Colegio Mexicano de Inmunología Clínica A.C. | CMICA

Revista Alergia México

Original article

The pragmatic role of nasal cytology: a point-of-care testing to implement precision medicine in clinical practice

El papel pragmático de la citología nasal: una prueba en el punto de atención para implementar la medicina de precisión en la práctica clínica

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Abstract

Background: Precision medicine is an up-to-date strategy aimed at individualizing precise pathophysiological mechanisms. Thus, precision medicine is the basis for personalized medicine, inasmuch as it seeks to define the most appropriate treatment for each patient. Nasal cytology requires only an optical microscope, stains, glasses, and nasal cytology curettes. The procedure may last very few minutes using quick staining and, therefore, it can be considered a reliable point-of-care test in the office setting.

Methods: Cross-sectional study that included 5030 outpatients with nasal disorders: 2612 males and 2418 females, with a mean age of 36.8 ± 17.1 years, who were attended to within a 5-year period. The patients were subdivided according to skin prick-test and nasal cytology results into subjects with allergic rhinitis or non-allergic rhinitis. Cellular forms were further subdivided based on their cytotype: NARNE (> 50% of neutrophils with absence of spores and bacteria); NARES (> 20% of eosinophils); NARMA (> 10% of mast cells); and NARESMA (> 20% of eosinophils and > 10% of mast cells).

Results: 453 subjects (9%) had negative nasal cytology, 1056 (21%) had allergic rhinitis, 538 (10.7%) had NARES, 493 (9.8%) had nasal polyposis, 251 (5%) had rhinosinusitis, 221 (4.4%) had NARESMA 201 (4%) had infectious rhinitis, 131 (2.6%) had NARMA, 89 (1.8%) had NARNE, with the remaining subjects having a miscellaneous inflammatory/infectious profile.

Conclusions: Nasal cytology provides quick information about phenotype and endotype and can be repeated during follow-up to assess post-treatment changes.

Keywords: Rhinitis; Allergy; Nasal cytology; Precision medicine

How to cite this article: The pragmatic role of nasal cytology: a point-of-care testing to implement precision medicine in clinical practice. Rev Alerg Mex. 2018;65(3):259-263

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Received: 2018-03-21
Accepted: 2018-05-05
DOI: 10.29262/ram.v65i3.373

Resumen

Antecedentes: La medicina de precisión es una estrategia actualizada que apunta a individualizar los mecanismos fisiopatológicos precisos. Entonces, la medicina de precisión es la base de la medicina personalizada, como definir el tratamiento apropiado en cada paciente. La citología nasal solo necesita un microscopio óptico, tinturas, gafas y curetas. El procedimiento puede durar muy pocos minutos usando tinción rápida, por lo tanto, se puede considerar una prueba confiable en el punto de atención en el consultorio.

Métodos: Estudio transversal que incluyó 5030 pacientes ambulatorios con trastornos nasales: 2612 hombres y 2418 mujeres, edad promedio de 36.8 ± 17.1 años, quienes fueron atendidos en un periodo de cinco años. Los pacientes se subdividieron conforme a la prueba cutánea y la citología nasal en sujetos con rinitis alérgica y con rinitis no alérgica. Las formas celulares se subdividieron en función del citotipo: rinitis no alérgica con predominio de infiltración eosinofílica (NARNE, neutrófilos > 50 % con esporas y bacterias ausentes); rinitis no alérgica con eosinófilos (NARES, eosinófilos > 20%); rinitis no alérgica con predominio de infiltrado de mastocitos (NARMA, mastocitos > 10 %) y rinitis no alérgica con eosinófilos y mastocitos (NARESMA, eosinófilos > 20 % y mastocitos > 10 %).

Resultados: 453 (9 %) sujetos tuvieron citología negativa a nasal, 1056 (21 %) rinitis alérgica, 538 (10.7%) NARES, 493 (9.8%) poliposis nasal, 251 (5%) rinosinusitis, 221 (4.4%) NARESMA, 201 (4%) rinitis infecciosa; 131 (2.6%) NARMA y 89 (1.8%) NARNE; los sujetos restantes tenían un perfil inflamatorio-infeccioso misceláneo.

Conclusiones: La citología nasal proporciona información rápida sobre el fenotipo y endotipo y puede repetirse en el seguimiento para evaluar los cambios posteriores al tratamiento.

Palabras clave: Rinitis; Alergia; Citología nasal; Medicina de precisión

Abreviaturas y siglas

AR, allergic rhinitis
MGG, May-Grunwald Giemsa
NAR, non-allergic rhinitis
NARES, non-allergic rhinitis with eosinophils
NARESMA, non-allergic rhinitis with eosinophils and mast cells
NARMA, non-allergic rhinitis with predominant mast cell infiltrate
NARNE, non-allergic rhinitis with predominant neutrophilic infiltrate
NC, nasal cytology
PM, precision medicine
POCT, point-of-care testing

Background

Rhinitis is an "umbrella" term that encompasses several types of rhinitis that are very different between each other. However, the word rhinitis implies the concept of inflammation. According to the definition provided by the Oxford Dictionary, inflammation is a localized physical condition in which part of the body becomes reddened, swollen, hot, and often painful, especially as a reaction to injury or infection.

