

REVIEW

Spider mites: common outdoor allergens among individuals living in rural areas

Y.-K. KIM*†‡, S.-H. CHO*†‡, K.-U. MIN*†‡ and Y.-Y. KIM*†‡

*Department of Internal Medicine, Seoul National University College of Medicine, †Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, ‡Clinical Research Institute, Seoul National University Hospital, Seoul, Korea

Introduction

Allergic diseases owing to domestic mites, such as house dust mites and storage mites, are a major health problem worldwide. House dust mites are important sources of allergens inside homes in humid areas worldwide [1,2]. Several studies conducted over the past few years have demonstrated that storage mites are major sensitizing allergens among farmers [3–5]. In addition, allergy to storage mites has not only been associated with occupational exposure, but also with damp housing conditions [6].

Spider mites (family *Tetranychidae*) form the family of phytophagous mites, which have a severe economic effect on agriculture [7] (Fig. 1). All spider mites are outdoor phytophagous mites which damage fruit leaves, and belong to the order Acari, and to the suborder Prostigmata, while house dust mites and storage mites belong to the suborder Astigmata [7,8] (Table 1). Spider mites rapidly develop large populations in early spring, damaging fruit leaves and in some cases causing defoliation (Fig. 2). Most spider mites feed to a depth of about 100 µm and completely remove cell contents so that no oxidized cytoplasm can develop. Each generation of spider mites lives for approximately 2 weeks at optimum spring temperatures (30 °C max. and 19 °C min.) with 10–12 generations per year [9]. Although predaceous mites attack spider mites, the current predator complex does not usually control spider mites, particularly when spraying programmes of organic phosphates or sulphur upset natural controls [10–13]. In fact, spider mites were negligible pests in fruit-cultivation before World War II. However, these mites have increased since pesticides were introduced to eliminate fruit moths 40 years ago [14]. From 102 species listed by McGregor in 1950, the total number of spider mite species reached 204 in 1955 as recorded by Pritchard and Baker, and has increased to nearly 1200 species today [8]. Surveys in the USA and Korea have demonstrated that the European red mite (*Panonychus ulmi*, ERM) and the two-

spotted spider mite (*Tetranychus urticae*, TSM) were the most common pests in apple orchards. TSM was the most common pest in pear orchards, and the citrus red mite (*Panonychus citri*, CRM) was the most common pest in citrus orchards [15–18]. There have been several case reports of occupational allergy to spider mites such as the TSM, ERM, and CRM [19–23]. Subsequently, cross-sectional studies have demonstrated that spider mites such as the CRM, ERM, and TSM are important allergens in the development of work-related asthma and rhinitis in fruit-cultivating farmers [24,25]. The aim of this review is to evaluate the clinical characteristics of spider mite-induced asthma, the prevalence of spider mite allergy in fruit-cultivating farmers and exposed children, the risk factors for the development of spider mite allergy, and spider mites' allergenic characterization and cross-reactivity with domestic mites.

Clinical characteristics of spider mite-induced asthma

Reunala *et al.* [19] first described type I allergy to TSM in two patients suffering from rhinitis, conjunctivitis and contact urticaria who worked in a greenhouse. Both patients had a high level of spider mite-specific IgE in their sera, and radioallergosorbent test (RAST) inhibition studies revealed no cross-reactivity between the spider mite and house dust mite allergens. Subsequently, Delgado *et al.* [20] described a case of TSM-induced occupational asthma and rhinoconjunctivitis confirmed by specific bronchial challenge with TSM extract. Meanwhile, Kroidl *et al.* [21] first described ERM-induced occupational asthma in residents of a fruit growing area.

We reported the first case of CRM-induced occupational asthma confirmed by bronchial challenge with CRM extract in a citrus farmer, as well as 15 subsequent cases among patients visiting our clinic [22]. In regard to asthmatic severity, based on a combination of symptoms and treatment requirements, as well as objective measurements of lung function [26], more than half of the asthmatics had severe asthmatic severity. On skin prick testing, all patients

Correspondence: Y.-Y. Kim, Department of Internal Medicine, Seoul National University College of Medicine, 28 Yonggondong, Chongnogu, Seoul 110-744, Korea.

