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"Overlapped" rhinitis: a real trap for rhinoallergologists

Key words
Vasomotor rhinitis; allergic rhinitis; nasal cytology; therapy rhinitis

Summary
Under the broad heading of "vasomotor" rhinitis two big groups can be distinguished: allergic rhinitis (IgE-mediated), and nonallergic rhinitis. Since they are two separate nosological entities, they can co-exist in the same patient, classifying themselves in the group of "overlapped" rhinitis (OR). Although not absolutely rare (indeed it is estimated a 15-20% incidence among all vasomotor rhinopathies), this condition is not investigated and diagnosed, with significant implications in the clinical-diagnostic and therapeutic field.

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Under the broad heading of "vasomotor" rhinitis, two big groups can be distinguished: allergic rhinitis (IgE-mediated) (1), and nonallergic rhinitis, better defined as "cellular" rhinitis, represented by NARES (non-allergic rhinitis with eosinophils), NARMA (non-allergic rhinitis with mast cells), and NARES-MA (non-allergic rhinitis with eosinophils and mast cells) (2-4), whose etiology is unknown to date. Since they are two separate nosological entities, they can co-exist in the same patient, as well as for other diseases (diabetes, arterial hypertension, etc.), classifying themselves in the group of "overlapped" rhinitis (OR) (5). Although not absolutely rare (indeed it is estimated a 15-20% incidence among all vasomotor rhinopathies), this condition is not investigated and diagnosed, with significant implications in the clinical-diagnostic and therapeutic field.

On clinical level, the patient with OR, if compared to the typical patient sensitized to house dust mite, shows a more intense (sneezing, rhinorrhea, nasal itching with bouts of sneezing) and persistent symptomatology. Indeed, in patients sensitized to house dust mite, symptoms are most often characterized by a "moderate" intensity. In the case of OR with sensitization to "persistent" pollens, such as gramineae and parietaria, symptoms remain even in the months when the presence of airborne pollen particles is almost absent.

The diagnosis of these clinical conditions requires: an accurate and in-depth anamnesis; a skin prick test correlated to the anamnestic history and to the pollen calendar of the area where the patient lives; a nasal fibre-endoscopy; and, finally, a nasal cytology (6,7).

By means of allergologic diagnostics, all the common "environmental" allergens should be tested in addition to those correlated to the patient's type of job, hobby, etc.

The endoscopic exam of nasal cavities will evaluate the characteristics of mucosa (edema, hyperemia, presence of secretions), and exclude anatomic alterations (septal deviations and perfora-

Table 1 *- When to suspect "overlapping" of different rhinopathies (allergic rhinitis + NARESMA, NARES or NARMA).*

Clinical criteria
• Chronic "vasomotor" rhinitis symptoms (nasal congestion, rhinorrhea, sneezing a salve), present even outside the pollen season, in a patient with positive skin prick test and/or RAST test • Increased "vasomotor"-type nasal reactivity to non specific stimuli (sudden changes in temperature, light stimuli, strong smells, cigarette smoke, exposure to chlorine (swimming), etc.) • Disturbances of taste and smell (suspect onset of nasal polyposis) • Positive family history of nasal polyposis, NARES, NARMA, NARESMA, asthma, sensitivity to acetylsalicylic acid, hypo-anosmia, vasomotor rhinitis labeled "non specific", previous turbinate surgery for nasal congestion which gave poor medium- to long-term results • Recurrent use of nasal decongestants • Little or no clinical benefit following turbinate surgery for nasal congestion • Little or no clinical benefit following a cycle of specific immunotherapy (SIT)
Cytologic criteria
• In the forms with "persistent" symptoms, overlapping should be suspected in all patients with a rhinocytogram showing a cell profile different from that associated with "persistent minimal inflammation" (i.e. different from that characterised by numerous neutrophils, some lymphocytes and occasional eosinophils, with rare signs of degranulation), where there are eosinophils > 20% and/or mast cells > 10%. • In the forms with "intermittent" symptoms, overlapping should be suspected in all patients with a positive rhinocytogram (eosinophils > 20% and/or mast cells > 10%) outside the pollen season for the allergen/s identified by allergy testing (skin prick test and/or RAST test).
In rhinocytology, November tends to be preferred for "unraveling" overlapping rhinopathies, as this is the month in which most airborne pollens are absent. The presence of immuno-inflammatory cells (eosinophils and/or mast cells) associated with rhinitis symptoms confirms the presence of overlapping diseases.

