Asthma

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Keywords: house dust mites ; allergic asthma

1. Introduction

Asthma is an inflammatory condition of the bronchial mucosa affecting 10% of children and 5% of adults in Western countries [1]. The disease imposes a high direct burden to health systems in medications, medical consultations, and hospitalizations [2]. Asthma is also associated with significant school and work absenteeism and presentism in children and adults [2]. Moreover, the condition is closely related to inflammatory diseases of the upper airways, further amplifying its impact [3].

Asthma is also a heterogeneous disease in phenotypes, evolution, and response to therapy [4]. Allergic asthma (AA) is the most frequent phenotype, and its prevalence is progressively increasing worldwide [5]. Among the different allergenic sources, house dust mites (HDMs) are the ones most commonly involved in airway allergy, including AA [6]. Nevertheless, asymptomatic HDM sensitization is also very frequent among healthy subjects and asthmatic patients [7]. Interestingly, recent data suggest that HDM can also trigger bronchial asthma in non-atopic individuals [8]. This new phenotype has been termed local allergic asthma (LAA). Of note, both AA and LAA are associated to nasal inflammatory diseases, which can be considered their counterparts in the upper airways. Therefore, as emphasized by the united airways concept, it would probably be more appropriate to use the terms atopic and local respiratory allergy. Regarding evolution, around 10% of asthma patients develop severe forms of the disease [5]. Despite not representing a majority of cases, severe asthma accounts for 80% of the costs attributable to the condition, mainly due to repeated exacerbations [2]. Allergens, especially those in the feces and bodies of HDM, are known triggers of asthma exacerbations [9], suggesting that allergic mechanisms are essential in severe asthma. Nevertheless, the role of allergy in severe asthma has been historically questioned [10], probably due to the difficulty of conducting bronchial allergen challenges (BAC) in moderate-to-severe asthmatics.

Identifying allergic triggers of asthma is interesting because AA patients can be treated with allergen immunotherapy (AIT). AIT is an etiologic intervention displaying a sustained clinical benefit after discontinuation and a capacity to prevent disease progression, as long as it is administered for a minimum cycle of three years [11]. In recent years, new HDM immunotherapy modalities registered as pharmaceutical products have been approved for the treatment of HDM-driven AA [12].

2. Phenotyping House Dust Mite-Driven Asthma

Asthma phenotypes can be divided into those with eosinophilic bronchial inflammation (usually termed T2 asthma) as those without eosinophilic inflammation (non-T2 asthma) [4]. T2 asthma has been classically divided between AA and eosinophilic non-allergic asthma based on the presence of atopy [5]. Nevertheless, IgE sensitizations are not always clinically relevant [7]. Because >50% of asthmatics are sensitized to HDM [9], there is a need to identify bona fide allergic individuals. Moreover, new data demonstrate that some non-atopic individuals with T2 asthma can experience a positive bronchial challenge with HDM [8]. These facts demonstrate that atopy and allergy represent two different phenomena and collectively challenge the atopy-based classification of T2 asthma (Table 1).

Table 1. Comparison of asthma phenotypes related to sensitization and/or bronchial reactivity to house dust mites.

HDM-Driven Allergic Asthma	HDM-Driven Local Allergic Asthma	Non-Allergic Asthma with HDM Sensitization	
Nasal affection	**Virtually always**	**Always**	**Common, but not always**
Nasal counterpart	**Allergic rhinitis**	**Local allergic rhinitis**	**Non-allergic rhinitis**
Atopy	**Present**	**Absent**	**Present**
Family history of allergy	**Frequent**	**Frequent**	**Infrequent**
Allergic triggers	**House dust mites. Others possible.**	**House dust mites. Others possible.**	**None**
Severity	**Mild to severe**	**Only demonstrated in mild to moderate cases**	**Mild to severe**
Age of onset	**Early (childhood/adolescence)**	**Probably early (childhood/adolescence)**	**Later than allergic phenotypes**
Natural evolution	**Progressive worsening and onset of new systemic sensitizations**	**Progressive worsening and onset of new local sensitizations**	**Stable severity since onset in most cases**
Eosinophilia	**Yes**	**Yes**	**Sometimes**
Bronchial sIgE	**Frequent**	**Unknown**	**Possible**
BAC needed for diagnosis	**Sometimes**	**Always**	**Sometimes**
Indication of ICS	**Yes**	**Yes**	**Yes**
Effect of ICS	**Beneficial**	**Beneficial**	**Variable**
Indication of omalizumab *	**Yes**	**No**	**Theoretically not, but often prescribed ****
Effect of omalizumab	**Beneficial**	**Probably beneficial**	**Not beneficial in most cases**
Indication of reslizumab mepolizumab, benralizumab and dupilumab *	**In most cases**	**Potential, but the phenotype is not identified yet among severe asthmatics.**	**Variable**
Effect of reslizumab, mepolizumab, benralizumab and dupilumab	**Beneficial in most cases**	**Potentially beneficial, but the phenotype is not identified yet among severe asthmatics.**	**Variable**
Indication of AIT	**Yes**	**No**	**No**
Effect of AIT	**Beneficial**	**Probably beneficial**	**Not beneficial**

HDM: house dust mite; sIgE: allergen-specific IgE; BAC: bronchial allergen challenge; ICS: inhaled corticosteroids; AIT: allergen immunotherapy; * in severe otherwise uncontrolled cases; ** See Section 4.1.

