Airway wall remodeling can occur in rhinitis, chronic obstructive pulmonary disease (COPD), asthma, as well as in cough-variant asthma with eosinophilic airway inflammation [19]. Approximately 30–40% of patients with COPD without a history of asthma and no bronchodilator reversibility have sputum eosinophilia [26]. These observations provide a possible explanation for the presence of eosinophilic airway inflammation in some patients with COPD without apparent pre-existing asthma in that EBWA may in some circumstances be a prelude to COPD. Brightling and colleagues [32] also described a patient with EBWA who developed fixed airflow obstruction in association with prolonged uncontrolled eosinophilic airway inflammation. COPD is thought to be the result of moderately accelerated decline in FEV$_1$ over many years. However, their patient had shown a different pattern, with a rapid fall in FEV$_1$ occurring after a period of several years when the patient had symptoms, but normal spirometry values.

**Conclusions**

In patients with chronic coughs who have normal chest radiography, normal spirometry findings and no evidence of variable airflow obstruction or airway hyperresponsiveness, a diagnosis of EBWA should be considered. In such patients, it is necessary to investigate the presence of an airway eosinophilia. If so, the possibility of an occupation-related cause needs to be considered. The first-line treatment is inhaled corticosteroids. Little is known about the natural history of the condition. We conclude that the presence of eosinophils in the airways is not a sufficient factor for the development of airflow obstruction and airway hyperresponsiveness.

**References**


26 Brightling CE: Chronic cough due to non-asthmatic eosinophilic bronchitis. ACCP evidence-based clinical practice guidelines. Chest 2006;129:1165–121S.