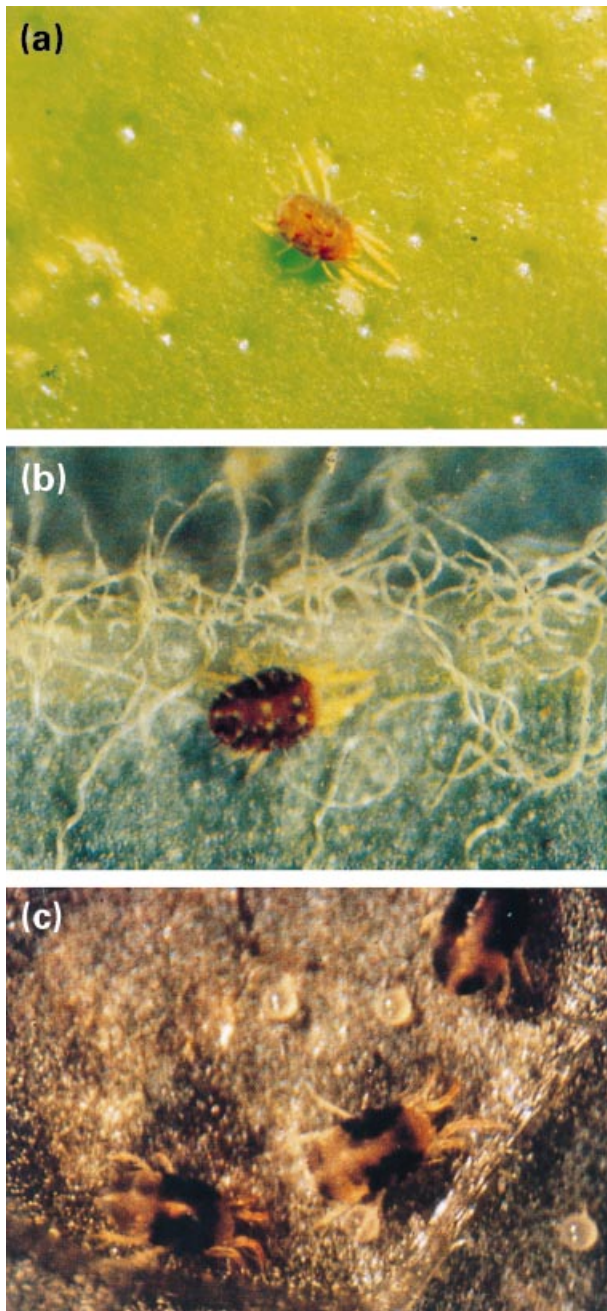


Fig. 1. Morphology of spider mites such as (a) citrus red mite (*Panonychus citri*), (b) European red mite (*Panonychus ulmi*), and (c) two-spotted spider mite (*Tetranychus urticae*).

showed strong reactions to CRM extract; 10 (62.5%) had an isolated positive response to CRM, while only six (37.5%) showed concurrent positive skin reactions to other common inhalant allergens.

The latent period between the first exposure and the onset of the symptoms of occupational asthma is highly variable,

ranging from several weeks to several years. The duration of latency seems to depend on the nature of the causal agent, and exposure duration and intensity to the sensitizing agent [27,28]. In patients with occupational asthma caused by high molecular weight agents, the latent period was longer than in those with asthma caused by low molecular weight agents [27]. In subjects who were continuously exposed to the causative agent, the latent period was shorter than in those who were intermittently exposed [28]. In patients with CRM-induced occupational asthma, the mean length of the latency period was more than 10 years, which was longer than in those with asthma owing to other causative agents. This may be explained by the fact that the CRM-derived allergens had a high molecular weight, and the citrus farmers had been intermittently exposed to CRM-derived allergens, which peak in late spring and mid fall, but are minimal during other periods, especially in winter [18].

Cross-sectional studies of workers in animal laboratories have suggested that asthma may be the end-response in the chain of occupational sensitization, which begins with eye and nose symptoms [29]. However, little evidence for such a temporal relationship was found in a longitudinal study on a similar workforce [30]. In our study, all of the patients with CRM-induced occupational asthma except one complained of concurrent nasal symptoms, which had developed before the development of asthmatic symptoms. This finding suggests that CRM-induced occupational rhinitis may occur earlier than asthma after sensitization to CRM-derived allergens.

