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Review

Non-astmatic Eosinophilic Bronchitis

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Abstract

Non-asthmatic eosinophilic bronchitis (NAEB) is eosinophilic inflammation of the respiratory tract, without any bronchospasm. In this article, we want to draw attention to the NAEB. It should also be considered in differential diagnosis of chronic cough. Eosinophilia is present in all induced or spontaneous sputum samples of NAEB patients. NAEB patients and asthmatic patients have similar airway inflammation. Remarkably, NAEB mainly occurs in the lower airways. Unlike asthma, mast cells in NAEB are active in the bronchial epithelium. Diagnosis is based on the clinical, radiological, and spirometric measurements of other causes of chronic cough (Post-nasal discharge syndrome, asthma, gastroesophageal reflux etc.) and the assessment of inflammation in the lower respiratory tract. Airway inflammation can be assessed by sputum induction. The main treatment is anti-inflammatory therapy with inhaled corticosteroids and taking protective measures if inflammation is due to occupational exposure or allergen inhalation. If NAEB is untreated, it may be transient, episodic, or persistent; rarely, long-term oral steroid treatment may be required in patients. There is a requirement for studies that investigate the role of non-invasive markers of chronic inflammation associated with NAEB and the effectiveness of other treatments.

KEYWORDS: Chronic cough, eosinophilic airway inflammation, bronchitis

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INTRODUCTION

Non-asthmatic eosinophilic bronchitis (NAEB) is a chronic disease and was first described in a small group of patients by Gibson et al. [1,2] in a relatively recent date. Without bronchospasm, it is defined as eosinophilic inflammation of the respiratory tract and is usually associated with eosinophilia in sputum. It is one of the most important causes of chronic cough [3].

When a cough lasting longer than 8 weeks is detected in clinical practice; if chest X-ray is normal, this situation is defined as chronic cough. Chronic cough is a common cause of complaints all over the world, especially at the centers giving outpatient care, and is responsible for about 40% of the applications [4-6]. However, the cause(s) leading to this condition can be detected in 75-90% [7-9]. NAEB is a disease that should be remembered in the differential diagnosis of chronic cough but it is often ignored [10]. Because the systematic examination of bronchial inflammation can be made rarely, it is probably diagnosed less than it exists [11]. When the other causes that may lead to chronic cough are eliminated in patients applying with the complaint of chronic cough, NAEB should be taken into consideration [12-19].

The purpose of this article is to make it possible to consider the differential diagnosis of patients with chronic cough by drawing attention to NAEB, and to compile and present the literature data that is relatively limited.

ETIOLOGY

Although the etiology of NAEB is not clear yet, environmental or occupational factors may be responsible for this situation in some of the patients. In a significant proportion of the diagnosed patients, occupational dust exposure was considered to be possibly etiologically responsible. For this reason, the possibility of occupation-related causes should be considered in patients with chronic cough due to NAEB [20]. Especially resin hardener, welding fume and formaldehyde exposures have been shown to lead to NAEB [21-24].

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PATHOLOGY

In these patients, active respiratory tract inflammation is detected without any airway hypersensitivity together with increased sputum eosinophils (eosinophilic airway inflammation). Patients with NAEB and asthmatic patients have similar airway inflammation. Therefore, it is histopathologically similar to asthma and can be confused with cough-variant asthma [25] (Table 1). However, it is physiologically separated from asthma by the absence of airway hypersensitivity [20].

Though eosinophils and basal membrane thickening are seen both in asthma and in NAEB, mast cell infiltration is seen only in asthmatic patients and this may explain the difference in hypersensitivity in the respiratory tracts [15,16,26].

Induced or spontaneous sputum specimens are completely eosinophilic. The level of eosinophils is similar to that of stable asthmatic patients; however, it is less common when compared to acute asthma attacks [1,27]. In the study of Zhang et al. [28], patients with NAEB were found to have a statistically significantly high level of eosinophil count and sputum eosinophil ratio in comparison with healthy subjects. In the histopathological examination of bronchial mucosa samples of NAEB patients, it was shown that eosinophilic infiltration was localized in the intraepithelial and subepithelial mucosa, the subepithelial basal membrane thickened and the intensity of present findings was similar to asthma [27,29]. In addition, it has been shown that IL-4, IL-5 and eosinophilic cationic protein release is not different from asthma in terms of eosinophil degranulation in the bronchial mucosa and the levels of nitric oxide (NO) in expiratory air [27-30]. Such as cysteine leukotrienes (cys-LTs), PGE2, PGF2α and TXB2; vasoactive, bronchoconstructors and mediators that cause airway damage play an important role in NAEB-associated eosinophilic inflammation [25]. Remarkably, inflammation in NAEB is especially in the lower respiratory tracts.