RAST, radio-allergo-sorbent test

tions) and hyperplastic-granulomatous (nasal polyposis, antrochoanal polyp, etc.) or infectious (rhinosinusitis) diseases.

Nasal cytology, by researching eosinophils, mast cells, neutrophils, lymphocytes, bacteria, and fungal spores correlated to patient's clinical history, allergy tests and endoscopy, will help to "unravel" the forms of OR (**table 1**).

Against this background, doctors could find themselves facing a set of clinical conditions which could be partly summarized in the following clinical cases:

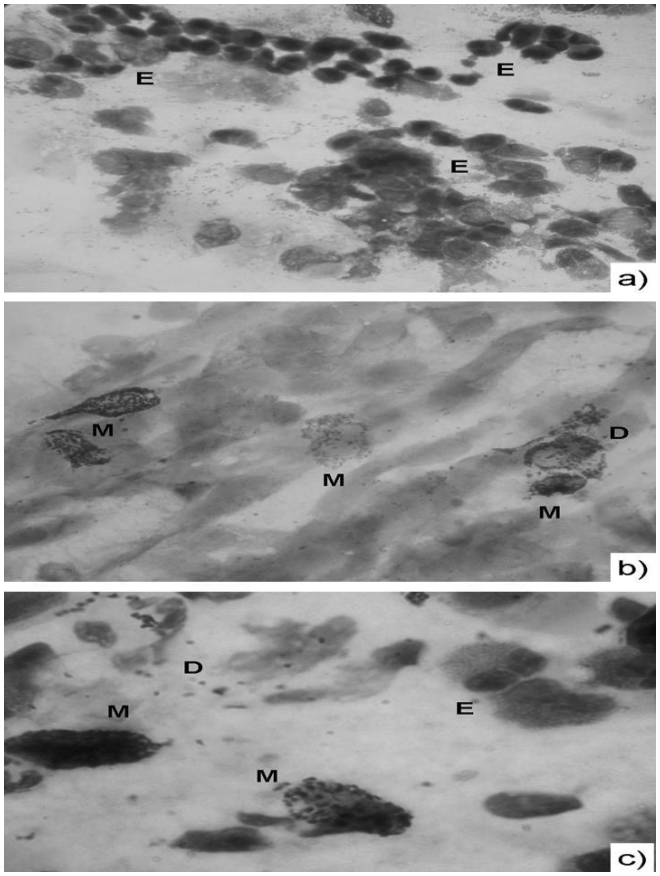
a) allergy to house dust mite associated to NARES. The patient will show an intense and persistent symptomatology, with a cytological framework dominated by a high number of eosinophils (> 20%), degranulated in the most part (**figure 1a**), contrary to "pure" allergic rhinitis to house dust mite only, characterized by a large number of neutrophils, occasional eosinophils, and almost no degranulation;

b) allergy to cypress, associated to NARMA. The patient will show symptoms no longer limited to the first 3-4 months of the year, but persistently, with a cytological framework represented by numerous mast cells, degranulated in the most part, even outside the correspondent pollen season (**figure 1b**);

c) allergy to gramineae and parietaria associated to NARESMA. The patient will show a rhinological symptomatology no longer limited to correspondent pollen periods (April-October), but persistently, with a cytological framework dominated by numerous eosinophils and mast cells, degranulated in the most part, even outside correspondent pollen seasons (**figure 1c**).