Generally speaking, an inflammatory reaction can be caused by physical, chemical, and biological agents, including mechanical trauma, exposure to excessive amounts of sunlight, X-rays and radioactive materials, corrosive chemicals, extreme heat and cold, or infectious agents such as bacteria, viruses, and other pathogenic microorganisms. Although these infectious agents can produce inflammation, the terms infection and inflammation are not synonymous. Of note, all these agents can be causal factors for rhinitis.

Inflammation classic signs are heat, redness, swelling, pain, and loss of function. All these signs are well represented in rhinitis, mainly as regards nasal obstruction, which is the sign that is more significantly associated with inflammatory events.

From the pathophysiological point of view, the three major components of inflammatory process are:

- Changes in the caliber of blood vessels and the rate of blood flow circulating within (hemodynamic changes).
- Increased capillary permeability.
- Leukocyte exudation.

Thus, the presence of inflammatory cells in the nose allows to identify inflammatory reaction and characterizes its nature. There are three main types of inflammatory rhinitis: infectious, allergic, and non-allergic. Inflammatory rhinitis accounts for a rather impressive epidemiological impact: up to 50% of patients that report chronic nasal symptoms, including itching, sneezing, watery rhinorrhea, and/or congestion, may have this disorder.[1] However, there are different subgroups of inflammatory rhinitis: they are classified based on documented sensitization (allergic rhinitis, AR) or on the predominant infiltrating inflammatory type of cell if IgE testing is negative (non-allergic rhinitis, NAR). Non-allergic rhinitis with eosinophils (NARES) is the best known type of inflammatory NAR. NARES was first described more than 30 years ago.[2] The diagnosis is based on typical symptoms, negative allergy assessment and documented eosinophil infiltrate > 10% of total cells.[2] Subsequently, a NARES variant was reported, characterized by the concomitant presence of eosinophil and mast cell infiltrate, the so-called NARESMA (Non-allergic rhinitis with eosinophils and mast cells), characterized by more severe symptoms than NARES.[3] Other phenotypes of inflammatory NAR are the NARNE type (with predominant neutrophilic infiltrate) and the NARMA type (with predominant mast cell infiltrate).[4] Needles to say, these well-characterized NAR phenotypes can be diagnosed only by documenting the presence of specific inflammatory cells that infiltrate the nasal mucosa. Without the performance of nasal cytology, it is not possible to diagnose them.

Very recently, precision medicine (PM) has been proposed as a strategy aimed at defining the best therapeutic option for each individual patient, the so-called Personalized Medicine.[5] Of course, the concept of PM implies the definition of specific phenotypes and endotypes that characterize particular pathophysiological mechanisms. This diagnostic work-up needs for appropriate biomarkers to be available.

In addition, practical medicine requires simple, quick, and inexpensive tools. In this regard, point-of-care testing (POCT) are simple medical tests that can be performed at the bedside or within the clinical setting in several disorders.[6,7,8,9]

Based on the above considerations, it seems to be clear that nasal cytology (NC) can be an effective and easy-to-apply diagnostic and prognostic tool in the management of rhinitis, as it allows to detect and measure the cell population at the nasal level.[10,11] Moreover, NC is helpful to discriminate different nasal disorders, to evaluate the impact of different stimuli on the nose, including allergens, microbes, physical and chemical agents, and pharmacological molecules, as well as to document the effect of treatments. The methodology is easy and well standardized, and it mainly involves sampling, staining, and interpretation. In addition, NC is not invasive, and is repeatable and inexpensive. In particular, NC represents the only test able to define rhinitis phenotype and endotype within the clinical setting. Overall, NC is an indispensable tool to diagnose allergic inflammation and inflammatory non-allergic rhinitis (NAR). Actually, rhinitis phenotypes can only be documented by the presence of specific inflammatory cells that infiltrate the nasal mucosa. Without nasal cytology being performed, it is impossible to diagnose them.

Method

We report our experience concerning 5030 outpatients (2612 males, 2418 females, mean age 36.8 ± 17.1 years) attended to due to rhinitis over the previous 5 years. The review board of the Policlinic of Bari approved the procedure and every subject gave written informed consent.

The NC procedure is performed by anterior rhinoscopy, using a nasal speculum and good lighting. Scrapings of nasal mucosa were collected from the middle portion of the inferior turbinate, using Rhinoprobe® (VWR International, Milan, Italy). Samples were placed on a glass slide, fixed by air drying, and then stained by the May-Grunwald Giemsa (MGG) quick stain method (Bio Optica, Milan, Italy). MGG staining is the most widely used method in diagnostic nasal cytology, because all cellular components of the nasal mucosa, from inflammatory cells (neutrophils, eosinophils, mast

cells, and lymphocytes) to bacteria, spores, fungal hyphae, and mucous secretions are easily stained. The slide was observed under a Nikon E600 light microscope (Nikon, Canada) equipped with a digital camera (Nikon Coolpix 3:34) for the acquisition of microscopic images. For the rhino-cytogram analysis, 50 microscopic fields were read at a magnification of × 1000 to assess for the presence of normal and abnormal cellular elements, along with any microscopic features (spots, special inclusions, etc.) important for diagnosis. Cell counts, bacterial analysis, and fungal analysis were carried out by semiquantitative grading, as proposed by Meltzer and Jalowayski.12 In particular, bacteria, and fungal spore assessment was determined as follows:

- Grade 0 (not visible).
- Grade 1 + (occasional groups).
- Grade 2 + (moderate number).
- Grade 3 + (easily visible).
- Grade 4 + (large numbers, covering the entire field of view).

