

Recall urticaria—A new clinical sign in the diagnosis of alpha-gal syndrome

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Clinical Implications

- Diagnosis of alpha-gal syndrome remains difficult. Thus, clinical signs such as recall urticaria at the location of previous tick bites may be helpful diagnostic tools, not only as symptoms in clinical history but also for evaluating the results of oral provocation tests.

TO THE EDITOR:

The alpha-gal syndrome, a new type I allergy entity to the carbohydrate epitope galactose- α -1,3-galactose (α -gal), was first described in 2009.¹ High concentrations of α -gal are found in mammalian food products (eg, beef, pork, and venison), especially in organ meats.² Patients tend to show anaphylactic symptoms 3 to 6 hours after ingestion of red meat,³ which sometimes makes diagnosis difficult.

Furthermore, a link between tick bites and alpha-gal syndrome has been described.⁴ The presence of α -gal in the gastrointestinal tract⁵ as well as in the saliva⁶ of ticks has been documented, which makes sensitization from tick bites even more likely.⁴

However, recall urticaria (RU) has been known as a clinical sign since its first description by Kelso et al⁷ in 1994. It is defined as a local reaction (wheal) in areas with previous antigen exposure when “antigens enter the body from another source.”⁸ First described in patients undergoing subcutaneous allergen-specific immunotherapy, it has also been observed in patients suffering from other allergies, such as heparin allergy.⁹

In the following text, we present 2 young male patients who developed alpha-gal syndrome with RU at the skin site of previous tick bites as the first symptom of an imminent anaphylactic reaction. To our knowledge, it is the first description of this clinical sign in such patients, but it may have been overlooked in many previous cases.

A 25-year-old male patient reported having 7 to 8 anaphylactic reactions during the past 15 months. The typical reaction included hives, nausea, dyspnea, and dizziness. All episodes occurred 3 to 5 hours after ingestion of red meat, once with alcohol as an augmenting cofactor. The patient did not take any medication.

As a first symptom, approximately 10 to 15 minutes before a generalized reaction was noticed, every episode started with a wheal measuring about 5 mm in exactly the same spot the patient had been bitten by a tick a few months before.

A skin prick test (SPT) with raw pork kidney suspension and Gelafundin 4% (a gelatin-based volume expander rich in α -gal; dilution 1:1) was performed, as well as intradermal testing with Gelafundin 4% (dilution 1:10). The levels of total serum IgE

(Siemens, Munich, Germany) and specific IgE to α -gal (ThermoFisher Scientific, Waltham, Mass) were measured, as well as the baseline tryptase level (ThermoFisher Scientific). In addition, an oral provocation test (OPT) with cooked pork kidney was performed to confirm the diagnosis.

The total serum IgE level was 48 IU/mL, and the level of specific IgE to α -gal was elevated to 2.55 kU/L. The results of SPT with raw pork kidney suspension (3 mm) and intradermal testing with Gelafundin 4% diluted 1:10 (5 mm) were positive, whereas the SPT results with Gelafundin 4% diluted 1:1 were negative. SPT in healthy control subjects with raw pork kidney suspension ($n = 10$) and Gelafundin 4% diluted 1:1 ($n = 152$), as well as intradermal testing with Gelafundin 4% diluted 1:10 ($n = 10$), elicited no irritation. The baseline tryptase level was 6.05 μ g/L.

We performed an oral challenge with cooked pork kidney under careful monitoring, which reproduced the RU as described by the patient 130 minutes after the first dose (3 g) and 10 minutes after the second dose (5 g) of pork kidney was administered (Figure 1, A). Tryptase levels (measured 30 and 90 minutes after first symptoms occurred) did not increase (5.55 μ g/L and 5.97 μ g/L, respectively). The challenge was stopped, and the patient was treated with an antihistamine (dimetindene 8 mg, intravenous) and corticosteroid (prednisolone 200 mg, intravenous) before other systemic reactions could occur (Figure 1, B). To better understand the underlying mechanisms of RU, we asked the patient for a punch biopsy but he refused. However, no further episodes have been observed under a strict red meat elimination diet (12 months) to date.

A 22-year-old male patient reported having several anaphylactic reactions within the past 4 years. His symptoms included abdominal pain, diarrhea, as well as dyspnea and loss of consciousness in one of the episodes. All episodes occurred several hours after ingesting food. Initially, a common trigger could not be identified. However, the patient remembered a tick bite several months before the first anaphylactic reaction, which showed a delayed healing process.

