Published in final edited form as:

J Allergy Clin Immunol Pract. 2019 February ; 7(2): 664–666. doi:10.1016/j.jaip.2018.07.014.

Could chiggers be contributing to the prevalence of galactose-alpha-1, 3-galactose sensitization and mammalian meat allergy?

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TO THE EDITOR:

It is now well recognized that IgE antibodies to galactose-alpha-1,3-galactose (alpha-gal) result in delayed anaphylaxis to mammalian meats, including beef, pork, and lamb, among others.^{1–3} Alpha-gal is an oligosaccharide that was originally described as a “B-like” blood group substance in nonprimate mammals.^{1,3} Cases of alpha-gal allergy have been reported around the world including in the United States, Europe, Australia, Asia, and Central America.^{1,4} In general, patients have reported symptoms of generalized urticaria, angioedema, or anaphylaxis anywhere from 3 to 6 hours after ingestion of mammalian meat, which was previously tolerated.^{2,3} A well-established mechanism of alpha-gal sensitization is tick bites. Multiple species of ticks including *Amblyomma americanum* (the lone star tick), *Ixodes ricinus*, *Ixodes holocyclus*, *Amblyomma cajennense*, *Amblyomma sculptum*, and *Haemaphysalis longicornis* have all been implicated in alpha-gal sensitization.^{1,2,4} Ticks are parasitic arthropods in the order Ixodida that live by sucking the blood of the host mammal (Figure 1).^{1,6} Alpha-gal has been demonstrated to be present in the gastrointestinal tract of the *I. ricinus* and the saliva of *A. sculptum*, which supports the theory that tick bites can cause the production of IgE to alpha-gal and subsequently mammalian meat allergy.^{7,8} This suggests that alpha-gal might be present in numerous species of ticks, either intrinsically within tick glycoproteins or as part of microbes within ticks, and raises the possibility of its presence in other mite species known to feed parasitically on mammals, including the Trombiculidae, whose larvae are commonly known as chiggers.^{1,6,9} This larval stage is the only point in the mites’ life cycle when they can bite host animals. Once they latch onto skin, they inject digestive enzymes and can transmit diseases to human hosts, such as scrub typhus. They also travel extensively along the epidermis and remain attached for several days. They most commonly affect the legs and waistline and are often drawn to areas of thin epidermis and high humidity. Their bites are not painful, but they do cause groupings of papular and papulovesicular lesions that are very erythematous and pruritic. The pruritus usually begins within hours of the bite and resolves within 72 hours. The lesions themselves

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

are generally present for 1 to 2 weeks. Other common names for trombiculid mites include harvest mites, harvest bugs, harvest lice, Mower's mites, and redbugs.^{6,9} Unfortunately, larval ticks, commonly called "seed ticks," and their bites can be very difficult to differentiate from chiggers for both a lay person and physician, though typically seed tick bites result in ticks embedded in the tissue, which one would expect to be reported by affected individuals.² In terms of mature adult ticks, patients usually only find a single tick and/or lesion on them at a time. However, there have been a few case reports of multi-infestations of larval ticks causing numerous pruritic papules, including a case report of more than 100 *Amblyomma testudinarium* larvae removed from a patient in Japan.¹⁰ Therefore, seed ticks and chiggers are easily confused and their bites can be almost indistinguishable.

Case 1 is a 67-year-old man with a past medical history significant for hypertension, hyperlipidemia, and chronic obstructive pulmonary disease who was referred for food allergy to mammalian meat in January 2018. He had no prior history of food allergy or atopic disease. Approximately 4 weeks before his initial reaction, he reported being bitten by 100 to 200 "chiggers" on his lower legs while hiking in North Carolina. The bites consisted of "red bumps" that were very pruritic and erythematous for approximately 48 hours, after which he received steroids resulting in prompt resolution of pruritus. He then began having reactions ranging from diffuse hives to oropharyngeal edema requiring epinephrine. He had a total of 4 different reactions approximately 3 to 4 hours after eating either beef or pork. The patient is an avid outdoorsman, and he did not have any known tick bites or find any ticks on his person at the time of this episode. He has been bitten by ticks several times in the past, but not in many years. On presentation to our clinic, the patient had an alpha-gal IgE level >100 kU/L (normal <0.35 kU/L) and a beef IgE level that was elevated at 43.8 kU/L (normal <0.10 kU/L).

Case 2 is a 28-year-old previously healthy man who was referred for evaluation of food allergy to mammalian meat in November 2017. He had no prior history of food allergy or atopic disease. He was bitten by 4 to 5 ticks while hunting in Adams County, Ohio, approximately 2 months before his visit. He was able to identify the ticks as Lone Star ticks by the characteristic white spot on their backs. Approximately 1 month later, he was bitten by more than 50 "chiggers," described as bright red, while working outdoors in close contact with dense shrubbery. The bites were small, erythematous, intensely pruritic, and localized to areas with tight-fitting clothing such as his waistband. Approximately 3 weeks after those bites, he developed diffuse hives approximately 4 hours after consumption of beef. This happened reproducibly on several occasions. In the interim between the tick and chigger bites, he reported being able to tolerate mammalian meat without issues. On presentation to our clinic, he had an alpha-gal IgE level of 50.6 kU/L.

Case 3 is a 46-year-old woman with little past medical history from the Eastern Shore of Virginia, who first developed urticaria and swelling in December 2017 at 3 am after a meal that included meatloaf. On subsequent allergy evaluation, she was found to have an alpha-gal sIgE level of 46 kU/L and has subsequently avoided red meat. Although she had a remote history of tick bites, the only recent exposures she recalled involved very pruritic

bites from small red “insects” that she and her husband identified as chiggers. On repeat testing at UVA, she had a total IgE level of 774 kU/mL and alpha-gal sIgE of 609 kU/mL.

The above patients’ histories illustrate the confusion that can arise between chiggers and seed ticks, which is a common dilemma when the organisms themselves cannot be expertly identified. These cases also raise the possibility that other species of mites, namely Trombiculidae (chiggers), might contribute to alpha-gal sensitization. In further support of this association, a questionnaire about exposures was answered by 311 alpha-gal IgE-sensitized subjects in ongoing studies at the University of Virginia. Of these, 301 reported positively to a history of either tick or chigger bites in the past 10 years. Interestingly, 17 (5.5%) reported a history of chigger bites, but no tick exposures. Whether these bites are from chiggers or seed ticks, they appear to be associated with very high levels of IgE to alpha-gal. Further studies searching for the alpha-gal epitope in the gastrointestinal tracts of chiggers should be performed to help determine if chiggers could potentially be another cause of mammalian meat allergy. More importantly, allergists should be aware that patients may report “chigger” bites, and based on that fact alone should not dismiss alpha-gal sensitization as a possible diagnosis.

Acknowledgments

No funding was received for this work.

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Clinical Implications

- Patients may report “chigger” bites before galactose-alpha-1,3-galactose sensitization. It remains unclear whether mammalian meat allergy can be caused by the bites of true chiggers, which are red, or if the bites are actually due to the often confused larval “seed ticks.”

FIGURE 1.

Reduced classification of Acari (ticks and mites) emphasizing important human associates.
 1,2,5,6 The asterisks (*) indicate the known genera of ticks that have been implicated in
 alpha-gal sensitization.