Mite-induced inflammation: More than allergy

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ABSTRACT

Clinical observations have suggested that there is an association of atopic conditions with hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). This relationship has been especially present in patients allergic to mites. This study was designed to review clinical and experimental evidence linking atopy, mite allergy, and hypersensitivity to aspirin and NSAIDs and discuss the possible mechanisms explaining this association. A review of the medical literature concerning the association of atopic diseases, mite hypersensitivity, and intolerance to NSAIDs using PubMed and other relevant articles is presented. NSAID-sensitive patients are frequently atopic and allergic to mites, and patients who develop oral mite anaphylaxis (OMA) show an increased prevalence of NSAID hypersensitivity. The study of atopic, mite-sensitive patients, who experience urticaria and angioedema when exposed to NSAIDs and patients with OMA suggests an interesting interaction between atopic allergy and disorders of leukotriene synthesis or metabolism. Various mechanisms that could be involved in this interaction are presented, including genetic factors, inhibition of cyclooxygenase-1, and other effects (not related to IgE sensitization) of mite constituents on the immune system. The association of mite hypersensitivity with aspirin/NSAIDs intolerance has been confirmed and provides additional clues to various nonallergic pathways that may contribute to the acute and chronic inflammatory process observed in atopic, mite-allergic, individuals. The clinical relevance of these observations is presently under investigation.

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Allergic respiratory diseases induced by domestic mites, such as rhinitis and asthma, are highly prevalent in most regions of the world and represent a significant medical problem with heavy impact on sanitary budgets and people's quality of life.[1] A number of mite allergens have been characterized and are currently being used for the diagnosis and treatment of respiratory allergic diseases.[2]

Although allergic inflammation induced by mites has received a great deal of attention in the literature, less interest has been devoted to additional pathogenic mechanisms due to mite constituents. In this article we discuss the pathophysiological implications of various types of reactions induced by mites based on information derived from the study of patients who developed the clinical picture of oral mite anaphylaxis (OMA), a recently recognized nature's experiment.

ORAL MITE ANAPHYLAXIS

Allergens hidden in food represent a difficult and challenging issue for patients and allergists, as recently emphasized by Puglisi and Frieri.[3] Hidden food proteins constitute a dangerous and even life-threatening source of allergen exposure for unsuspecting hypersensitive individuals and efforts to increase public awareness have led to such proposals as the Food Allergen Labeling and Consumer Protection.[3] The first case of systemic anaphylaxis induced by the ingestion of foods (more often wheat flour) contaminated with mites was published by Erben *et al.* in 1993.[3] Later on, a number of investigators have reported isolated cases or small series of patients with OMA. Table 1 summarizes the information presently available in the literature on 102 cases observed in the United States, Japan, Canary Islands (Spain), Venezuela, Brazil, Taiwan, and Singapore. There are also unpublished cases in the Dominican Republic, Israel, and Peru.[4–18]

Among precipitating foods, beignets, pizza dough, "okonomi-yaki," polenta, flour-coated fish, and scones have been reported. However, the most frequently incriminated food has been pancakes, and therefore the term "pancake syndrome" was proposed.[19,20] Various mite species have been associated with OMA, including domestic (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) and storage mites (*Tyrophagus spp.*, *Suidasia spp.*, *Blomia freemani*, and *Aleuroglyphus ovatus*). A young female patient who developed exercise-induced anaphylaxis after the ingestion of pancakes made with wheat flour containing mites of the species *Suidasia* was also reported by our group.[21]

As shown in Table 1, it is remarkable that a significant proportion of patients with OMA also showed hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs), especially NSAID-induced angio-

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Table 1 **Publications on oral mite anaphylaxis**

Reference	*n*	Age (yr)	Gender M/F	Location	Foods	Mites	NSAID Hypersensitivity
Erben *et al.*[4]	1	48	1/0	Detroit, MI	Beignets	*D. farinae*	No
Spiegel *et al.*[5]	1	17	0/1	Philadelphia, PA	Beignets	*D. farinae*	No
Skoda-Smith *et al.*[6]	1	14	1/0	Birmingham, AL	Pizza dough	*D. farinae*	Family history
Matsumoto *et al.*[7]	2	11, 14	1/1	Kumamoto, Japan	"Okonomi-yaki"	*T. putrescentiae*	No
Blanco *et al.*[8]	16	13–38	4/12	Canary Islands, Spain	Various	*D. farinae T. entomophagus*	14 (87%)
Sánchez-Borges *et al.*[9]	31	13–45	14/17	Caracas, Venezuela	Various	*D. farinae Suidasia* spp. *A. ovatus*	20 (66%)
Guerra-Bernd *et al.*[10]	1	18	0/1	Porto Alegre, Brazil	Polenta	*Tyrophagus D. farinae D. pteronyssinus*	Yes
DeMerrell *et al.*[11]	1	11	1/0	New Orleans, LA	Beignets	*D. pteronyssinus*	No
Ott[12]	1	54	0/1	Minnesota	Pancakes	*D. pteronyssinus*	No
Wen *et al.*[13]	1	8	1/0	Taipei, Taiwan	Pancakes	*B. freemani*	No
Miller and Hannaway[14]	1	52	0/1	Massachusetts	Pancakes	*D. farinae*	No
Tay *et al.*[15]	2	15–30	0/2	Singapore, Indonesia	Wheat flour-coated fish, and scones	*D. farinae*	Yes
Iglesias-Souto *et al.*[16]	1	13	1/0	Canary Islands, Spain	Pancake	*T. entomophagus*	Yes
Geller[17]	1	36	0/1	Rio de Janeiro, Brazil	Pancake	*A. ovatus*	Yes
Sánchez-Machín *et al.*[18]	42	11–57	21/21	Canary Islands, Spain	Crepes	*T. entomophagus*	21 (50%)

