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Case report

Persistent FeNO Elevation Despite Clinical Control in Pediatric Allergic Asthma: a Case Report Emphasizing the Impact of Allergic Rhinitis

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ABSTRACT

Introduction. FeNO is a non-invasive biomarker of eosinophilic airway inflammation increasingly used during pediatric asthma follow-up, although it may not always correlate with symptoms and lung function.

Materials and methods. We describe a 12-year-old boy with allergic asthma and allergic rhinitis in outpatient follow-up.

Results. Despite good clinical control and normal spirometry, FeNO remained elevated; optimization of nasal therapy led to FeNO reduction.

Discussion and Conclusions. FeNO should be interpreted within the global clinical context to avoid overtreatment, thereby supporting the united airways disease concept.

KEYWORDS: FeNO, paediatric asthma, allergic rhinitis, united airways disease

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INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by bronchial hyperresponsiveness, variable airflow obstruction, and recurrent respiratory symptoms such as wheezing, cough, and dyspnea [1]. In childhood, it represents one of the most common chronic respiratory disorders and a major cause of morbidity. Recent global estimates indicate that asthma affects approximately 300 million people worldwide and remains the most common chronic disease in children, affecting nearly 1 in 10 children globally. A recent meta-analysis reported an overall prevalence of 10.2% (95% CI 9.5-11.0%) among school-age children, with substantial geographic variability across regions [2,3].

Current management of asthma is mainly guided by symptom burden, exacerbation history, and lung function. However, these parameters do not always accurately mirror the degree of ongoing eosinophilic airway inflammation, potentially leading to undertreatment or overtreatment [1,4].

Fractional exhaled nitric oxide (FeNO) is a rapid, reproducible, and non-invasive biomarker of T2-high eosinophilic airway inflammation and is currently considered one of the most extensively studied tools for non-invasive assessment of pediatric airway inflammatory burden [4,10]. Its biological rationale relies on the upregulation of inducible nitric oxide synthase (iNOS) within bronchial epithelial cells under the stimulus of T2 cytokines, particularly

interleukin (IL)-13, resulting in increased production of nitric oxide that is detectable in exhaled breath [4].

Recent biomarker-based analyses in Italy further emphasized that FeNO, together with blood eosinophils and IgE, represents a key tool for phenotypic characterization and longitudinal therapeutic monitoring in severe pediatric type 2 asthma. Notably, FeNO is also emerging as a valuable tool to guide selection of biologic therapy in patients with severe T2-high asthma, and especially in identifying candidates for anti-IL-4Rα agents such as dupilumab [10].

According to current American Thoracic Society recommendations, FeNO values in children are interpreted as low when <20 ppb, intermediate between 20 and 35 ppb, and high when >35 ppb (Tab. I) [5]. Nevertheless, FeNO levels may be influenced by several host- and environment-related variables, including age, atopy, allergic rhinitis (AR), environmental allergen exposure, dietary factors, and, to a lesser extent, anthropometric characteristics, which may create discrepancies between biomarker levels and actual asthma control [4,9].

Herein, we describe the case of a clinically controlled asthmatic child with persistently elevated FeNO, in whom optimization of upper airway treatment led to biomarker normalization without intensification of asthma therapy.

CASE PRESENTATION

A 12-year-old boy had been followed in our pediatric allergy outpatient clinic for approximately three years for allergic asthma and concomitant AR.

At initial evaluation, when the patient was 10 years old, he presented with recurrent wheezing episodes, mainly occurring during winter and spring, associated with seasonal nasal symptoms. Skin prick testing documented sensitization to dog dander, grass pollen, and olive pollen. Baseline spirometry revealed a positive bronchodilator response, with an FEV_1 increase >12% after administration of 400 µg salbutamol, while FeNO measurement showed a value of 35 ppb.

TABLE I. Factors that influence FeNO levels (adapted from Loewenthalet al., 2022) [4].

FeNO levels reduced with:	FeNO levels increased with:
Corticosteroids (inhaled and/or oral)	Nasal polyps
Bronchoconstriction	Allergic rhinitis
Obesity	Rhinovirus in healthy people
Smoking	Morning (diurnal variation)
Reduced age (children)	Height
	Consumption of dietary nitrates (including caffeine, lettuce, radishes

In accordance with current international recommendations for asthma management, treatment with low-dose inhaled corticosteroids (ICS) administered with a spacer was initiated, together with oral antihistamines and repeated 3-week courses of intranasal mometasone for AR [1].

At the 6-month follow-up visit, the patient reported marked clinical improvement with no further wheezing episodes, and spirometric parameters normalized. Asthma control was assessed using the Childhood Asthma Control Test (c-ACT) with a value of 24, which confirmed well-controlled disease (score ≥ 20). However, FeNO values remained persistently >20 ppb.

After approximately 18 months, the child remained free from asthma exacerbations and had spontaneously discontinued ICS therapy for nearly 6 months. The clinical evaluation was normal and lung function testing remained within normal limits, bronchodilator reversibility was negative, although FeNO was still elevated at 27 ppb.

A more detailed anamnesis revealed poor adherence to ICS treatment and continued daily exposure to a domestic dog.

Considering the absence of lower airway symptoms, normal spirometry, and evidence that FeNO should not be interpreted in isolation from the clinical-functional setting, no escalation of asthma therapy was undertaken. Instead, treatment was focused on upper airway disease through regular nasal irrigations and repeated 3-week courses of intranasal mometasone spray over 2 months [4,5].

