



## Challenging Clinical Cases

# Sublingual immunotherapy and omalizumab cured allergic chronic rhinosinusitis and asthma: coincidence or synergistic effect?

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## Introduction

A 21-year-old man with chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) and comorbid asthma for the last 10 years was referred for allergy evaluation. The diagnosis of CRSwNP was based on the patient's symptomatology (nasal congestion, atypical facial pain, hyposmia/anosmia), nasal endoscopy, and the objective evidence of mucosal inflammation (complete opacification of the paranasal sinuses on computed tomography [CT] scan that revealed marked mucosal thickening with partial opacification of right maxillary sinus, near complete opacification of left maxillary sinus, and complete opacification of right and left frontal and anterior ethmoid sinuses, and right and left osteomeatal complexes with associated bone remodeling). The Lund-Mackay Sinusitis Staging Score (LM) for this CT study was for the right sinus 7 of 12, for the left sinus 10 of 12, and the total score 17 of 24 (Fig 1).

Chronic rhinosinusitis is defined as an inflammatory disorder of the mucosa of the nasal passages and the paranasal sinuses that lasts for at least 12 weeks with<sup>1–3</sup>:

I. relevant symptomatology or signs with at least 2 of i) nasal obstruction, ii) facial pain/pressure/fullness, iii) hyposmia/anosmia, and iv) mucopurulent drainage; and: II. objective evidence of mucosal inflammation: at least 1 of i) polyps in the nasal cavity or the middle meatus, ii) edema in the middle meatus or anterior ethmoid region, and iii) purulent mucus.

Based on these symptoms and signs, the differential diagnosis of CRS includes syndromes with facial pain (eg, migraine headaches), rhinitis without sinusitis syndromes, laryngopharyngeal reflux, olfaction disorders (eg, anatomic abnormalities, prior sinus surgery, head trauma), ciliary dyskinesia, and immune deficiency.

Two subtypes of CRS comprise distinct clinical syndromes: i) CRS without nasal polyposis, and ii) CRSwNP, accounting for 25% to 30% of all CRS cases.<sup>4</sup>

Disorders that are associated with CRSwNP and should be additionally considered in the differential diagnosis include: i) allergic fungal rhinosinusitis, ii) aspirin-exacerbated respiratory disease, iii) vasculitis, iv) cystic fibrosis, and v) idiopathic nasal polyps.

The self-reported prevalence of CRS ranges around the world between 5% and 15% of the general population. This percentage seems to be an overestimation, because the doctor-diagnosed CRS is only 2% to 4%.<sup>2</sup> Although CRS can affect all ages, it is typically diagnosed in middle-aged adults.<sup>5</sup>

Approximately 20% of CRS patients have asthma, and up to 70% of patients with asthma have CRS symptoms and signs.<sup>6</sup>

Asthma is reported to occur in 26% to 48% of patients with CRSwNP, whereas among all asthma patients, CRSwNP occurs in 7%.<sup>2,7</sup>

At least 3 mucus samples at different time points were negative for fungal stain and fungal culture. The patient had no history of unusual or excessive infections outside of the sinuses, and no nonsteroidal anti-inflammatory drug (NSAID)–related respiratory disease exacerbation. Measurement of serum levels of immunoglobulin (Ig) G, IgA, and IgM, and IgG subclass levels were within normal range.

Skin prick testing to common environmental allergens indicated sensitization to *Alternaria alternata*, grass pollen (cocksfoot, festuca, ryegrass, timothy, meadow), and *Parietaria judaica/officialis* pollen.