Hypersensitivity to NSAIDs 59/102 (57.8%).
NSAIDs = nonsteroidal anti-inflammatory drugs.

edema, which was present in 59 of the 102 published cases (57.8%). We proposed a "new aspirin triad" of allergic rhinoconjunctivitis, aspirin/NSAID hypersensitivity, and severe systemic reactions to mite-contaminated foods.[22]

The diagnosis of OMA is suspected through patient interrogation where a history of symptoms temporarily related to the ingestion of foods prepared with wheat flour is obtained. Microscopic identification of mites in the flour is required to confirm the diagnosis, together with positive skin-prick tests to extracts of contaminated flour and negative prick tests to commercial allergenic wheat extracts and to uncontaminated flour. These patients are tolerant to foods made with wheat flour that do not contain mites. The prevalence of OMA in the population has not been established, although in a recent series of 179 patients with anaphylaxis attending our institution 13 cases of OMA (7.2%) were observed.[23] It is likely that OMA occurs more frequently in tropical/subtropical areas where climatic conditions (heat and humidity) are favorable for mite proliferation.[24]

Increased Prevalence of Atopy and Mite Allergy in Patients with NSAID Hypersensitivity

In 1992 we reported a high prevalence of atopic diseases in patients with cutaneous hypersensitivity to NSAIDs (urticaria and angioedema).[25] This initial observation was confirmed in a study of cases and controls showing that an increased proportion of patients with urticaria/angioedema induced by NSAIDs had concomitant rhinitis, asthma, conjunctivitis, and positive prick tests to inhalant allergens.[26]

More recently, we observed that patients with cutaneous hypersensitivity to NSAIDs have significantly increased levels of total and mite-specific IgE in the serum when compared with control individuals.[27] The relation of atopy and NSAID hypersensitivity has also been observed by a number of other investigators.[28–37]

POSSIBLE MECHANISMS OF THE RELATION BETWEEN ATOPY AND NSAID HYPERSENSITIVITY

Because atopic diseases are mediated by specific antibodies of IgE class, and most cross-reactive reactions to aspirin and other NSAIDs are likely caused by cyclooxygenase 1 (COX-1) inhibition,[38,39] the relation between atopic diseases and aspirin/NSAID hypersensitivity constitutes an intellectual challenge. We have considered various pathogenic pathways that could explain this interaction.

1. Genetic factors. A critical enzyme for the synthesis of cysteinyl leukotrienes, leukotrienes C4 synthase (LTC4S), is controlled by a gene located in the long arm of human chromosome 5, close to genes related to atopy such as those determining the production of IL-4, IL-5, and IL-13.[40] Then, it could be hypothesized that a genetic linkage of atopic genes and LTC4S gene could be responsible for the association between atopy and hypersensitivity to NSAIDs. In this regard, various genetic polymorphisms including LTC4S gene and other loci that are associated to NSAID hypersensitivity have been reported.[41,42]
2. Inhibition of COX-1. As previously mentioned, respiratory and cutaneous reactions to aspirin and NSAIDs are mediated through inhibition of COX-1 isoenzyme.[38,39] Because OMA was observed with increased prevalence in atopic patients who concomitantly show NSAID intolerance, we investigated the presence of COX-1 inhibitory substances in commercial mite allergenic extracts using recombinant human COX-1 microsomal assays. COX-1 enzymic activity was inhibited by 76 and 70% with a 2000 AU/mL concentration of *D. farinae* and *D. pteronyssinus* extracts, respectively. It was proposed that inhibition of COX-1 by mite-derived constituents might contribute to the clinical picture of severe allergic reactions observed in some NSAID-sensitive atopic patients immediately after oral exposure to foods contaminated with mites.[43]

A related observation, recently published by Barret *et al.*, is that extracts from *Dermatophagoides* spp. and *Aspergillus fumigatus* stimulate the production of cysteinyl-leukotrienes by bone marrow-derived dendritic cells. Furthermore, using the Fluorescence-activated cell sorter they showed that extracts from *D. farinae*, *D. pteronyssinus*, and *A. fumigatus* enhanced the generation of leukotrienes by bone marrow mast cells transfected with Dectin-2. A glycan–dectin-2 interaction was postulated as the mechanism responsible for this stimulatory activity.[44]

To investigate the association between OMA and aspirin hypersensitivity, Blanco *et al.* investigated the presence of salicylates in mite-contaminated wheat flour by means of high-pressure liquid chromatography. No salicylates were shown.[7] However, Sato *et al.* have observed that opisthonotal gland secretion from *D. pteronyssinus* contains salicylaldehyde analog 2-formyl-3-hydrobenzyl formate.[45]

OTHER PATHOGENIC PATHWAYS

Other mite-activated mechanisms contributing to the inflammation and tissue damage observed in allergic diseases have been studied in recent years. Four of them are relevant in the context of nonallergic effects of mites.

