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REVIEW

The meaning of sputum eosinophil in childhood asthma and its current application

La signification de l'expectoration d'éosinophile dans l'asthme infantile et son application actuelle

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ABSTRACT

Eosinophil infiltration plays an important role in the pathogenesis of asthma. It is important for a health care provider to determine which subtype of asthma a person might have, because there are now new therapies that target specific subgroups of asthma, like eosinophilic asthma.

The term *"eosinophilic asthma"* describes a subphenotype of asthma that is characterised by elevated levels of eosinophils in bronchial biopsies or sputum despite chronic and correct use of adequate doses of inhaled corticosteroids (ICS). Traditionally, airway biopsies or bronchoalveolar lavage through bronchoscopy is considered as the gold standard for assessing airway inflammation but the invasiveness of these methods limits their use in clinical practice.

Biomarkers for type 2 (TH2) inflammation, including FENO (fractional exhaled nitric oxide) levels and blood/sputum eosinophilia and serum periostin levels, have helped to identify a type 2 molecular phenotype of asthma. Sputum induction and differential cell count, unfortunately, are available only in a limited number of specialized centers. Although numerous studies in adults have shown induced sputum analysis to be a useful and safe tool in the evaluation of asthma, very few studies have evaluated this tool in children.

In Vietnam, hardly no clinical setting has applied sputum eosinophil in monitoring asthma because of strict requirements of the method. Thus, here is really avoid space for Vietnamese researchers, especially pulmonologists, that they need to compensate it in the future.

KEYWORDS: Asthma, eosinophilic asthma, inhaled corticosteroids, induced sputum.

RÉSUMÉ

L'infiltration des éosinophiles joue un rôle important dans la pathogenèse de l'asthme. Il est important pour le personnel médical de déterminer quel sous-type d'asthme une personne pourrait avoir, car il existe maintenant de nouvelles thérapies ciblant des sous-groupes spécifiques d'asthme, comme l'asthme à éosinophile.

Le terme «asthme éosinophilique» décrit un sous-phénotype de l'asthme qui est caractérisé par des taux élevés d'éosinophiles dans les biopsies bronchiques ou les expectorations malgré l'utilisation chronique et correcte de doses adéquates de corticostéroïdes inhalés (CSI). Traditionnellement, la biopsie des voies aériennes ou le lavage broncho-alvéolaire par bronchoscopie sont considérés comme les critères d'or pour évaluer l'inflammation des voies aériennes, mais le caractère envahissant de ces méthodes limitent leur utilisation dans la pratique clinique.

Les biomarqueurs de l'inflammation de type 2 (TH2), y compris la concentration de FENO (fraction de monoxyde d'azote expiré) et les taux d'éosinophilie et de périostine dans le sang et les expectorations, ont aidé à identifier un phénotype moléculaire de type 2 de l'asthme. L'induction des expectorations et le nombre de cellules différentielles ne sont malheureusement disponibles que dans un nombre limité de centres spécialisés. Bien que de nombreuses études chez l'adulte aient montré que l'analyse des expectorations induites est un outil utile et sûr dans l'évaluation de l'asthme, très peu d'études ont évalué cette technique chez les enfants.

Au Vietnam, il n'y a aucun contexte clinique appliquant difficilement l'expectoration éosinophile dans la surveillance de l'asthme en raison des exigences très strictes de cette méthode. Ainsi, les chercheurs vietnamiens, en particulier les pneumologues, ont vraiment besoin d'en compenser dans l'avenir.

MOTS CLÉS: Asthme, asthme éosinophilique, corticostéroides inhalées, expectoration induite.

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INTRODUCTION

Asthma treatments are predominantly nonspecific anti-inflammatory drugs (corticosteroids) and bronchodilators (beta2-agonists), which works in most patients. However, even responses to these treatments vary. Otherwise, while forced expiratory volume during the first second (FEV_1) is used to measure lung function in asthma, inflammation and remodeling can persist even when FEV_1 has returned to normal. Although multiple factors can contribute to poor responses, underlying pathobiological differences are increasingly recognized to play a role. Specific subgroups of asthma patients could be identified, either on the basis of clinical characteristics (with or without frequent exacerbations), age of asthma onset (childhood onset *versus* adult onset), lung function abnormalities (with or without persistent airflow limitation), trigger factors (allergic, nonallergic or aspirin induced) or type of airway inflammation (eosinophilic *versus* noneosinophilic) [1]. Although various phenotype clusters and endotypes have been proposed, there is still much unknown about gene expression, the effect of environment and comorbidities, the stability of phenotypes over time, and the appropriate use of biomarkers.