Up to 80% of CRS patients are sensitized to at least 1 aero-allergen. Most of them are polysensitized, having very often at least 1 perennial sensitization.<sup>8</sup> The percentage of CRSwNP patients with allergic rhinitis (AR) seems to be similar to that of the general population (0.5%–4.5%).<sup>2</sup>

Control of his baseline respiratory symptoms was assessed with the Rhinitis Control Assessment Test (RCAT, RCAT<sub>baseline</sub> = 12) and the Asthma Control Test (ACT, ACT<sub>baseline</sub> = 21). At the time of the first evaluation, he was using mometasone furoate nasal spray, 100 µg/per nostril twice daily, and cetirizine tablets 10 mg once daily. His forced expiratory volume in the first second (FEV<sub>1</sub>) FEV<sub>1baseline</sub> was 79% on the fixed-dose inhaled corticosteroid and long-acting

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**Disclosures:** none.

**Funding Sources:** none.

<https://doi.org/10.1016/j.anai.2019.08.010>

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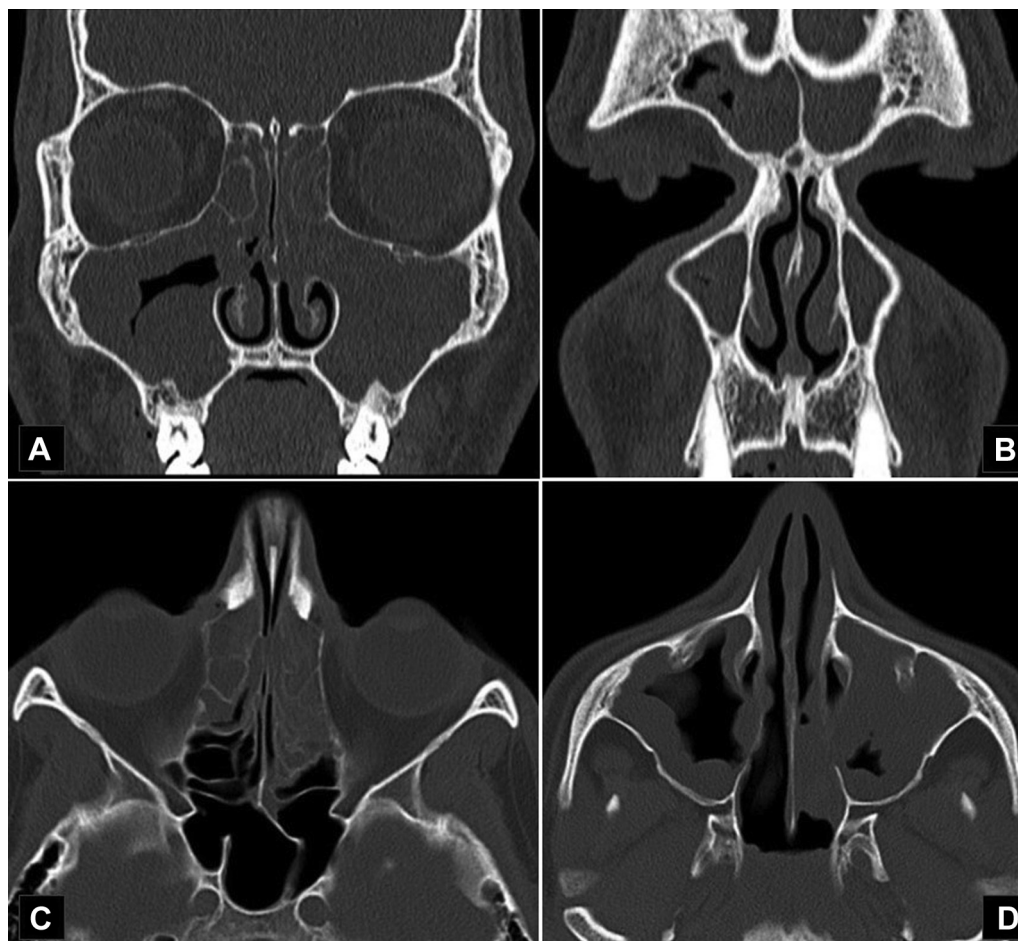


**Figure 1.** Coronal (A, B) and axial (C, D) sinus computed tomography (CT) without contrast enhancement, bone algorithm. Marked mucosal thickening with partial opacification of the right maxillary sinus, near complete opacification of the left maxillary sinus, and complete opacification of right and left frontal and anterior ethmoid sinuses, and the right and left osteomeatal complexes with associated bone remodeling. The Lund-Mackay Sinusitis Staging Score for the first CT study (December 2012) is for the right sinus 7 of 12, for the left sinus 10 of 12, and total score 17 of 24.

