

Pathogenesis of respiratory inflammation

Patogenesi dell'inflammatione respiratoria

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Airways 'inflammation' plays a key role in the pathogenesis of airways disease and remodeling in COPD as well as in a number of other disease states including bronchial asthma, respiratory tract infections, cystic fibrosis, bronchiolitis and bronchiectasis. Inflammatory cells such as macrophages, neutrophils, eosinophils, CD8+ T lymphocytes, and subsequent changes which include epithelial damage and mucus hypersecretion have been investigated in a number of studies. Notably in COPD, which is also characterized by parenchymal destruction, the heterogeneity of the disease has hindered data interpretation, while extrapolation of the results of relatively non-invasive studies to the actual pathology found in the distal lung is difficult. Thus, major studies have frequently elicited conflicting interpretation, and a detailed profile of disease phenotype-specific inflammation of COPD as well as the importance of spill-over of inflammatory mediators into the circulating blood has yet to emerge. Further investigations are needed to link the different clinical and functional phenotypes of COPD to their respective inflammatory profiles in the airways thus improving the understanding of the pathogenesis of the disease as a whole. The acute effects of cigarette smoking on inflammation and oxidative stress in acute smoke exposure can result in tissue damage, as suggested by increased reactive oxygen species and products of lipid peroxidation and degradation of extracellular matrix pro-

teins. Acute cigarette smoke exposure, however, has also a suppressive effect on the number of eosinophils and several inflammatory cytokines, possibly due to the anti-inflammatory effect of carbon monoxide. Hopefully, in the near future data from studies on airway and parenchymal inflammation in COPD will prove useful to identify and assess the causes, severity, prognosis, and response to treatment.

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Cytology of inflammation

Citologia dell'inflammatione

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Infective and inflammatory diseases of the nasal-sinus cavities are microscopically characterized by the presence of cell populations and microbial agents that are not present under normal conditions. Characteristically, the nasal-sinus mucosa is made up of pseudo-stratified ciliated epithelium, represented by ciliated cells, mucin producing cells, striated and basal cells, and the presence of few neutrophils. In inflammatory conditions there may be bacteria, mycotic spores, eosinophils and mast cells, in different percentages, depending on the disease [1].

Nasal inflammation with signs of rhinitis can be

caused by numerous factors, among which the common cold and allergic diseases (allergic rhinitis) are the most frequent. There are other causes, such as non-infective, non-allergic rhinitis and vasomotor conditions of nasal inflammation that give rise to particularly serious forms of rhinitis, very difficult to treat and which require advanced methods of diagnosis [2].

Cytological investigation of the nasal mucosa represents the gold standard for diagnosis of numerous rhinological diseases. In particular, through cytological investigation it is possible to diagnose a group of non-allergic "infective rhinitis", such as:

non-allergic rhinitis with eosinophilia (NARES) (Figure 1A), non-allergic rhinitis with mast cells (NARMA) (Figure 1B), non-allergic rhinitis with neutrophilia (NARNA) (Figure 1C), and non-allergic rhinitis with eosinophilia and mast cells (NARESMA) (Figure 1D) [3,4]. These forms are usually termed "aspecific", a definition showing the poor knowledge of the etiological factors causing these specific diseases and a premise for the many diagnostic and therapeutic failures seen in common practice. The pseudo-allergic symptoms of these diseases are usually accompanied by nasal obstruction, pruritus, sneezing, burning sensation of the nasal mucosa, rhinorrhea, etc. These symptoms are often confused with IgE mediated rhinitis. They also present with an aspecific reactivity, which manifests with symptoms deriving from a change in posture, temperature changes, cold air, intense odours, and tobacco smoke. These symptoms are often misdiagnosed as vasomotor rhinitis.

The intense and persistent nasal symptoms, together with the tendency to associate these symptoms with more serious diseases, such as bronchial asthma, aspirin sensitivity, rhinobronchial syndrome, nasal polyps, and sinusitis, is a negative aspect of these rhinopathies which should not be taken lightly in terms of health care spending and the quality of life of these patients. [5]

A careful history of patients with these forms of rhinological disorders has revealed that a large number of them have consulted more than one specialist, e.g. ear, nose & throat (ENT) (specialists, allergologists, pediatricians and lung specialists) before arriving at a definitive diagnosis. In our opinion nasal cytology is an essential item of evidence that allows a correct diagnosis of these rhinological diseases. In fact, ENT specialists rarely arrive at a cor-

rect diagnosis in the course of the first visit, especially if the specialist does not advise routine tests for allergic rhinitis disorders (history, prick test, endoscopy, nasal cytology, rhinomanometry, diagnostic kits for specific nasal provocation tests, etc.). Since these are cellular disorders, it is indispensable to perform a microscopic diagnosis of the nasal mucosa in order to determine the prevalent cellular type to arrive at a precise diagnosis.

Another frequent finding during history taking of these patients is the surgical treatment of the turbinates to resolve the "obstructed nasal passages". These surgical procedures are however insufficient and sometimes damaging to the patient, causing scarring (turbinate-septal synechiae), crusting rhinitis, and atrophy of the mucosa. Typical of these forms of rhinitis is the chronic use of nasal decongestants containing nafazoline, or similar compounds to reduce nasal congestion. It must be kept in mind that chronic use of nasal decongestants can cause a serious form of rhinitis ('pharmacological rhinitis') that can be superimposed on the pre-existing condition.