1. Stimulation of innate immunity. It has been shown that antigen-presenting cells and cytokine production can be directly stimulated by mite products such as Der p2 and Der p7.[46]
2. Protease activity. Some allergenic proteins, mainly Der p1, Der p3, and Der p9, from mites are peptidases that are able to break mucosal barriers and activate dendritic cells.[2,47] Group 1 mite allergens (Der p1 and Der f1) are cysteine proteases that can activate eosinophils to release proinflammatory mediators.[48]
3. Toll-like receptor (TLR) 4–mediated inflammation. Der p2, a member of the ML (MD-2–related lipid recognition) domain lipid-binding family, promotes TLR4 signaling and TH2-mediated inflammation *in vivo* in a TLR4-dependent manner.[49]
4. Epigenetic changes. The strong contribution of environmental factors in the induction of epigenetic modifications resulting in the increase of asthma prevalence observed in the last 30 years has recently received a great deal of attention. Dust-mite allergens are among these environmental agents able to produce epigenetic changes through the expression of miRNA-16, mi-RNA 21, and miRNA-126 and the activation of TLR4, leading to increased inflammation, a TH2 response, suppression of GATA-3, and airway hyperresponsiveness.[50]
5. Effects on remodeling of the airways. Various studies have investigated the possible participation of house-dust mites in airway remodeling. First, mite proteases can cleave cell adhesion, induce cell death, and increase the permeability of lung epithelium.[51] Second, *Dermatophagoides* sp. peptidases can induce apoptosis in a bronchial cell model independent of tight junction perturbation.[52] Third, dust-mite allergen may stimulate airway cells to increase vascular endothelial growth factor (VEGF) secretion, potentially contributing to edema in airway remodeling. *Dermatophagoides* sp. extract stimulates A549 cells to secrete factors that dysregulate mesenchymal cell growth *in vitro*, increase VEGF secretion and expression of cell-associated VEGF, and stimulate those cells to secrete mediators that stimulate normal human lung fibroblasts to increase secretion of VEGF.[53,54] These investigators observed a dose-

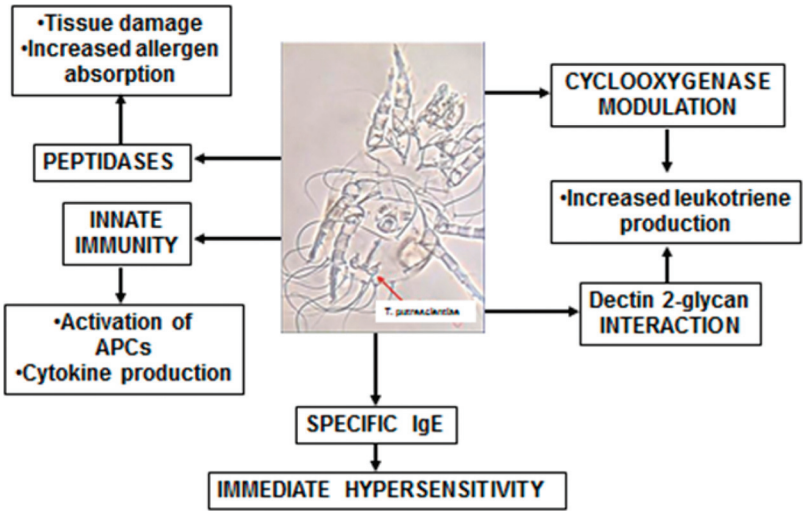

Figure 1. *Mechanisms of inflammation induced by mite constituents.*

dependent increase of aggregation and decreased adhesion of human lung microvascular endothelial cells in response to transforming growth factor β in conditioned media from confluent alveolar epithelial cells treated with *D. pteronyssinus* extracts.[53,55] Furthermore, *D. pteronyssinus* extract induced apoptosis and stimulated secretion of transforming growth factor β1 in A549 cells.[56]

These results led investigators to propose that dust-mite proteases and proteinase-activated receptors play a role in stimulating fibroblast-mediated events and reactivation of the epithelial-mesenchymal trophic unit involved in airway remodeling.[57] This can also occur in rhinitis and possibly sinusitis and additional studies are needed to further understand the mechanisms of this process and to examine alternative airway, nasal models, and additional allergens.

CONCLUSIONS

A subset of atopic individuals shows increased risk and severity of reactions to mites, aspirin, and NSAIDs. Various products released by domestic mites induce inflammatory processes through the activation of both immunologic (IgE-mediated) and nonimmunologic mechanisms, as depicted in Fig. 1. Although allergic reactions have been extensively studied, we are only beginning to understand additional nonallergic pathways that are activated by mite constituents. The relative clinical importance of these is presently unknown and deserves further consideration by basic and clinical investigators.

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