Patients with nasal disorders were subdivided based on skin-prick test and nasal cytology results in subjects with allergic rhinitis or non-allergic rhinitis. Cellular forms were further subdivided based on their cytotype: NARNE (> 50% of neutrophils with absent spores and bacteria); NARES (> 20% of eosinophils); NARMA (> 10% of mast cells); and NARESMA (> 20% of eosinophils and > 10% of mast cells).

Results

Overall, 453 (9%) subjects had negative NC, 1056 (21%) had allergic rhinitis, 538 (10.7%) had NARES, 493 (9.8%) had nasal polyposis, 251 (5%) had rhinosinusitis, 221 (4.4%) had NARESMA, 201 (4%) had infectious rhinitis, 131 (2.6%) had NARMA; 89 (1.8%) had NARNE, with the remaining subjects having a miscellaneous inflammatory/infectious profile. Figure 1 shows the most common features found in clinical practice.

Discussion

Precision Medicine (PM) is an up-to-date strategy aiming at individualizing precise pathophysiological mechanisms. Thus, PM is the basis for Personalized Medicine, inasmuch as it seeks to define the most appropriate treatment for each patient. In this regard, nasal cytology is increasingly advisable and recommended. In this context, nasal cytology has been recently shown to allow a PM-based approach in the non-surgical management of nasal polyps.[9] In other words, without NC, it is impossible to define the phenotype, and without a phenotype, it is impossible to prescribe Personalized Medicine. In this context, NC is well defined, standardized, and validated, as it

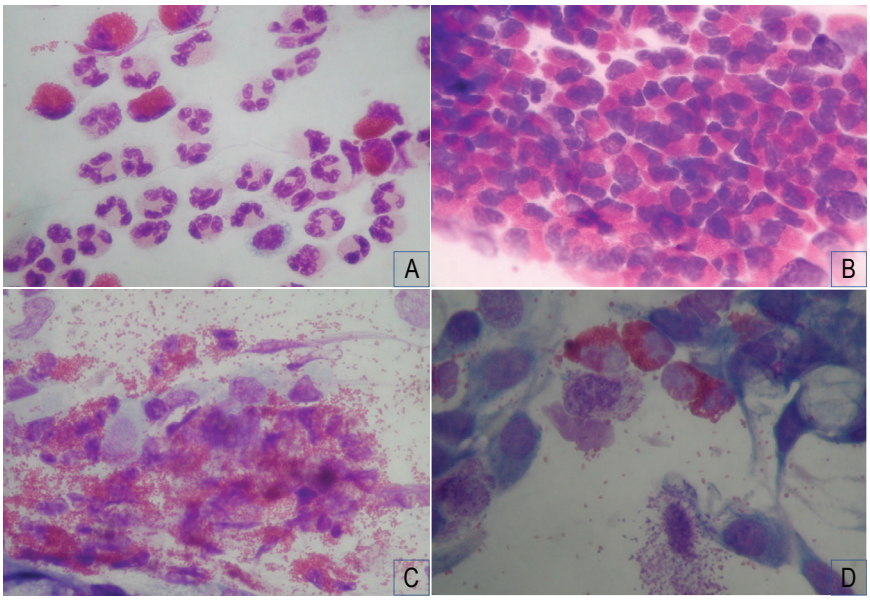

Figure 1. A) Allergic rhinitis typical features. B) NARES typical features. C) NARESMA typical features. D) Mast cell degranulation.

has been widely documented by several studies. Our experience confirms the pragmatic role of NC: without NC, it would be actually impossible to diagnose most outpatients.

In addition, NC only needs one optical microscope, stains, glasses, and Rhinoprobe® curettes. The procedure may last very few minutes using quick staining. Therefore, NC can be regarded as a reliable point-of-care test in the office setting. NC provides rapid information about inflammatory rhinitis phenotype and endotype and can be repeated during follow-up to assess post-treatment changes.

Conclusions

We believe that nasal cytology represents a relevant and reliable step in the diagnostic work-up and prognosis of patients with nasal disorders and that it deserves adequate consideration as a point-of-care testing tool in clinical practice. In fact, nasal cytology is a low-cost test that is of great utility in chronic rhinitis differential diagnosis. In addition, the pragmatic approach of phenotyping and endotyping is effective for precision medicine, as it enables personalized treatment in order to avoid anti-inflammatory medication abuse when not indicated.

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