2.1. Allergic Asthma

AA is characterized by the onset of typical asthma symptoms upon the exposure to one or more aeroallergens in sensitized (atopic) individuals [4]. Thus, by definition, AA patients test positive at least in one of the two classical markers of atopy: skin prick test (SPT) and allergen-specific (s)IgE in serum [5]. The relevance of HDM as triggers of AA has increased in the last decades [6], probably mirroring the global expansion of the Western lifestyle. Individuals in Western cultures spend most of their time indoors, which favors sensitization to indoor allergens [13]. In the indoor environments of coastal areas with humid and temperate climates, HDM are present year-long, yet they can experience seasonal variations [14]. Interestingly, indoor allergens are associated with more severe forms of AA as compared to outdoor pollen allergens [6]. HDMs typically induce persistent forms of AA, and a significant proportion of patients remain uncontrolled or

partially controlled despite continuous inhaled therapy [6]. Besides viral infections, HDM exposure frequently triggers exacerbations in these patients, especially during the warm and humid seasons (e.g., autumn and spring) [15]. Moreover, patients with AA frequently suffer from concomitant rhinitis [3]. According to the united airways concept, allergic rhinitis (AR) and AA can be considered the organ-specific manifestations of a single chronic airway disease (atopic respiratory allergy, ARA). Of note, the onset of ARA often occurs during childhood and can persist lifelong with progressive aggravation and development of new IgE sensitizations [3].

2.2. Local Allergic Asthma

Recently, a new phenotype of HDM-driven asthma (LAA) has been described in individuals with local allergic rhinitis (LAR) [8]. LAR is a newly identified phenotype of chronic rhinitis characterized by the absence of atopy and positivity of the nasal allergen challenge (NAC) [16]. LAR is an independent rhinitis phenotype that does not progress to systemic atopy, although typically occurs in patients with a family history of atopy [17]. The disease often commences during childhood and progresses towards clinical worsening and asthma development [18]. In a 10-year follow-up study of 176 LAR individuals conducted by our group, the prevalence of asthma guide symptoms significantly increased from 18.8% at baseline to 30.7% at the end of the study period [19]. Similar to ARA, HDMs are the most frequent triggers of LAR [20]. These observations prompted us to evaluate the nature of bronchial symptoms in LAR patients and their relationship with allergen exposure. We recruited 28 and 18 individuals with HDM-driven LAR and AR, respectively, who also reported asthmatic symptoms [8]. Nineteen patients with non-atopic non-allergic rhinitis (NAR) suffering from concomitant asthmatic symptoms and eight healthy non-atopic control (HC) individuals were also included. All LAR and AR patients and all NAR and HC subjects had previously tested positive and negative, respectively, in a nasal challenge with HDM. Among LAR and AR patients, 28.6% and 83% displayed a positive result in the bronchial challenge with HDM, respectively, thus confirming the presence of LAA and AA. Conversely, none of the NAR and HC individuals tested positive in the BAC. Asthma was confirmed by methacholine provocation in 50%, 83%, and 58% of LAR, AR, and NAR patients, respectively, but only HDM-allergic patients experienced an increase in airway hyperresponsiveness after the BAC, regardless of their atopic status. Importantly, LAA was diagnosed in patients with LAR, which indicates that both conditions can be considered the organ-specific manifestations of a single airway disease (local respiratory allergy, LRA), and that this new phenotype also participates in the united airways concept [18]. Of note, specific reactivity to HDM is associated with eosinophilic airway inflammation in both LAR and LAA patients. On the other hand, in a recent Polish study conducted in 36 individuals with birch pollen-driven LAR, the presence of asthma and LAA was specifically investigated [21]. Of note, asthma diagnosis was confirmed in 76% of LAR patients reporting suggestive bronchial symptoms, whereas 58% of them tested positive in the bronchial challenge with birch pollen. These data illustrate that, similar to LAR, both seasonal and perennial allergens can trigger LAA.