In this patient, each of the reactions started with pruritus and a wheal at the site of the previous tick bite as the first symptoms of generalized anaphylaxis, approximately 10 minutes before other systemic symptoms occurred.

As in the other patient described above, SPT with cooked pork kidney and Gelafundin 4% (dilution 1:1) and intradermal testing with Gelafundin 4% (dilution 1:10) were performed. Total serum IgE and specific IgE levels were measured. In addition, a basophil activation test (Flow CAST, Bühlmann Laboratories AG, Basel, Switzerland) with α -gal-carrying protein was performed.

The SPT yielded a positive reaction to cooked pork kidney (3 mm) and Gelafundin 4% (4 mm). Again, the intradermal test to Gelafundin 4% (8 mm) showed a positive result. The patient's total serum IgE level was 52.6 IU/mL, whereas that of specific IgE to α -gal was elevated to 4.37 kU/L. A basophil activation test with α -gal-carrying protein (33.5% CD63 expression at a concentration of 1.6 ng/mL; 17.1% CD63 expression at a concentration of 0.32 ng/mL) also showed positive results (basal level, 2.5% CD63 expression).

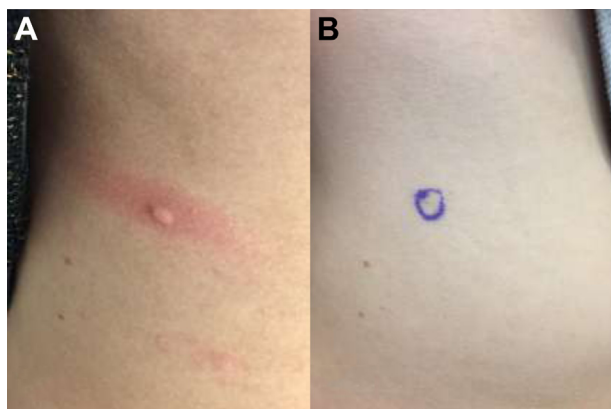


FIGURE 1. A, RU at the site of a previous tick bite as first symptom of an imminent anaphylactic reaction during oral challenge with kidney preparation. B, The same tick bite site (blue circle), 20 hours after the local reaction to challenge, had declined after treatment.

With the patient having refused oral challenge tests and based on these findings, a red meat elimination diet was initiated and has been maintained to date, resulting in the absence of further symptoms.

The diagnosis of alpha-gal syndrome with RU at the site of a previous tick bite was made in both patients. However, diagnosing this syndrome often is difficult owing to lack of awareness and the delayed appearance of the reactions. Moreover, elevated sIgE to α -gal can be found with no clinical relevance. Therefore, clinical signs such as RU can be helpful diagnostic tools.

Although the underlying mechanisms of RU remain unclear, possible explanations include increased local mast cell numbers. Weber et al,⁹ however, could not find increased numbers of local mast cells in a punch biopsy of a patient suffering from RU and heparin allergy. Alternative explanations include increased sensitivity of local mast cells or increased sensitivity further downstream, for example, in endothelial cells. Epigenetic imprinting might provide another answer for the persistent reactivity even with low antigen concentrations, which needs to be further investigated in the future. In any case, it is commonly hypothesized that RU is caused by a local long-lasting “type I tissue memory.”^{7,9}

Thus, the workup of relevant patients should also include questioning for tick bites and consecutive RU at the same location. Apart from being an important clinical sign in medical history, the observation of RU has the potential to be an important safety feature for OPT. As shown in our patient who underwent oral challenge, we were able to perform the OPT using small amounts of cooked pork kidney, thus allowing us to avoid more severe anaphylaxis. Reactions to pork kidney often occur faster than to red meat, presumably owing to higher

accessible α -gal content.² The RU sign appeared 130 minutes after ingestion of 3 g and 10 minutes after ingestion of another 5 g of kidney (cumulative dose 8 g), and it gradually resolved in time with antiallergic treatment.

Our report underlines that RU at the location of previous tick bites in patients with alpha-gal syndrome—apart from being a helpful clinical sign for physicians in diagnosing this syndrome and evaluating results of oral challenge tests—has the potential to make OPT safer.

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