ONLINE SUPPLEMENT

INTRODUCTION

The most common presentation form of upper airway disease is rhinitis, which is defined as a symptomatic inflammation of the nasal mucosa with at least two symptoms, among which are nasal obstruction, rhinorrhea, itchy nose and/or sneezing.[1] When this inflammation extends to the mucosa of the paranasal sinuses, the consensus term of rhinosinusitis is used.[2] Rhinosinusitis is defined as inflammation of the sinonasal mucosa characterized by at least two of the following symptoms: nasal obstruction, facial pain or headache, smell dysfunction, and/or anterior or posterior secretions. Based upon duration of symptoms we distinguish acute rhinosinusitis (ARS; <12 weeks) and chronic rhinosinusitis (CRS; >12 weeks) which again has two major clinical phenotypes based on the findings of nasal polyposis (NP): CRS with NP (CRSwNP) and CRS without NP.[2]

The close link between upper and lower airway inflammation is well known in the context of "global airway disease.[3] The majority of asthmatic individuals suffer from rhinitis and, conversely, patients with rhinitis or CRS have an increased risk of developing asthma.[4-8] However, the nose is not involved only in asthma, 75-88% COPD patients also have sinonasal symptoms [9-11] and 45-84% of bronchiectasis patients suffer from CRS.[12, 13] Additionally, treating nasal pathology has beneficial effects on the lower airway symptoms in chronic airway disease.[14-16]

ENDOGENOUS FACTORS ASSOCIATED WITH UPPER AIRWAY DISEASE

Immune deficiencies

More subtle abnormalities of the innate immune system are linked to the occurrence of CRS. Thus, associations have been described between CRS and defects in epithelial barrier function,[17] reduced expression of antimicrobial proteins, such as S100 proteins [18] and lactoferrins,[19], and abnormalities in the novel Palate, Lung, and Nasal Epithelial Clones (PLUNC) protein family.[20]

EXOGENOUS FACTORS ASSOCIATED WITH UPPER AIRWAY DISEASE

Viruses

Nasal epithelial cells of allergic rhinitis patients showed an upregulation of TLR 3, the key receptor for the recognition of viral RNA, as well as the downstream signaling adaptor NFκB.[21, 22] Additionally, nasal allergen provocations induced an upregulation of the adhesion molecule ICAM-1, the principal receptor for HRV, in both nasal and bronchial epithelium of allergic rhinitis patients without asthma.[23] However, the functional relevance still remains unclear, since allergy does not necessarily alter symptomatology nor inflammation during a common cold.[24, 25]

Bacteria

Within the concept of global airway disease, chronically inflamed sinuses might in some cases serve as a reservoir for pathogens that can descend into the lower airway tract, as it has been shown that identical genotypes of *S. aureus* and *P. aeruginosa* were present in the upper and lower airways of CF patients.[26]

Allergens

When genetically predisposed or so-called atopic individuals who are exposed to respiratory allergens, inhaled allergens are taken up and processed by antigen presenting cells (dendritic cells) present in the respiratory mucosa. These antigenpresenting cells drain to the local lymph nodes where they present the processed allergen to naïve $CD4^+$ cells. The local cytokine environment causes the $CD4^+$ cells to shift towards the Th2-subtype with production of Th2 cytokines such as IL-4, IL-5 and IL-13. These cytokines activate B-cells to secrete antigen-specific IgE, which binds to mast cells residing in the airway mucosa. Renewed contact with the allergen results in cross-linking of its mast cell-

bound IgE leading to mast cell degranulation with release of preformed mediators such as histamine, tryptase and leukotrienes that act on the surrounding tissues causing the acute allergic symptoms of sneezing, rhinorrhea and itch. Th2-cytokines are responsible for the late allergic response by inducing growth and attraction of eosinophils and lymphocytes that leads to a persistent inflammation causing swelling of the nasal mucosa with symptoms of nasal blockage, and finally tissue remodeling.[27]

Allergic rhinitis is relatively easy to diagnose based on the combination of typical symptoms and positive skin prick tests (SPT) or antigen-specific IgEs in the serum.[28]

Several studies from Rondon suggest that some patients with negative SPT or serum IgEs against the clinically suspected allergens, may be wrongly considered as having non-allergic rhinitis. They describe the existence of a "locally mediated allergic rhinitis", showing a local production of specific IgE antibodies and a Th2-type inflammation in the nasal mucosa in combination with a positive nasal allergen provocation test.[29] Although further studies are needed to establish this new entity, the concept of local allergic rhinitis emphasizes the need for proper diagnostics and provocation testing in patients, initially diagnosed with non-allergic rhinitis.

Occupational agents

LMW agents with a sentizing capacity or 'LMW sensitizers' are mostly synthetic chemicals (di-isocyanates, persulphate salts, aldehydes, and several drugs), but various metallic agents (platinum salts, chromium, nickel) and wood-derived chemicals (red cedar, mansonia) also exhibit sensitizing potential. A second group of LMW agents consists of irritants with the best-known examples being chlorination products, ozone, acids and ammonia, but the list is extensive.

The production of (detectable) antigen-specific IgE against these LMW sensitizers is variable and, hence, SPT or serum IgE testing cannot be used to diagnose

sensitization and a positive nasal provocation test with the the suspected agent is required for the diagnosis of occupational rhinitis or asthma.[30]

De novo asthma caused by an acute inhalation accident is known as “acute-onset irritant-induced asthma” [31] (previously Reactive Airways Dysfunction Syndrome (RADS)). Persistent nasal blockage, runny nose or sneezing may also follow inhalation accidents and this phenomenon has been referred to as Reactive Upper Airway Dysfunction Syndrome (RUDS).[32]

Additionally, several studies suggest that patients suffering from pre-existing rhinitis show exaggerated nasal responses to inhalation of irritants. For example, allergic rhinitis patients showed an immediate nasal congestion in response to nasal provocations with chlorine gas in contrast to healthy subjects.[33]

[34] [35] [36] [37]

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