3. Endotyping House Dust Mite-Driven Asthma

3.1. Allergic Asthma

Mouse models of HDM-driven AA showed a division of labor among antigen-presenting cells in the different phases of allergic airway inflammation. Whereas myeloid CD11b+ conventional dendritic cells were the main drivers of sensitization to HDM (by priming allergen-specific (s)Th2 cells), monocyte-derived dendritic cells behaved as the master local orchestrators during the re-challenge phase [22]. Upon allergen reencounter, massive amounts of monocytes migrate from the circulation to the bronchial mucosa, where they differentiate into inflammatory cells to release chemokines, recruit other immune cells, and locally reactivate memory sTh2 cells [22]. This labor division was later confirmed in clinical studies of AR [23] and AA [24] patients.

Primed sTh2 cells interact with naïve B cells in the secondary lymphoid tissues to induce class switch recombination to IgE (εCSR) [25]. Nevertheless, IgE-switched B cells cannot undergo efficient somatic hypermutation in the B cell follicles of germinal centers [26]. This fact determines a low frequency and insufficient affinity maturation of germinal center-derived sIgE. Conversely, IgG- and IgA-switched B cells can complete their maturation in secondary lymphoid tissues and become systemically available [25]. On the other hand, efficient IgE immune responses are preserved through the sequential εCSR of IgG_1+ B cells in peripheral tissues [27]. Most sIgE is synthesized in AR patients through this sequential switching at the nasal mucosa after re-exposure to the allergen [28]. In AA individuals, the source of sIgE is less characterized, probably due to the greater difficulty in obtaining bronchial samples. Nevertheless, recent evidence indicates that the bronchial mucosa is a relevant site for sIgE synthesis also in allergic asthmatics [29]. Markers of εCSR and high amounts of IgE+ and high affinity receptor for IgE (FcεRI)+ cells have been identified in the bronchial mucosa of AA patients [30][31]. Moreover, a study analyzing bronchial tissue homogenates demonstrated HDM-sIgE in all AA patients included [32].

3.2. Local Allergic Asthma

Several studies have investigated the presence and synthesis of IgE in the airway mucosa of non-atopic individuals with rhinitis and asthma. Similar to AA, markers of εCSR and IgE+ and FcεRI+ cells have been identified in the bronchial mucosa of non-atopic eosinophilic asthmatics [29][30][31]. Similarly, sIgE+ cells were demonstrated in the nasal mucosa of non-atopic rhinitis individuals [33]. Nevertheless, there are conflicting data about the specificity and functionality of local IgE in non-atopic patients. One study detected HDM-sIgE in the sputum of 39 out of 39 non-atopic asthmatics [34]. Conversely, another work reported that HDM-sIgE was not observed in the bronchial homogenates of any of the non-atopic asthma patients analyzed [32]. In any case, none of these studies correlated the absence or presence of mucosal sIgE with the bronchial response to HDM exposure. In another work, HDM-sIgE was found in the sputum of 26 out of 27 non-atopic asthmatics, yet the patients failed to develop a positive BAC [35]. In contrast, sputum HDM-sIgE from three non-atopic asthmatics from the same series activated peripheral basophils in vitro. Nevertheless, given the heterogeneity of non-atopic rhinitis and asthma phenotypes, it seems reasonable to focus the quantification of local sIgE on those individuals with confirmed allergen-specific airway reactivity.

The pooled analysis of HDM-driven LAR individuals revealed that sIgE in the nasal secretions increases progressively during the 24 h following a positive NAC [36]. In any case, the values detected were very low, and not every patient tested positive in at least one determination. Several studies have confirmed that sIgE can only be detected in the nasal secretions of a minority (20–40%) of LAR subjects [36][37][38][39]. Although methodological factors might account for this low detection rate, it cannot be excluded that sIgE is not present in the respiratory secretions of patients with LRA [40]. Of note, individuals with LRA do not have detectable sIgE in serum, and both biological fluids are ultimately connected through the lymphoid vessels. Notably, a study using postoperative sinus sponge packs (which grow inside the nostril to perfectly adapt to the anatomy and scratch a significant amount of mucosal cells when they are removed) demonstrated that nasal sIgE is present in >90% of LAR individuals [41].

In our study defining the LAA phenotype, HDM-sIgE was not detected in the sputum of any individual experiencing a positive BAC (AA or LAA subjects) neither at baseline nor after the provocation [8]. The absence of sputum sIgE in AA patients seems to indicate that methodological aspects are at least partially related to this lack of detection [40]. The study also investigated the BAC-induced changes in tryptase, eosinophil cationic protein (ECP), T cells, natural killer (NK) cells, monocytes, and eosinophils in sputum [8]. The BAC induced a significant increase of sputum ECP, eosinophils, and monocytes in LAA and AA patients, whereas non-allergic asthma and HC subjects experienced no modification. No differences were observed for the other parameters. These findings demonstrate the allergen specificity of the inflammatory response experienced by BAC-positive individuals, regardless of their atopic status. Moreover, similar to AA [24], monocyte recruitment seems to be involved in the effector phase of LAA. Collectively, these data suggest that the immunopathology of LAA/LRA closely resembles that of AA/ARA.

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