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"Who is it?" in rhinology

When I was a kid, we used to play a game called "Who is it?". Two players each hold a platform with drawings of some twenty different persons. Each will have selected a card displaying one of them; the other has to find out which one it is by asking the right questions about gender, colour of hair, eyes or clothing, and the use of accessories such as glasses or a hat. Now, as an adult, I still get to play this game every time I have an outpatient clinic. By asking the right questions, I figure out whether a person has chronic rhinosinusitis (CRS) or not. As we have a very clear diagnostic construct for this disease (a certain combination of nasal complaints combined with abnormalities on nasal endoscopy or imaging for at least twelve weeks [1]), the game should be simple, right?

Unfortunately, it is not. As our understanding of the pathophysiology of CRS deepens, we find out that CRS itself merely is an umbrella term encompassing many diseases or subforms of CRS. It is like asking the question: "Does your character have blond hair?" and then thinking you have won the game, while in fact Eric, the blond man with the glasses and the beard is an entirely different character from Janet, who is blonde and wears earrings. We have to be more specific to understand what type of CRS our patient has, and, thus, what treatment is best advised. A major step in this direction is the classification of CRS as described in the latest version of the European Position Paper on Rhinosinusitis and Nasal Polyps [1]. Beyond the diagnostic construct of CRS, other items/questions need to be addressed: is it primary/secondary CRS, is it localized or diffuse, and what is the underlying endotype or mechanism?

With the advent of biological therapies, special emphasis is now placed on identifying patients with a type 2 inflammatory endotype. Important markers are interleukins 4, 5, and 13, eosinophils and immunoglobulin E (IgE). However, the determination of a type 2 profile in clinical practice is not as easy as asking your patient "Do you have a type 2 inflammatory endotype?". There are of course some strong indicators, such as the presence of comorbid asthma (especially if late-onset), sensitivity to non-steroidal anti-inflammatory drugs, anosmia, and a generally quick but short-lived response to oral corticosteroids. Still, the proof of the pudding is in the eating. As it is now, a type 2 profile can be established by determining a total IgE and/or eosinophils in blood. Eosinophils in nasal (polyp) tissue can also be used. Furthermore, it seems feasible to determine eosinophils in nasal fluid samples [2]. New biomarkers are being researched but are not yet readily available.

Last year, this journal published a meta-analysis by Toro et al., showing that there is a large variation between studies regarding the histopathologic methodology to determine eosinophilic (type 2) CRS [3]. In the previous issue, a comment on this systematic review was published [4], and a new comment is now published in the current issue, together with replies by Toro et al. to both. Apparently, the subject of "how and where to draw the line" for the level of tissue eosinophils as cut-off for type 2 is a hot topic!

Using blood eosinophils can also give problems. Values can vary over time, and are influenced by the (recent) use of oral corticosteroids. Furthermore, it is not necessarily a good predictor of treatment response: in a large cohort of patients receiving dupilumab, also those with low eosinophils responded well [5]. Does that mean that this drug also treats non-type 2 CRS, or is a single measurement of blood eosinophils not a reliable marker of type 2 disease?

Back to my game of "Who is it?". I have stopped being satisfied when having identified a patient as being blond (having CRS). Next-level gaming pushes us to look, ask, and investigate further. For now, we have to work with eosinophils and total IgE as tools alongside the right questions, while looking forward to coming upgrades of our armamentarium. So that we can become, in the words of my son, "pro-gamers"!

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References

1. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1-464.
2. Zhu Z, Wang W, Zhang X, Wang X, Zha Y, Chen Y, et al. Nasal fluid cytology and cytokine profiles of eosinophilic and non-eosinophilic chronic rhinosinusitis with nasal polyps. Rhinology. 2020;58(4):314-22.
3. Toro MDC, Antonio MA, Alves Dos Reis MG, de Assumpcao MS, Sakano E. Achieving the best method to classify Eosinophilic Chronic Rhinosinusitis: a systematic review. Rhinology. 2021;59(4):330-9.
4. Pan L, Liu Z. Classification of eCRS: Based on disease outcome or normal range?: Comment on Toro et al. Rhinology. 2022;60(2):159-60.
5. Fujieda S, Matsune S, Takeno S, Ohta N, Asako M, Bachert C, et al. Dupilumab efficacy in chronic rhinosinusitis with nasal polyps from SINUS-52 is unaffected by eosinophilic status. Allergy. 2022;77(1):186-96.