TSM is known to be the most important mite which damages pear and apple leaves in Korea [12,14,17]. Recently, we evaluated the clinical significance of TSM-derived allergens in asthmatic nonfarmers living near pear orchards [31]. Sixteen (31.3%) out of the 50 asthmatics enrolled in this study revealed positive skin responses to TSM extracts. Ten out of the 16 asthmatics with positive skin responses to TSM showed significant bronchoconstriction following inhalation of TSM extract. Their asthmatic symptoms were aggravated seasonally, especially in summer and early fall, which are the seasons when the levels of TSM densities on the pear leaves are at their highest [12,14].

Both immunological and nonimmunological mechanisms are involved in occupational asthma owing to high molecular weight agents. The immunological mechanism can have either an IgE or a non-IgE reaction. The IgE-mediated reaction is likely to be responsible for the asthmatic symptoms in spider mite-induced occupational allergy. In our study [22], all of the patients with CRM-induced occupational asthma had strong positive responses to the CRM antigen on skin prick tests and high serum-specific IgE antibodies to the CRM antigen. The ELISA inhibition test confirmed the specificity of specific IgE binding. Moreover,

Table 1. Relationship between spider mites and domestic mites

Order	Suborder	Family	Genus	Species
Acari	Astigmata	Pyroglyphidae	Dermatophagoides	<i>D. pteronyssinus</i>
				<i>D. farinae</i>
				<i>E. maynei</i>
				<i>G. domesticus</i>
		Glycyphagidae	Lepidoglyphus	<i>L. destructor</i>
			Blomia	<i>B. tropicalis</i>
				<i>A. siro</i>
		Acaridae	Acarus	<i>A. siro</i>
			Tyrophagus	<i>T. putrescentiae</i>
				<i>T. urticae</i>
	Prostigmata	Tetranychidae (spider mites)	Tetranychus	<i>T. urticae</i>
			Panonychus	<i>P. ulmi</i>
				<i>P. citri</i>

in our survey of citrus farmers [24], the prevalence of asthma was higher in farmers with high levels of serum IgE antibody to CRM than in those with low serum-specific IgE. These findings suggest that it is the high molecular weight proteins within the spider mite extracts that may induce IgE-mediated bronchoconstriction in exposed workers.

Epidemiology of spider mite allergy in fruit-cultivating farmers

A cross-sectional survey [24] was performed to evaluate the prevalence of spider mite allergy in 181 citrus farmers in Korea. On skin prick tests, the most common sensitizing allergen was the CRM (16.5%), followed by cockroach (11.0%), *D. pteronyssinus* (9.9%), and *D. farinae* (9.3%). Nine percent of the citrus farmers revealed a positive skin

response only to CRM. Fifty-five (30.3%) of the 181 subjects complained of asthmatic symptoms, and when methacholine bronchial provocation tests were performed on these subjects, 22 of them (12.1%) exhibited bronchial hyperresponsiveness to methacholine. Among the 22 asthmatic subjects, 12 (54.5%) had positive skin responses to CRM. Eleven (50%) of these were CRM-sensitive asthmatics whose asthmatic symptoms had developed after work and had been aggravated in the workplace. On skin prick tests, 18 (60%) of 30 farmers with positive skin response to CRM showed an isolated positive skin response to CRM, although 12 (40%) showed positive skin responses to house dust mites. ELISA inhibition test showed that minimal inhibitions were noted with additions of *D. pteronyssinus* in subjects with an isolated skin reaction to CRM, while in those with positive skin responses to both CRM and *D. pteronyssinus*, moderate inhibitions were noted. They had worked on citrus farms for an average of 21.9 years (range seven to 25 years). The mean duration of latency between beginning work on the citrus farm and the onset of asthmatic symptoms was 13.5 years (range seven to 25 years). This was similar to that of patients with CRM-induced occupational asthma visiting our outpatient clinic, in whom it was 12.4 years [23].

