

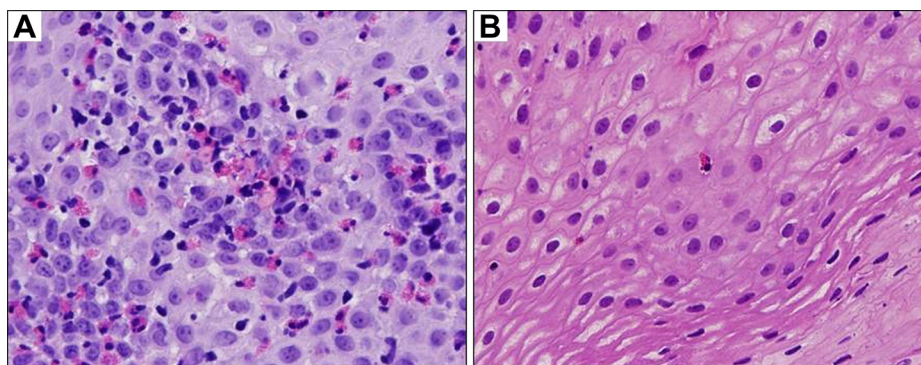


Figure 1. Esophageal mucosal biopsy showing remarkable eosinophilic infiltration before swallowed budesonide treatment (A) and markedly decreased eosinophils 2 years after treatment with swallowed budesonide (B).

positive to garlic and cottonseed, which we initially did not think clinically relevant until the patient admitted his frequent consumption of garlic-containing foods. This demonstrates the crucial role of performing skin testing in this case. Third, his esophageal mucosa appeared healthy on endoscopy; yet, a biopsy revealed eosinophils. Hence, a normal appearance of the mucosa should not deter from a biopsy examination.¹ Fourth, garlic as a spice would not have been identified if the evaluation was by the “six-food elimination diet.”^{2–4} Fifth, the common practice of testing (skin prick testing, patch, or specific IgE) to a limited number of foods would not have identified the culprit, particularly because no food was suspected by the history. Our patient may be the first documented case of garlic-related EoE. With the increasing use of various spices, attention should be given to such ingredients that are often hidden or unsuspected by patients.¹⁰

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The nebulous diagnosis of type III hereditary angioedema

I am concerned about the growing trend of assigning a diagnosis of type III hereditary angioedema (HAE) to patients in what still remains an ill-defined condition. In well-described cases of type III HAE, patients have a family history of angioedema without urticaria, there is a marked female preponderance with estrogenic triggers of attacks, and characteristic mutations in the factor XII gene that result in activation of the prekallikrein–bradykinin system.^{1,2} For instance, a case recently published by Ebo et al³ describes a patient with angioedema without urticaria, a normal level of C1 inhibitor and function, and no mutation in the factor XII gene. Although this patient may still have this condition, given the absence of the hallmarks of type III HAE, a more appropriate diagnosis is non-histaminergic idiopathic angioedema. This condition is also characterized by angioedema without urticaria and normal C1 inhibitor function.⁴

Further research may reveal different pathogenic mechanisms in non-histaminergic idiopathic angioedema in what is likely to be a heterogeneous disorder from which more robust diagnostic criteria

can be formulated and specific targeted therapies can be developed and administered. Type III HAE may be an entity that belongs to this group of conditions. However, the role of particular factor XII mutations needs to be verified, because there is no evidence of enhanced activation of the factor XII–prekallikrein–bradykinin forming cascade in patients with these mutations.⁵ The precise role of estrogen also needs to be further elucidated. It is intriguing that it increases levels of factor XII and decreases levels of C1 inhibitor and bradykinin-degrading enzymes.^{6,7} However, its effect on the bradykinin levels is not sufficient to cause the severe episodes of angioedema involving the gastrointestinal tract and upper airways observed in cases of type III HAE. Further studies may better define type III HAE, but until then, the term *non-histaminergic idiopathic angioedema* is preferable in those with histamine-resistant angioedema, normal C1 inhibitor function, absence of family history, and where no mutations are detected in the factor XII gene.

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Persistent specific nasal reactivity to occupational allergens after removal from exposure

The outcome of occupational rhinitis (OR) confirmed by specific inhalation challenge (SIC) after removal from exposure is unknown. Paralleling occupational asthma (OA), it is plausible that some subjects continue manifesting rhinitis symptoms despite removal from exposure whereas others may become asymptomatic.¹ Besides, whether loss of specific nasal reactivity occurs with time after cessation of exposure is unknown. Presumably, further occupational exposure in sensitized subjects may exacerbate rhinitis symptoms.