At reassessment 3 months later, the patient reported clear improvement in rhinitis symptoms, no asthma instability, and FeNO had decreased to 16 ppb. All FeNO measurements throughout follow-up were performed using the same electrochemical device (HYPAIR FeNO®, medisoft) in the morning, prior to any bronchodilator use, in accordance with American Thoracic Society standardization guidelines, to minimize intra-individual variability [5].

DISCUSSION

The present case demonstrates a clinically meaningful discordance between FeNO values and conventional indicators of asthma control. FeNO is widely recognized as a surrogate marker of eosinophilic T2 airway inflammation rather than a direct marker of airflow limitation or bronchial obstruction [4,5]. In bronchial epithelium, T2 inflammation induces production of IL-4, IL-5, and IL-13, which orchestrate the eosinophilic inflammatory milieu characteristic of allergic asthma [15]. Among these cytokines, IL-13 in particular, through the JAK/STAT pathway, upregulates iNOS, which promotes the conversion of L-arginine into nitric oxide (NO) [4]. Elevated FeNO values have also been associated with corticosteroid responsiveness and increased risk of subclinical persistent airway inflammation during follow-up [4,10].

In our patient, persistent FeNO elevation in the setting of complete lower airway clinical and functional control suggested that the biomarker was not reflecting active uncontrolled bronchial disease, but rather persistent T2 inflammatory activity involving the upper airways.

This hypothesis is strongly supported by two elements: the coexistence

of poorly controlled AR and the persistent domestic exposure to dog dander, in the context of documented inhalant sensitization on allergy testing [13].

AR is known to significantly influence FeNO values, even in patients without overt bronchial symptoms, due to the close inflammatory interplay between the upper and lower respiratory tract; moreover, recent consensus documents further emphasize that inadequate AR control may negatively affect lower airway inflammatory burden and asthma monitoring [8,9,14]. Moreover, recent pediatric case-based evidence has shown that FeNO values may rapidly decrease after optimization of anti-inflammatory treatment, paralleling clinical and functional improvement, thus confirming its role as a dynamic biomarker of airway inflammatory activity [11].

The marked reduction in FeNO following optimization of ICS therapy, without reintroduction of inhaled asthma treatment, further supports the concept of the united airways disease, according to which allergic inflammation should be considered as a continuum involving both nasal and bronchial mucosa [7,8].

This observation also carries a relevant therapeutic implication. Reliance on FeNO alone could have led to unnecessary re-escalation of ICS therapy. Current evidence suggests that biomarker-guided therapeutic decisions should always be integrated with symptom control and objective lung function assessment rather than based on isolated inflammatory markers alone [4,6,12]. In parallel, elevated FeNO values may show limited specificity for active asthma when interpreted outside the broader clinical context, largely because concomitant allergic comorbidities may generate false-positive inflammatory signals [4,9].

Finally, the case reinforces the broader concept that FeNO should be regarded as a complementary inflammatory biomarker within a multidimensional management strategy rather than as an isolated therapeutic trigger. Furthermore, follow-up visits every 3–6 months appear appropriate in this type of patient. In cases of persistent biomarker-clinical discordance, it is crucial to assess therapeutic adherence, implementation of environmental prophylaxis measures, and reduction of exposure to relevant risk factors. Because FeNO rapidly responds to corticosteroid exposure, serial measurements during follow-up may also provide indirect information regarding the effectiveness of and adherence to anti-inflammatory treatment [4,12].

This concept is consistent with recent Italian evidence supporting the simultaneous and repeated assessment of FeNO and other type 2 biomarkers to optimize selection of biologic treatment and monitor treatment response over time [10].

It is important to recognize some inherent limitations of the single-case study design, as the results obtained from a single patient cannot be generalized to larger pediatric asthma populations. In this specific case, although the temporal association between optimized intranasal therapy and FeNO reduction is clinically relevant, causal inference remains limited; spontaneous fluctuations in disease, seasonal variations in allergens, and improved allergen avoidance represent potential confounding factors that cannot be formally ruled out. Nonetheless, the case provides a clinically significant example of discordance between biomarkers and clinical data and its management in pediatric allergic asthma.

CONCLUSION

This case report highlights several clinically relevant messages:

- FeNO reflects eosinophilic T2 airway inflammation rather than bronchial obstruction [4,5];
- Persistent elevation of FeNO may occur despite apparent asthma remission [4,5];
- AR and continuous allergen exposure are major confounders influencing FeNO values [8,9];
- Isolated FeNO elevation should not automatically prompt escalation of asthma therapy [4,6,12];
- Adequate treatment of upper airway inflammation may significantly improve lower airway inflammatory biomarkers, supporting the united airways concept [7,8,14].

A holistic interpretation of FeNO, integrated with clinical, functional, and environmental assessment, is therefore essential during follow-up for pediatric asthma.

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Not applicable.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of University of Campania Luigi Vanvitelli (approval number: 0029524/i). Written informed consent was obtained from the parents or legal guardians of all participants.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

Authors' contributions

Conceptualization: S.C and M.M.d.G. Methodology: S.C. Investigation: S.C. Writing-Original Draft: S.C. Writing-Review & Editing: S.C., A.K, G.D., C.G., N.M., G.I., F.D., C.I., M.M.d.G. Supervision: S.C., A.K, G.D., C.G., N.M., G.I., F.D., C.I., M.M.d.G. Project Administration: S.C and M.M.d.G.

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