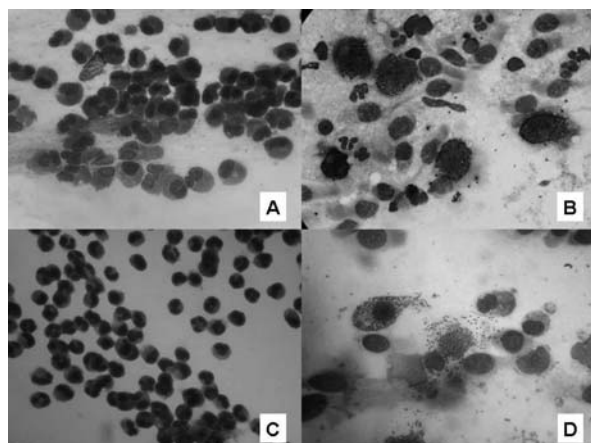
Concerning the medical therapy of chronic nasal congestion, the point of no return exists where either systemic or topical therapy does not have any effect on the symptoms; therefore surgical intervention on the turbinates appears to be justified with a return to medical therapy after surgery (topical or systemic corticosteroids, antihistamines, antileukotrienes, etc.).

The correct therapeutic orientation is very often "personalized" temporally, depending on the disease, in the hope of not intervening surgically once again, or developing complications. Another important aspect of these "cellular" rhinological disorders is the frequent association with nasal polyps to hypothesize a natural evolution of the disease. In fact, it has been clear since 1980 that it is not allergic rhinitis that determines such evolution, since nasal polyps accompany non-allergic rhinitis in 70-80% of the cases. We are in the process of confirming the predisposition of these cellular rhinological disorders to complications that include polyposis and asthma [6].

The data show a greater incidence of polyps and asthma in cellular rhinological diseases than in allergic rhinitis (polyps: 11.5% vs 1.7%; asthma 12% vs 6.7%). In final analysis, the clinical concept that cellular rhinological diseases are all associated must be reaffirmed. Since they are chronic diseases, chronic therapy is necessary plus a personalized follow up aimed at controlling the symptoms and prevention of the complications (rhinosinusitis, polyposis, asthma, etc.) [7].

It is the specific duty of the specialist to explain clearly and exhaustively all the information regarding the specific rhinological disease and to institute a programmed therapeutic protocol, but letting the patient know all the limitations or the strengths of the therapy and the limits of pharmacological treatment in controlling the disease, in order not to induce false expectations of a definitive recovery.

FIGURE 1: FOUR MAIN TYPES OF NON-ALLERGIC (INFLAMMATORY) RHINITIS AS DEFINED BY CYTOLOGICAL INVESTIGATION OF THE NASAL MUCOSA



A: non-allergic rhinitis with eosinophilia (NARES); B: non-allergic rhinitis with mast cells (NARMA); C: non-allergic rhinitis with neutrophilia (NARNA); D: non-allergic rhinitis with eosinophilia and mast cells (NARESMA). Tutte e 4 le foto microscopiche sono state rilevate ad un ingrandimento di 1000x con colorazione di May-Grumwald - Giemsa (MGG).

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Inflammation in upper and lower airways: similarities and differences

Infiammazione nelle vie respiratorie superiori e inferiori: somiglianze e differenze

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Many diseases affect both the upper and lower parts of the respiratory tract - which should really be considered as one organ, e.g.

- allergic rhinitis/asthma
- non allergic rhinitis + eosinophils/asthma
- chronic rhinosinusitis + nasal polyps/asthma
- chronic rhinosinusitis without nasal polyps/ ? Lower respiratory tract infection (Japan panbronchiolitis)/?bronchiectasis
- rhinitis/chronic obstructive pulmonary disease
- cystic fibrosis
- primary ciliary dyskinesia
- hypogammaglobulinaemia
- Wegener's granulomatosis
- Churg Strauss syndrome
- sarcoidosis
- tuberculosis/leprosy
- non allergic rhinitis without eosinophils/?neurogenic asthma

Inflammatory processes in both areas are probably similar - but constrained by anatomy and physiology of airways:

Upper respiratory tract (URT):

- no smooth muscle,
- highly reactive vasculature
- bony or cartilaginous skeleton
- resists expansion,
- designed to cope with large volumes of particulate material/pathogens.

Lower respiratory tract (LRT):

- smooth muscle,
- reactive vasculature,
- no skeleton,
- designed to be protected by URT.

Neurogenic influences are also likely to be involved in disease symptomatology, but are outside the scope of this article. Recent evidence suggests that in some of these conditions an aberrant response to bacteria or viruses may be highly relevant to aetiopathogenesis. Only a few of these can be considered in detail.

Allergic rhinitis/asthma

The overall view of respiratory allergy has changed profoundly in recent times with increasing attention focused on the relationship between rhinitis and asthma (i.e. between the upper and lower respiratory tract), first noted in epidemiological studies. Clinical observations provide compelling evidence for the co-existence of rhinitis and asthma, rhinitis as a risk factor for developing asthma, the occurrence of bronchial hyper-responsiveness in rhinitis, the association between upper respiratory infections and asthma exacerbations, the existence of common pathogenic mechanisms between rhinitis and asthma, and the exacerbating role of rhinosinusitis in asthma.

More detailed knowledge of the mechanisms of inflammation has clarified the functional relationships between the nose and bronchi. It is therefore reasonable to consider respiratory allergy as a disorder of the whole respiratory tract manifest clinically as rhinitis and/or asthma, rather than as distinct diseases confined to specific organs. This approach has therapeutic implications because treating upper airways disease can improve the lower airways, and drugs affecting common inflammatory mechanisms can act on both compartments. The bronchial inflammatory response following allergen-specific challenge in patients suffering from asthma alone or rhinitis alone has been studied utilizing bronchial biopsy and lavage. No mor-