Recently, we also performed a cross-sectional study to evaluate the prevalence of type I hypersensitivity to spider mites in 725 apple farmers, particularly the ERM and TSM. The results of skin prick tests in the apple farmers indicated that ERM (23.2%) and TSM (16.6%) were the most common sensitizing allergens. Forty (8.6%) of the farmers had isolated skin responses to spider mites. One hundred and nineteen farmers (16.4%) complained of work-related asthmatic symptoms. This was higher in farmers with positive skin responses to spider mites than in those with negative skin responses to spider mites and those with positive skin responses to any allergen tested. The results



Fig. 2. Damage of citrus leaf caused by citrus red mites. The colour of the damaged citrus leaf (right) is yellow compared to the undamaged leaf (left).

of our cross-sectional studies suggest that spider mites, especially the CRM, ERM and TSM, are important causative allergens in the development of occupational asthma in fruit-cultivating farmers.

Epidemiology of spider mite allergy in children living in rural areas

We performed a cross-sectional survey in order to evaluate the prevalence of sensitization to CRM and its relationship with bronchial responsiveness among children living near citrus orchards [31,32]. On skin prick tests, the most common sensitizing allergens in order of decreasing frequency were *D. pteronyssinus* (26.6%), *D. farinae* (22.7%), CRM (14.2%), and cockroach (11.3%). The prevalence of asthma, evaluated by a questionnaire and methacholine bronchial provocation testing, was significantly greater in children who were sensitized to the CRM than in those who were not (5.4% vs 4.0%, 95% CI 2.9–5.3). Moreover, rate of positive bronchial responsiveness to methacholine was significantly higher in nonasthmatic children with positive skin responses to the CRM than in those with negative responses (48.2% vs 22.9%, 95% CI 26.2–38.2). These findings suggest that spider mites such as the CRM are common sensitizing outdoor allergens and important causative allergens in the development of asthma in exposed children living in rural areas.

Risk factors for the development of spider mite allergy

Among the potential determinants for sensitization to certain allergens, four factors are worthy of particular attention. Two are measures of environmental exposure: the level of exposure to the sensitizing agent and concomitant exposure to potential modifying factors, particularly respiratory irritants, such as tobacco smoke. The other two are expressions of genotypes: atopic status and human HLA constitution. Environmental exposure may conveniently be divided into two factors: length (or duration) and level (or intensity). Although sensitization to a causative allergen requires exposure to only a small dose, it is possible that high doses may be associated with a greater risk of sensitization. The relationship between environmental exposure and sensitization to indoor allergens has been previously studied. The results from a follow-up of a cohort of children by Sporik *et al.* [33] showed that exposure to high levels of house dust mite allergens increased the risk of sensitization. Recently, we performed a cross-sectional study to evaluate the effect of environmental exposure on the sensitization to the CRM on children living in rural areas [34]. This study demonstrated that children who visited citrus orchards frequently, or had been living near citrus orchards, exhibited enhanced skin responses to the CRM. These findings

suggest that environmental exposure is a major determinant of the risk of sensitization to spider mites such as CRM.

Human leucocyte antigen (HLA) class II genes encoding for HLA class II molecules are likely candidates for controlling the immune response to allergens. Many associations between class II alleles and specific IgE responses to specific allergens have been investigated. In general, significant associations have only been found with simple, highly purified allergens, but not with the more complex ones [35–37]. We investigated whether susceptibility or resistance to CRM-induced asthma was associated with HLA-DRB1 alleles [38]. The results of our study showed that CRM-induced asthma not only had a strong positive association with HLA-DRB1*07, but also had a strong negative association with HLA-DRB1*04. These associations were more remarkable in the patients who showed positive skin responses both to the CRM and to the house dust mite. These findings suggest that DRB1*07 is involved in the susceptibility to the development of CRM-sensitive asthma, and that HLA-DRB1*04 plays a role in protecting against the development of CRM- and house dust mite-sensitive asthma. However, we cannot preclude the possibility of an association between HLA-DQ alleles and CRM-sensitive asthma, because HLA-DR4 exhibits a linkage disequilibrium with HLA-DQ4 and DR7 exhibits a linkage disequilibrium with DQ2 in Koreans [39].