From a purely therapeutic perspective, ORs are real "traps" for the rhinoallergologist. Within the field of allergology, indeed, the patient with OR, when it is not diagnosed, will be subjected to Allergen-specific Immunotherapy (SIT). Besides the real and proven therapeutic effects of SIT, as reported by international literature (9), the patient will have poor clinical outcome from this therapy. While acting on the IgE-mediated rhinopathy, the SIT will have no therapeutic action on the associated non-IgE-mediated vasomotor component, generating dissatisfaction at the end of the treatment. The same problem will affect the patient subjected to surgical treatment of the turbinates, regardless of

Figure 1a, b, c *- "Overlapped" rhinitis. a) Allergic rhinitis to house dust mite associated to NARES (cytological sampling performed during the summer period under conditions when house dust mite concentration is reduced). There is a large number of partially degranulated eosinophils (E); b) allergic rhinitis to cypress associated to NARMA (sampling performed in November, in the absence of cypress pollens). There is a large number of partially degranulated mast cells (M); c) allergic rhinitis to gramineae and parietaria associated to NARESMA (nasal cytological sampling performed in November, outside the pollen period). There is a large number of partially degranulated eosinophils and mast cells. MGG staining, x 1,000.*



the type of surgical procedure used (laser, radiofrequencies, submucous resection of the turbinate, etc.), whose benefits will be limited in time as well. We do believe that these conditions are the expression of some syndromes nowadays classified as Severe Chronic Upper Respiratory Disease (SCUAD) (10). Therefore, reaching a precise diagnosis is always necessary, in order to inform the patient of his/her clinical condition, since we are more convinced that "diagnosis is always helpful for the therapy".

When treating the ORs, the SIT has the same indications as in the "pure" IgE-mediated forms, and therefore the therapy will be advised to the patient who will be informed in advance that, even after terminating the SIT, s/he will have to continue the medical treatment (corticosteroid and topical and/or systemic antihistamine). Likewise, a program of SIT and cycles of corticosteroid and topical and/or systemic antihistamine therapy will be recommended, right after the post-surgery recovery period, even to those patients who undertake surgical treatment of the turbinates, in order to monitor rhinitis symptomatology and prevent relapses.

In the light of the above, it is desirable that the diagnosis of rhino-allergy increasingly relies on investigations such as rhinoendoscopy and nasal cytology, still considered today as "second level" (1), which are necessary in order to "unravel" the ORs, clinical conditions still too often little known and, therefore, not diagnosed.

References

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, Baena-Cagnani CE, Canonica GW, van Weel C, et al.World Health Organization; GA(2)LEN; AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). Allergy. 2008;63(Suppl.86):8-160.
2. Jacobs RL, Freedman PM, Boswell RN: Non allergic rhinitis with eosinophilia (NARES syndrome): clinical and immunologic presentation. J Allergy Clin Immunol. 1981;67:253-7.
3. Connell JT: Nasal mastocytosis. J Allergy. 1969;43:182-9.
4. Gelardi M, Maselli Del Giudice A, Fiorella ML, Fiorella R, Russo C, Soleti P, Di Gioacchino M, Ciprandi G. Non-allergic rhinitis with eosinophils and mast cells (NARESMA) constitutes a new severe nasal disorder. Int J Immunopathol Pharmacol. 2008;23:325-31.
5. Gelardi M, Russo C, Fiorella ML, Fiorella R, Canonica GW, Passalacqua G. When allergic rhinitis is not only allergic. Am J Rhinol Allergy. 2009;23(3):312-5.
6. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, Canonica GW, and Global Allergy and Asthma European Network; Allergic Rhinitis and its Impact on Asthma. Practical guide to skin prick tests in allergy to aeroallergens. Allergy. 2012;67(1):18-24.
7. Gelardi M. Atlas of nasal cytology. Edi Ermes Milan, Italy. 2012.
8. Gelardi M, Incorvaia C, Passalacqua G, Quaranta N, Frati F. The classification of allergic rhinitis and its cytological correlate. Allergy. 2011;66:1624-5.
9. Hankin CS, Cox L, Bronstone A,Wang Z. Allergy immunotherapy: reduced health care costs in adults and children with allergic rhinitis. J Allergy Clin Immunol. 2013;131(4):1084-91.
10. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, Zuberbier T; Extended Global Allergy and Asthma European Network, World Allergy Organization and Allergic Rhinitis and its Impact on Asthma Study Group. Unmet needs in severe chronic upper airway disease (SCUAD). J Allergy Clin Immunol. 2009;124(3):428-33.