In the clinical trials that they conducted with 24 asthmatic patients, 7 patients with NAEB and 16 healthy volunteers; Siddiqui et al. [31] reported that IL-13 expression from peripheral T-lymphocytes and eosinophils was higher in asthmatic patients compared to healthy volunteers and NAEB patients, and emphasized that this was important in terms of pathogenesis and differential diagnosis.

We have already mentioned that the airway inflammation in patients with NAEB is similar to the airway inflammation in asthma. However, the localization of mast cells on the bronchial wall is different in NAEB patients. Unlike asthma, mast cells in NAEB are activated in the bronchial epithelium. In NAEB patients; bronchial brushing materials have higher numbers of mast cells and histamine concentrations with PGD2 in sputum than in asthma [25,27]. However, the increase in the number of active mast cells in the bronchial smooth muscle of asthmatic patients is absent in NAEB [27,32]. The most important key factor that creates functional differences associated with airway inflammation between patients with asthma and NAEB is the airway hypersensitivity developing due to the activation of mast cells in the airway smooth muscle in asthma and is the airway obstruction with reversible feature [33].

CLINICAL FEATURES

At present, NAEB has been defined as normal airway hypersensitivity (eg. methacholine provocative concentration less than 16 mg / mL, which provides a 20% reduction in FEV1) and as the presence of sputum eosinophilia (> 3%) in patients who applied to our polyclinic with the complaint of chronic cough that lasted more than 2 months without the symptoms or objective evidences of variable airway obstruction [12].

There is not any PEF variability, and NO levels in expiratory air are increased [31,34]. Coughing responds to inhaled and/or oral corticosteroid treatment quite well [35]. Patients are usually middle-aged, they have no cigarette and atopy stories and their only complaints are chronic cough [1]. Present findings in the literature suggest that cough reflex sensitivity in NAEB contributes to cough and eosinophilic inflammation is associated with increased cough reflex sensitivity. The severity of coughing, increased cough reflex sensitivity (C5 <3.9 mM) and sputum eosinophil ratio are reduced by inhaled and/or oral corticosteroid therapy [34,36]. However; in

Table 1. Clinical and pathological features of NAEB compared with classical asthma and cough variant asthma

Features	NAEB	Classical Asthma	Cough Variant Asthma	Atopic Cough
Symptoms	It is associated with upper respiratory tract symptoms	Shortness of breath, cough, wheezing	Isolated cough	Isolated cough
Atopy	Similar to the general population	Frequent	Frequent	Frequent
Respiratory tract hyperresponsiveness	None	None	None	None
Cough reflex hypersensitivity	Increased	Normal or increased	Normal or increased	increased
Bronchodilator responsiveness	None	Yes	Yes	None
Response to Corticosteroids	Yes	Yes*	Yes*	Yes*
Sputum eosinophilia	Always	Usually	Usually	Usually
Bronchial biopsy eosinophilia	Quite Frequent	Frequent	Frequent	Frequent
Mast cells in airway smooth muscle bundles	None	Yes	Yes	Not known

NAEB: non-astmatic eosinophilic bronchitis
**In the presence of sputum eosinophilia

another study which was conducted by Park et al. [37] and in which long-term follow-ups of the patients were made, the recurrence of sputum eosinophilia (3%) in the asymptomatic period in a group of patients suggested that chronic cough in NAEB patients was not always associated with eosinophilic inflammation.

DIAGNOSIS

The diagnosis of NAEB is made by eliminating the other causes with clinical, radiological and spirometric measurements and by the evaluation of inflammation in the lower respiratory tract. Respiratory tract inflammation can be assessed by sputum induction [38,39]. With this method, which is extremely simple, reliable and noninvasive, adequate sputum can be obtained from lower respiratory tract in 80% of adults and children when hypertonic saline is administered with the help of an ultrasonic nebulizer. Hypertonic saline is thought to make induction by accelerating the flow of fluid out of the airway epithelium, stimulating cough receptors or increasing mucociliary clearance. However; if the method cannot be applied or if the outcome is unsuccessful, nitric oxide (NO) levels can be measured in the expiratory air before resorting to invasive methods such as bronchial lavage. In asthmatic patients, NO levels have increased in expiratory air as a marker of airway inflammation. NO is used to assess whether the disease is under control and to assess the efficacy of anti-inflammatory therapy. Although it has been suggested that NO levels measured in low levels may exclude NAEB diagnosis in patients with non-asthmatic chronic cough, its role in NAEB has not fully become definite [29,30]. In a meta-analysis which Song et al. [40] compiled from 15 studies involving 2187 cases, the measurement of fractional exhaled nitric oxide (FENO) was found to have a moderate diagnostic accuracy in cough variant asthma. However, diagnostic accuracy is lower in NAEB. For this reason, it has been stated that FENO measurement may not be useful in the prediction of NAEB diagnosis.

In the study in which they compared the probable causes of chronic cough with definitive diagnoses in 109 cases, Yu et al. [41] found 27.5% of mismatch between the definite diagnoses and probable diagnoses, and suggested that starting with the treatment of probable causes might be a solution in this respect.