SIC is regarded as the gold standard for confirming the diagnosis of OR. However, there is some concern about its value as diagnostic tool because the methodology to assess nasal responses during challenge lacks standardization.² In this clinical case series, we assessed the persistence of specific nasal reactivity after removal from exposure as well as the ability of SIC to reproduce nasal responses over time by examining the nasal congestive response to SIC on 2 occasions, namely, at the time of diagnosis and after a mean follow-up of 28 months. The study group consisted of 5 patients (4 males) with a confirmed diagnosis of allergic OR, aged 36 to 58 years at follow-up investigation. All subjects were nonsmokers or ex-smokers. All were atopic, defined as at least 1 positive reaction to common inhalants as well as a positive reaction to the agent causing OR. After initial diagnosis, all subjects stopped exposure to causal agents because most of them (4 subjects) had associated OA, and 1 subject retired from working. Informed consent was obtained from all subjects.

On both occasions, subjects underwent standardized SIC as previously described with control and specific agents on consecutive days.³ The first day they were exposed to a sham substance (lactose) and the next day to flour (4 patients) and to tea (1 patient) by recreating working conditions in an isolated exposure chamber according to international recommendations.⁴ The total exposure time was 30 minutes on both days. Total nasal volume and nasal symptoms were measured before and serially for 6 hours after exposure by acoustic rhinometry and a visual analog scale, respectively. Nasal response was recorded as the greatest decrease in total nasal volume between 2 and 5 cm into the nose (Vol₂₋₅) (eMethods). It was expressed as a percentage of the baseline Vol₂₋₅ (nasal response = fall in Vol₂₋₅/baseline Vol₂₋₅ × 100). For the interpretation of SIC results, a decrease in Vol₂₋₅ of 30% or more from baseline values represented a clinically significant nasal congestive response.^{3,5}

At follow-up, subjects reported significant improvement of rhinitis symptoms, and they were not taking medications for nasal symptoms. As shown in eTable 1, prechallenge values of Vol₂₋₅

were lower at follow-up compared with those at diagnosis in all subjects. On both occasions, the challenge with the control agent did not induce nasal symptoms or clinically significant changes in Vol₂₋₅ in all subjects (Fig 1A). By contrast, the challenge with the causal agent induced clinically significant changes in nasal volume in both occasions manifested by a percentage fall in Vol₂₋₅ from baseline values of at least 30% in all subjects (Fig 1B and eTable 1). For the whole group, the average maximum percent (standard deviation) decrease in Vol₂₋₅ from baseline values at diagnosis and follow-up was –42% (13%) and –38% (11%), respectively. Individual results are shown in Figure 1B.

At diagnosis, all subjects experienced isolated immediate rhinitis reactions after challenge. At follow-up, 3 subjects experienced immediate reactions, and 2 showed isolated late reactions (eTable 1).

Reduction or avoidance of exposure to occupational allergens remains a key objective in the management of OR.² The outcome of OR after removal from exposure has not been specifically investigated. There is some evidence from follow-up studies involving OA patients with associated work-related rhinitis symptoms showing that the severity of rhinitis symptoms improves after reduction of exposure to platinum salts⁶ and latex.⁷ However, to our knowledge, no study has been conducted examining the outcome of specific nasal reactivity to occupational allergens after removal from exposure. This study showed persistence of specific nasal reactivity 2 years or more after removal from exposure in 5 patients with allergic OR. The study also showed that the SIC method with occupational allergens repeated over time is reproducible in sensitized OR patients.

Similar studies have not been conducted to make comparisons. However, a comparable study conducted in our hospital assessing the outcome of specific bronchial reactivity to high-molecular-weight agents in OA patients showed persistence of specific bronchial reactivity (estimated as the duration of exposure that induced a 20% decrease in forced expiratory volume in 1 second) to these agents in most but not all subjects.⁸ In our study, we observed persistence of specific nasal reactivity several years after removal from exposure in all subjects. However, because of the small numbers of patients, we cannot speculate about potential differential physiologic responses between the upper and lower airways. Likely the SIC investigation of larger number of patients with OR may identify cases without persistence of specific nasal reactivity.

We believe that the observed results during both visits are accurate. The ability to accurately reproduce the challenge exposure conditions on both occasions was a key feature to achieve the objectives of the study. The SIC method has been proposed as the gold standard tool to investigate occupational respiratory diseases^{2,9,10} because it reproduces working exposure conditions and besides, the means to assess the nasal congestive response during SIC including acoustic rhinometry have recognized validity

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