$\beta$ -agonist (ICS/LABA) combination budesonide + formoterol (320 + 9)  $\mu$ g twice daily and montelukast 10 mg once daily. At least 3 times per year he had asthma exacerbations that needed a short oral corticosteroid course, at least 2 years before the initial assessment. His exacerbations were associated with his sensitization profile, occurring every August, late autumn, and spring, substantially affecting his quality of life (QoL). Because of these characteristics, he was diagnosed on top of his asthma with perennial AR as an associated condition of his CRSwNP.

The RCAT is a patient-based tool used to measure control of rhinitis symptomatology. The RCAT was developed to identify patients whose nasal or ocular symptoms might warrant a change in therapeutic strategy or referral to an allergy specialist. A cut-point score of 21 or less can be used to identify patients who are experiencing uncontrolled rhinoconjunctivitis symptoms. Its minimal important difference score is 3. Its use provides an easy way to cross-sectionally record rhinitis self-assessment and longitudinally follow control fluctuations in association with rhinoconjunctivitis management.<sup>8</sup>

Similarly, the ACT is a patient-based questionnaire for self-assessment of asthma control. A cut-point score of 19 or less suggests uncontrolled asthma. Its minimal important difference score is also 3. Score across time provides a quantitative measure of asthma control in association with regular and as-needed asthma medication intake.<sup>9</sup>

Chronic rhinosinusitis significantly impacts the QoL in an amount that equals the QoL in patients with chronic heart and lung disorders.<sup>10</sup> At the same time, it has a considerable economic burden because of direct costs of medical consultations, diagnostic evaluations, and surgical procedures, and the indirect cost of absenteeism (the fact of being frequently away from work), presenteeism (the practice of coming to work despite illness), and reduced work and school productivity.<sup>11</sup>

Based on the sensitization profile, the patient started sublingual immunotherapy (SLIT) with standardized extracts of *Parietaria* spp (100%), *Alternaria alternata* (100%), and *mixed grasses* (100%) (SUBLIVAC, HAL Allergy, The Netherlands) on June 2013. During the first year of SLIT, the patient had 2 asthma exacerbations (November 2013 and March 2014) that needed a short course of oral corticosteroids, whereas SLIT had to be stopped for 2 weeks until complete asthma control was achieved. His rhinitis was improved with a median RCAT = 16 under the same medications.

Allergen immunotherapy (AIT) is indicated as a therapeutic option for treating moderate-to-severe AR, especially when it is not controlled with pharmacotherapy. Rhinitis has an impact on asthma control and severity. Therefore, it is suggested for patients with asthma associated with AR.<sup>12</sup> Poorly controlled or uncontrolled asthma is an absolute contraindication for allergen immunotherapy, which can be, however, resumed after asthma control has been obtained.<sup>13</sup>