ROLE OF SPUTUM EOSINOPHIL IN CHILDHOOD ASTHMA

Eosinophil infiltration plays an important role in the pathogenesis of asthma. It is important for a health care provider to determine which subtype of asthma a person might have, because there are now new therapies that target specific subgroups of asthma, like eosinophilic asthma. The term *"eosinophilic asthma"* describes a subphenotype of asthma that is characterised by elevated levels of eosinophils in bronchial biopsies or sputum despite chronic and correct use of adequate doses of ICS [1]. Sputum eosinophil percentage identifies patients who have eosinophilic or non-eosinophilic asthma phenotype. Cai et *al.* demonstrated that the maximum percentage of eosinophils in the sputum of normal children is 2.5% [2]. It has been shown that sputum eosinophil numbers are higher in atopic as compared to non-atopic childhood asthma [3]. Asthma management guided by eosinophils in sputum rather than according to asthma controlmeasures results in better outcomes [4].

Diagnosing eosinophilic asthma is important. Many studies demonstrated that airway inflammation, especially eosinophilic inflammation, was associated with asthma severity and reduced pulmonary function in children [5-7]. A study of Simpson et *al* [8] that examined eosinophil and neutrophil percentage sin induced sputum found four inflammatory subtypes: eosinophilic,neutrophilic, mixed granulocytic, and pauci-granulocyticasthma. There has been long standing evidence that patients with eosinophilic asthma have greater responsiveness to steroids compared with those with neutrophilicasthma [9]. Patients with symptoms and evidence of eosinophilic inflammation are likely to respond to ICS, but in the absence of airway eosinophilia, patients should not be treated with ever increasing doses of corticosteroids.

Those with persistent eosinophilia despite being treated with inhaled or oral corticosteroids are at risk of severe exacerbations and airway remodeling and should thereforebe monitored more intensively. Several studies have shown that late-onset eosinophilic asthma is associated with more severe disease than non-eosinophilic asthma. High levels of eosinophils in sputum and bronchial biopsies are associated with poor asthma control, more severe asthma and fatal or near-fatal asthma attacks. In a biopsy study of patients with severe asthma, it appeared that the patients who had eosinophilic inflammation despite systemic corticosteroids had an almost 20 times higher odds of being intubated than those without eosinophilic inflammation. In patients who died from asthma, significantly more eosinophils were found in large and small airways, as compared to biopsies from patients with milder exacerbations [1]. Significant heterogeneity in response to therapy exists even within eosinophilic asthma, as exemplified by patients with eosinophilic asthma that is refractory to medical therapy with steroids [10]. Some patients might respond better to one biologic agent than another or not at all. The reasons for these differential responses are unknown [11]. The current hope is that a better understanding of asthma heterogeneity will allow us to select treatments based on the greatest likelihood of therapeutic response, thereby improving asthma control and quality of life for patients [12].

HOW TO DIAGNOSE EOSINOPHILIC ASTHMA IN CHILDREN

Traditionally, airway biopsies or bronchoalveolar lavage through bronchoscopy is considered as the gold standard for assessing airway inflammation [13] but the invasiveness of these methods limits their use in clinical practice. Therefore, there has been great interest in methods to assess airway inflammation noninvasively and in a convenient and inexpensive way. Induced sputum analysis is a less invasive alternative to bronchoscopy for assessing airway inflammation in children with mild to moderate asthma. The most common and best validated method to diagnose eosinophilic asthma is

detection of eosinophils in induced sputum [14]. Sputum induction was developed in the late 1980s for diagnosis of *P.jirovecii* pneumonia among immunocompromised adults. Induced sputum is a relatively safe, semi-invasive method which can be generally performed well by school-age children. Among asthmatic children >6 years undergoing sputum induction, 76-100% of patients successfully complete the procedure [15]. Evaluation of sputum allows direct evaluation of bronchial inflammation, brings data on early inflammatory response and allows the identification of different phenotypes of asthma. A phenotype involves the complex interaction of many genetic and environmental factors in conjunction with observable characteristics, such as lung function (for asthma) or specific IgE responsiveness to particular allergens. The eosinophilic asthma phenotype appears to be more common in patients with adult-onset asthma than in those with childhood-onset asthma [1].

