Concomitant cystic fibrosis and NSAID-exacerbated respiratory disease

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Rhinology 63: 4, 0 - 0, 2025
https://doi.org/10.4193/Rhin25.132

Received for publication:
March 6, 2025
Accepted: April 14, 2025

Associate Editor:
Ahmad Sedaghat

Dear Editor:

Chronic rhinosinusitis (CRS) with nasal polyps occurs in 6-57% of individuals with cystic fibrosis (CF) [(1)]. According to the EPOS 2020 guidelines, CF-related CRS is classified as secondary diffuse, non-type-2 CRS [(2)]. In contrast, most nasal polyposis in the general population is associated with primary, type-2 CRS. This educationally-oriented classification system facilitates the categorization of CRS in distinct groups. However, it may suggest that each type of CRS is caused by a single underlying mechanism, potentially leading clinicians to overlook that, in reality, multiple factors can drive CRS development. The incidence of CRS stemming from multiple etiologies remains currently underexplored. We report an illustrative case of a CF patient with concomitant NSAID-Exacerbated Respiratory Disease (NERD), necessitating two distinct targeted therapies to achieve effective symptomatic relief.

A woman diagnosed at birth with CF developed nasal polyps, nasal obstruction, and anosmia during childhood, which progressively worsened over time and became unbearable. Topical and systemic courses of corticosteroids, and functional endoscopic sinus surgery, at age 26, offered only short-lived relief. Pathological analysis of the operated polyps showed significant eosinophilia and Charcot-Leyden crystals. At age 28, she experienced two separate episodes of angioedema triggered by aspirin and ibuprofen, suggesting NERD. Progressive pulmonary deterioration eventually placed her on the lung transplant waiting list.

In 2022, at age 33, she began treatment with elexacaftor-tezacaftor-ivacaftor (ETI) therapy, a fixed-dose combination of modulators targeting the dysfunctional CF protein that is proven efficient for CF-related CRS patients [(3)]. She experienced substantial improvements across all CF symptoms shortly after. Consequently, she was taken off the transplant waiting list and could participate in sports again, which she had not done for years.

Despite the impressive general improvements, no noticeable effect on nasal polyposis and olfactory loss was observed. The persistence of these symptoms was attributed to a comorbid condition of NERD which led the patient to begin treatment with dupilumab, a monoclonal antibody blocking interleukins 4 and 13, known to be effective in treating type-2, eosinophilic inflammation such as NERD. Nasal breathing and smell recovered within less than 2 months after the first Dupilumab injection, as shown by her Nasal Obstruction Symptom Evaluation (NOSE) score [(4)] and Sniffin' Sticks [(5)] test results, respectively (Figure 1). Despite these symptomatic improvements, there was only a marginal decrease in the endoscopic polyp score, a phenomenon recently described [(6)].

Although we report only a single case, it highlights the possibility of two frequent causes of nasal polyps and anosmia occurring simultaneously. A few studies have investigated olfactory outcomes using psychophysical testing in CF patients with CRS after ETI therapy, reporting conflicting results, from no measurable improvement to significant gains [(3,7-9)]. This underscores the need to consider concomitant etiologies in patients who do not respond as expected. Given the relative prevalence of CF (1 in 2500 live births) and that of type-2 airway inflammation with polyps (4 % of the population), the coexistence of CF with type-2 CRS (such as NERD) might be more widespread than previously acknowledged. Considering the novel ETI treatments that are fundamentally changing the disease burden and life expectancy of CF patients, otorhinolaryngologists and pulmonologists should investigate other possible pathologies in "nasal" nonresponders to ETI who are otherwise well-responding CF patients.

Clinical cues such as good response to corticosteroids, elevated tissue and/or blood eosinophil counts, Charcot-Leyden

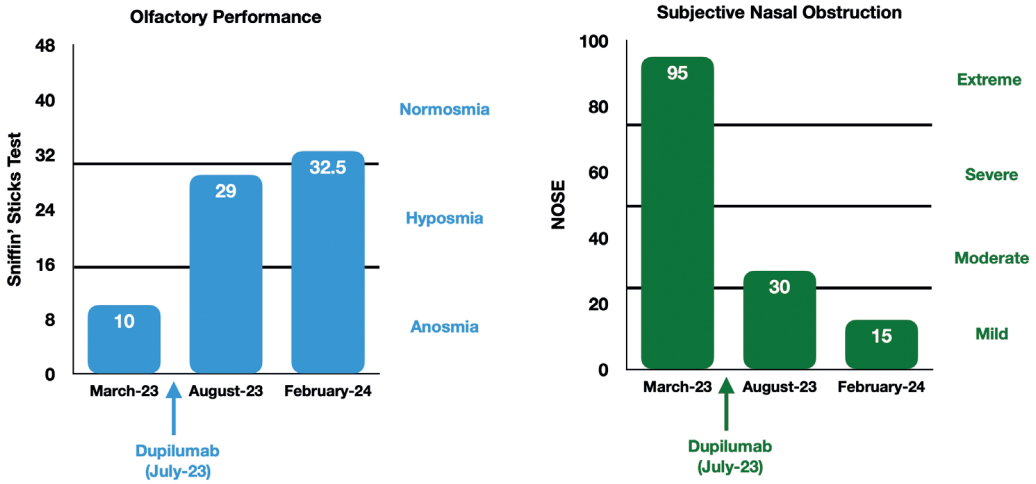

Figure 1. Clinical scores. The patient's olfactory function and nasal obstruction score were chronically impaired throughout her life, even despite elexacaftor-tezacaftor-ivacaftor therapy. However, they improved significantly and rapidly following the initiation of Dupilumab therapy.

crystals, episodes of NSAID-mediated angioedema and isolated nasal nonresponse to ETI therapy may suggest a secondary mechanism behind seemingly CF-related nasal polyps. With the increased use of biotherapies, we will likely gain more insight into patients with multiple simultaneous disease mechanisms underlying CRS.

Clinicians often face the heuristic challenge of attributing a patient's diverse symptoms to a single, established diagnosis. Although less common, a patient may have two or more reasons for having CRS with polyps. Based on our experience, we suggest investigating possible concomitant eosinophilic inflammation in CF patients.

List of abbreviations

CF: cystic fibrosis; CRS: chronic rhinosinusitis; EPOS: European position paper on rhinosinusitis and nasal polyps; ETI: elexacaftor-tezacaftor-ivacaftor; NERD: NSAID-exacerbated respiratory disease; NOSE: nasal obstruction symptom evaluation; NSAID: non-steroidal anti-inflammatory drugs.

Authorship contribution

SDLB: writing-original draft, visualization; JP: investigation; writing-review; YC: investigation; supervision; writing-review; BNL: writing-review, investigation, conceptualization, supervision.

Conflict of interest

None to disclose.

Funding

None.

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