THE NATURAL COURSE OF NON-ASTHMATIC EOSINOPHILIC BRONCHITIS

Our knowledge about the course of the disease is limited to a few studies in the literature. The first data obtained from 12 patients followed up for 10 years with NAEB diagnosis suggest that it is a benign and self-limiting disease [38]. However, 3 of 32 patients (9%) followed up for at least 1 year with the diagnosis of NAEB were observed to have asthma with typical symptoms and airway hypersensitivity, 5 (16%) of them had fixed airway obstruction, and symptoms and/or airway inflammation persisted in 21 (66%) of them [20]. In the study of Lai et al. [42], 234 patients were identified to have NAEB and 141 of them were followed up for more than 1 year. Up to 59.6% of the patients had recurrence after treatment. Mild asthma developed in eight patients (5.7%). During the follow-up period, no progressive reduction in FVC, FEV1 and FEV1 / FVC was observed. In all groups, however, there was a marked increase in small airway dysfunction (maximal middle expiratory flow [MMEF] <65%) on the last visit.

Whether or not NAEB is a precursor of asthma is not yet clear. If it is the precursor, it is thought that an effective treatment to be applied during this period of illness will reduce the prevalence of asthma [26].

Brightling et al. [43] reported that fixed airway obstruction developed in a case who was followed up for 2 years with the diagnosis of NAEB. Although a symptomatic recovery was achieved with corticosteroid therapy in the case, sputum eosinophilia persisted. It has been suggested that progressive irreversible airflow limitation may develop due to reconstruction developing secondary to persistent eosinophilic inflammation caused by inadequate corticosteroid therapy [20]. Because of studies showing that 30-40% of patients with COPD can maintain life with sputum eosinophilia without any evidence of asthma and reversibility, it is also thought that NAEB may be the beginning of COPD [44,45].

There are studies reporting that the natural course of NAEB is variable. In a 1-year follow-up of the cohort of 367 NAEB patients with normal respiratory function and eosinophilic inflammation; it was detected that 55% of the patients were still symptomatic with normal spirometry, 32% were asymptomatic, and asthma developed in 13% [29]. Especially patients with symptomatic eosinophilic bronchitis with recurrent episodic course have been found to be at increased risk for chronic obstructive airway obstruction and asthma [32].

TREATMENT

The main treatment for patients with non-asthmatic eosinophilic bronchitis is antiinflammatory therapy including inhaled corticosteroids, and if the inflammation has developed due to occupational exposure or allergen inhalation, protective measures should be taken [20]. Administration of 400 µg of inhaled budesonide twice a day or equivalent dose of fluticasone for 4 weeks has been shown to improve symptoms and markedly reduce the number of eosinophils in sputum [2,12,20,34,37,46]. It is not yet clear whether the treatment will be discontinued in patients in whom symptom control has been provided with inhaled corticosteroid therapy. Repetitive sputum eosinophilia was reported in patients in whom symptomatic improvement was provided through treatment [39]. Heterogeneous response to inhaled corticosteroid treatment suggests that different mechanisms required to be elucidated may play a role in the pathology of the disease [47].

Oral corticosteroid therapy may be required in cases with cough that is resistant to high-dose inhaled corticosteroid treatment and with eosinophilic inflammation [20]. In recent years, it has been suggested that leukotriene receptor antagonists may be a potential therapeutic agent in the treatment of NAEB. In a pilot study developed by Cai et al. [46]; in patients who did not previously use steroids, it has been shown that montelukast (10 mg/day) that is administered with inhaled corticosteroid (400 µg/day) has an antitussive and antiinflam-

matory effect similar to high dose (800 µg/day) of inhaled corticosteroid therapy, and the possible role of cys-LTs in the pathogenesis of NAEB was emphasized. Montelukast combined with budesonide in the 65-patient study of Wuping et al. [48] was found to be effective in improving the quality of life, in the suppression of eosinophilic inflammation and in eliminating cough in patients with NAEB.

If NAEB is untreated, it may be temporal, episodic or persistent, and rarely long-term oral steroid therapy may be required in patients [47].

In conclusion, NAEB is a chronic inflammatory disease in which eosinophilic infiltration predominates in respiratory tracts. Chest X-ray and spirometric measurements are normal in patients and there is no evidence of airway obstruction or airway hypersensitivity. Though it is an asthma-like airway inflammation, the localization of mast cell infiltration in the bronchial wall is different. Cough responds to inhaled corticosteroid treatment. However, it has been reported that irreversible airflow limitation and asthma may develop in the natural course of the disease, and even sputum eosinophilia may continue in the asymptomatic period. This shows the role of other inflammation-related noninvasive markers in cough that is associated with NAEB, and shows that there is a need for studies investigating the efficacy of other treatments.

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