RELATIONSHIPS OF SPUTUM EOSINOPHIL WITH OTHER BIOMARKERS

Biomarkers for type 2 (TH2) inflammation, including FENO (fractional exhaled nitric oxide) levels and blood/sputum eosinophilia and serum periostin levels, have helped identify a type 2 molecular phenotype of asthma. Patients with eosinophilic asthma should ideally be diagnosed by analysing sputum samples. However, sputum induction is not easy to perform in routine clinical practice and requires access to specific laboratories with trained personnel. Therefore, the use of several alternatives to sputum cell counts, including peripheral blood eosinophils, FENO and serum IgE have recently been evaluated in a systematic review. The results show that overall, blood eosinophils, FENO and IgE have only moderate accuracy to distinguish between patients with and without airway eosinophilia [16]. Study of Hastie et *al* found that FENO levels, IgE levels, and blood eosinophil are poor surrogates for accurately predicting sputum eosinophil percentages [17].

Because sputum eosinophil measurement is not generally available, subsequent studies identified ''eosinophilic (type2–high) asthma'' in relation to blood eosinophil counts. The use of blood eosinophils to identify sputum eosinophilia is still debated because of the relatively high false-negative and false-positive rates [17]. Study of Palomino et *al* suggested that eosinophils in sputum were the most accurate marker of inflammation of the airways, since eosinophils in peripheral blood can be elevated in other conditions such as rhinitis and eczema and are not related with asthma severity [2]. Merely for the diagnosis of "eosinophilic asthma", one single measurement of blood eosinophilsdoes not seem to be of great value. The most important rolefor blood eosinophils is probably its role in identifying patientswho are likely to respond to treatment with the new biologicalagents against type 2 inflammation [18]. However, blood eosinophils seemto be less suitable to monitor treatment response.

CURRENT APPLICATION OF SPUTUM EOSINOPHIL

Although it had been reported for years that corticosteroid responses were dependent on lung eosinophils, asthma phenotype was rarely considered when planning therapy. With the continued presence of severe refractory asthma and the emergenceof new biologics, there is a resurgence of interest in identifying treatment-responsive phenotypes. Sputum induction and differential cell count, unfortunately, are available only in a limited number of specialized centers. Although numerous studies in adults have shown induced sputum analysis to be a useful and safe tool in the evaluation of asthma, very few studies have evaluated this tool inchildren. Despite the relative safety and tolerability ofsputum induction in children, it has several potential limitations. First, the procedure requires a substantial amount of time to perform and process (average of 3 hours). Second, significant technical support and expertiseare required to process, stain, and interpret the samples. This also means that theresults are not readily available. Third, some children arenot able toprovide technically adequate or acceptable samples. Finally, fewpatients can develop bronchospasm despite pretreatment [5].

There are no consensus guidelines from the large respiratory societies that advocate foruse of biomarkers in guiding asthma management [19]. NHLBI—National Asthma EducationPrevention Program states that "biomarkers, such as sputum eosinophils and FENO, are increasingly used in clinical research and will require further evaluation in adults and children before they can be recommended as a clinical tool for routine asthma management"[20]. Also, Global Strategy for Asthma Management and Prevention (GINA) does not make a recommendation about measurement of sputum eosinophilia or FENO [21]. On the other hand, the British Thoracic Society (BTS) and ScottishIntercollegiate Guidelines Network (SIGN) guidelines recommend clinicians "considermonitoring induced sputum eosinophil counts to guide steroid treatment" in patients with "difficult asthma" [22]. More precisely, International ERS/ATS Guidelines suggest that in adults with

severe asthma, treatment should be guided by clinical criteria and sputum eosinophil counts in centers experienced in using this technique rather than by clinical criteria alone [14].

In Viet Nam, hardly no clinical setting has applied sputum eosinophil in monitoring asthma because of strict requirements of the method. Thus, here is really avoid space for Vietnamese researchers, especially pulmonologists, that they need to compensate it in the future.

CONCLUSION

Sputum eosinophil, being a marker of airway inflammation, can serve as a tool for assessing severity and response to treatment in asthma patients. Sputum induction has been used as a surrogate measureof airway inflammation.

However, only a few studies have evaluated the value of induced sputum analysis in children with asthma. Combinations of two or more biomarkers could increase sensitivity and specificity for detection of eosinophilic airway inflammation. Given the genetic and molecular heterogeneity of asthma, the identification of that perfect biomarker to provide comprehensive data on the disease seems unlikely. More likelyit is to identify a set of markers able to constitute a clue for diagnostic, therapy and prognostic and able to identify those individuals who are at risk of developing asthma [23].

CONFLIT OF INTEREST

The authors declare no conflit of interest.

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