Characteristics of spider mite-derived allergens and their cross-reactivity with domestic mite-derived allergens

Crude *D. pteronyssinus* is a source of many allergens. Extracts have been shown to contain as many as 32 different IgE-binding components, as assessed by SDS-PAGE and immunoblotting [40]. In our study [41], CRM extracts were shown to contain five different IgE-binding components in 10 citrus farmers with CRM-induced asthma, as assessed by SDS-PAGE and immunoblotting. Of these five protein bands, 23.6 kDa and 34 kDa molecular weight proteins may be the major allergens of CRM extracts, because 80% of these 10 citrus farmers exhibited IgE binding components to these protein bands. In apple farmers, both the TSM and ERM extracts contained more than 10 different IgE-binding components. Among these, at least three IgE-binding components were shown to major allergens on SDS-PAGE and IgE immunoblotting.

Spider mites belong to the order Acari, the suborder Prostigmata, and the spider mite family (Tetranychidae). CRM and ERM belong to the genus *Panonychus*, and TSM belongs to the genus *Tetranychus* (Table 1). Domestic mites such as house dust mites and storage mites belong to the order Acari, but to the suborder Astigmatia. Because of the dual domestic exposure in some populations, many

investigators have been able to evaluate the allergenic cross-reactivity between house dust mites and storage mites [42–47]. Park *et al.* [47] reported a marked inhibition of *T. putrescentiae*-specific IgE with *D. pteronyssinus* extract, but found that *D. pteronyssinus*-specific IgE was not inhibited by *T. putrescentiae* in urban areas in Korea. They suggested that many of the allergenic determinants of *T. pteronyssinus* may be cross-reactive to *Dermatophagoides* spp. However, few studies have been performed to determine the allergenic cross-reactivity between spider mites and domestic mites. Burches *et al.* [48] reported that the specific IgE to *T. urticae* could not be detected in the absence of the specific IgE to *D. pteronyssinus*. However, Astarita *et al.* [21] reported that TSM-specific IgE binding was not inhibited by *D. pteronyssinus* in farm workers. Our previous study [24] revealed that CRM-specific IgE binding was partially inhibited by *D. pteronyssinus* extract in citrus farmers with positive skin responses to both CRM and *D. pteronyssinus*. However, minimal inhibition was noted with additions of *D. pteronyssinus* in farmers with isolated skin responses to the CRM. In the sera of rural children, ELISA inhibition tests showed that IgE binding to the CRM was minimally inhibited with additions of *D. pteronyssinus* and *T. putrescentiae*, among those with positive skin responses to both CRM and *D. pteronyssinus*, as well as to only CRM. However, the IgE bindings were inhibited significantly with the additions of spider mites ERM and TSM [34]. In a study on apple farmers [41], ELISA inhibition tests showed that ERM-specific IgE binding was completely inhibited by the CRM, but only partially inhibited by the TSM, *T. putrescentiae*, and *D. pteronyssinus*, in decreasing order. However, TSM-specific IgE binding was only partially inhibited by the CRM, ERM, *T. putrescentiae*, and *D. pteronyssinus*, in decreasing order. These findings suggest that spider mite-derived extracts contain common shared allergens with domestic mite-derived extracts, in addition to species-specific allergens. With regard to the allergenic cross-reactivity between spider mites and domestic mites, it seems that the closer the taxonomic relationship between mite species, the greater the level of cross-allergenicity.

Conclusion

In parallel with changes in lifestyle over the last 50 years (sedentary living in warm houses with extensive furnishing and low ventilation rates), there has been a progressive increase in the prevalence and morbidity of asthma in many parts of the world. A large proportion of the patients are sensitized to one or more of the allergens found predominantly inside houses, that is, indoor allergens. However, there have been also changes in outdoor environments. Although predaceous mites attack spider mites, the current predator complex does not usually control spider mites,

particularly when spraying programs of organic phosphates or sulphur upset the natural controls. In fact, spider mites were negligible pests in fruit-cultivation before World War II, but have increased and have a severe economic effect on agriculture worldwide since pesticides were introduced 40 years ago to eliminate fruit moths. These environmental changes may play a role in the development of spider mite allergy. In fact, epidemiological studies, performed after there had been several case reports of occupational allergy due to spider mites, have demonstrated that spider mites such as the CRM, ERM and TSM are important allergens in the development of work-related asthma and rhinitis in fruit-cultivating farmers. Moreover, outdoor spider mites are not only common sensitizing allergens in workers, but are also associated with the development of asthma in children living in rural areas. Therefore, further basic and clinical studies will be needed in order to develop preventive techniques and therapies for outdoor spider mite-induced allergic diseases.

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