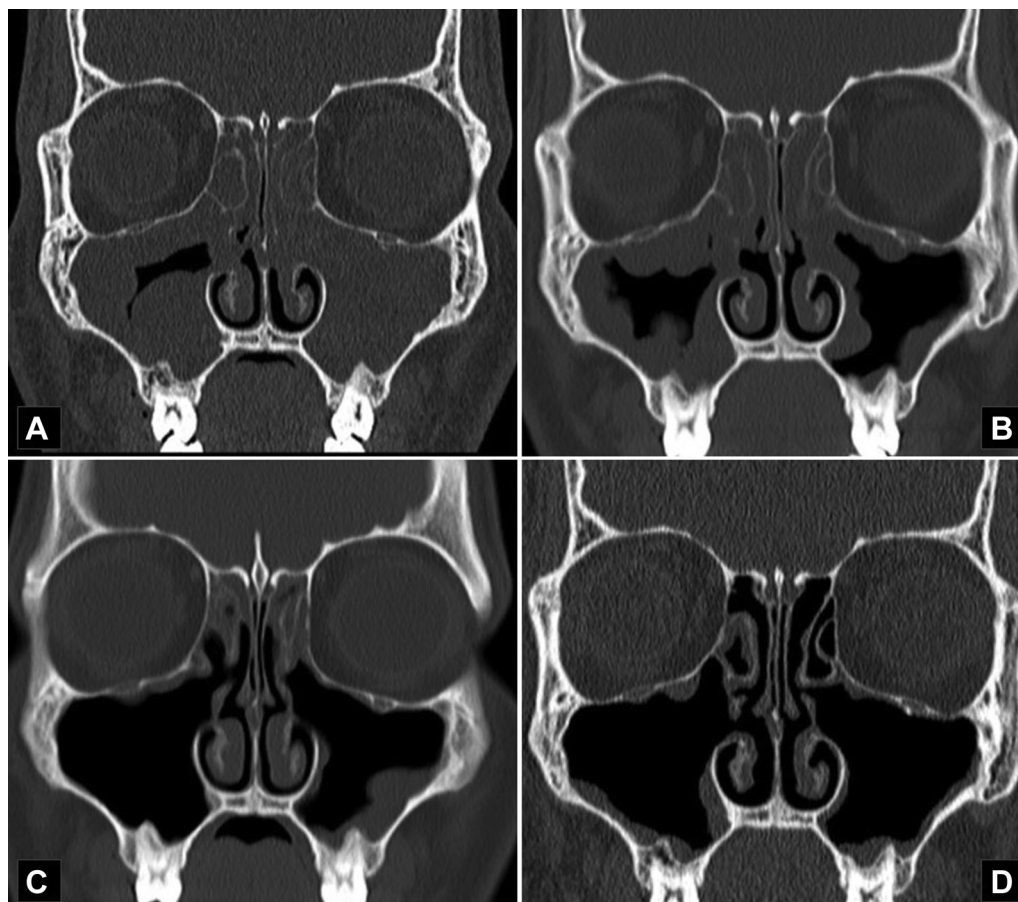


**Figure 2.** Coronal sinus computed tomography (CT), bone algorithm, showing remarkable resolution of mucosal thickening and opacification of maxillary, ethmoid sinuses, and osteomeatal complexes throughout 5 years (A: December 2012, B: March 2014, C: March 2015, and D: July 2016). The osteomeatal complex has been used as an anatomical landmark to ensure that the representative figures taken at different dates illustrate the same anatomical area. The associated Lund-Mackay Sinusitis Staging Score confirmed the response to therapy (with a total decrease from 17 to 8).

Because of his uncontrolled asthma, the initiation of omalizumab was decided as add-on therapy in April 2014. Based on his weight (83 kg) and his serum IgE levels (543 kU/l), he was administered 450 mg omalizumab every 2 weeks.

Omalizumab is a humanized monoclonal antibody directed against free circulating IgE, which prevents the binding of these antibodies with the high-affinity FcεRI receptors on mast cells, basophils, and dendritic cells. It is approved for use in patients from 6 years of age with severe, uncontrolled allergic asthma. Allergy has to be associated with a perennial aeroallergen.

Since the omalizumab initiation, the patient had no other asthma exacerbations, and 6 months after ( $FEV_1 = 83\%$ ,  $ACT = 24$ ), his treatment consisted only of budesonide + formoterol (160 + 4.5)  $\mu\text{g}$  twice daily for 6 more months. Afterward, ICS/LABA was replaced with inhaled budesonide 100  $\mu\text{g}$  twice daily for 6 more

months, when asthma and CRSwNP treatment stopped (monthly median, RCAT:27).

Although omalizumab has approved indication for perennial allergic asthma, clinical evidence suggests that it is expected to improve not only asthma symptoms but also symptoms from other related allergic multimorbidities that may co-exist in these patients, including allergic rhinitis and CRSwNP.<sup>14</sup>

Sublingual immunotherapy lasted for 5 years (until May 2018) and omalizumab for 3 years (until May 2017). Interestingly follow-up sinus CT scans showed a remarkable resolution of paranasal sinus opacification. The Lund-Mackay Sinusitis Staging Score was used to assess response to therapy (Fig 2). From May 2018 until now (May 2019), the patient remains symptom-free with no need for rescue medication to alleviate either asthma or CRS symptoms.

## Commentary

Allergen immunotherapy is a unique and effective therapeutic option for allergic disorders, affecting the specific immune response to allergens themselves at various levels, thus resulting in symptom relief of AR and as a consequence to asthma.<sup>15</sup> However, most studies supporting AIT as an option excluded patients with comorbid CRS attributed to environmental allergens, thereby precluding any conclusions regarding the effect of AIT on CRS outcomes. Only a few studies have evaluated AIT in

atopic CRS patients, and only 1 systematic review analyzed its efficacy in these individuals.<sup>16</sup> One study suggested that in randomized clinical trials (RCTs), a significant reduction in symptom scores occurred in patients receiving adjuvant immunotherapy compared with standard medical treatment, and that improvements also were noted in endoscopic and radiographic parameters. Unfortunately, the generalizability of these results was limited by the quality of the available evidence and the fact that

no studies were found to evaluate the effectiveness of SLIT specifically.<sup>16</sup>

On the contrary, an abundance of recent literature concerns biologic therapy as a potentially significant therapeutic alternative. A recent prospective study, taking the ‘1 airway concept’ into consideration, showed that omalizumab treatment for severe allergic asthma also improved coexistent CRSwNP.<sup>17</sup> Moreover, another systematic review and meta-analysis concluded that anti-IgE therapy reduced the nasal polyp score in patients with severe comorbid asthma, although only 5 studies fulfilled their eligibility criteria.<sup>18</sup> These results were in line with those of another systematic review in 2017 on all biologic agents tested on CRSwNP. In this review, only RCTs were included, and although the need for further larger, well-designed RCTs was stressed, omalizumab was again highlighted as a promising alternative option for a subgroup of patients with asthma.<sup>19</sup>

## Conclusion

In summary, combined AIT and omalizumab in the appropriate patients may be considered as an option to significantly reducing respiratory symptomatology, improving QoL, while minimizing the underlying inflammation, at least in the paranasal sinuses. In the presented case, the improvement was not only subjective but also objective, with radiologically CT scan findings depicting nearly

Based on the LM scores in our patient, SLIT did not seem to play a significant role in the improvement of the radiological findings (LM<sub>2012</sub>[before SLIT]: Right = 7 – Left = 10 – Total = 17, vs LM<sub>2014</sub> [9 months on SLIT]: Right = 11 – Left = 9 – Total = 20). However, a clinically significant improvement in the RCAT score was recorded ( $\Delta$ RCAT: 4, with a minimally important difference of 3). After omalizumab was started, not only were the symptoms almost completely resolved, but also the scores were significantly reduced (LM<sub>2015</sub> [after being a year under omalizumab]: Right = 5 – Left = 6 – Total = 11, and LM<sub>2016</sub> [2 years under omalizumab]: Right = 4 – Left = 4 – Total = 8). Omalizumab has been shown to play a significant role in reducing the LM score, but possibly SLIT can enhance this effect (or the opposite). Anyhow, the sustained effect after omalizumab cessation (May 2017 until May 2019) can only be attributed to SLIT.

complete remission of the mucosal abnormalities attributable to CRSwNP. Interestingly, the combined effect seems to be sustained, mainly suggesting an important role of AIT but possible synergistically with omalizumab. Further research and RCTs are needed to consider AIT as a potential add-on therapeutic option on top of omalizumab in respiratory allergies with evidence of CRSwNP.

## Acknowledgments

The authors thank Elpida Skouvaklidou for helping with data collection.

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