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Short communication

Delayed hypersensitivity reaction to mammalian galactose-α-1,3-galactose (α-Gal) after repeated tick bites in a patient from France

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ABSTRACT

The α-Gal syndrome is a tick-associated and emerging IgE-mediated hypersensitivity reaction directed against the carbohydrate Galα1-3Galβ1-(3)4GlcNAc-R (α-Gal) epitope after red meat intake. Herein, we describe a clinical case of a 44-year-old French patient who suffered from recurrent anaphylactic reactions after mammalian meat consumption for five years before the final diagnosis of the α-Gal syndrome was established in 2018. The patient also reported multiple tick bites prior to symptom onset. This unique type of allergy has increasingly been reported across the world, but it is still unknown in many European countries. Therefore, the present clinical case should increase awareness among primary care practitioners and further improve the early diagnosis of the α-Gal syndrome in affected individuals.

1. Introduction

During the course of evolution, humans, apes and Old World monkeys lost the ability to synthesize the carbohydrate Galα1-3Galβ1-(3)4GlcNAc-R (α-Gal) epitope due to functional inactivation of the gene coding for α-1,3-galactosyltransferase (Galili and Swanson, 1991). The selective advantage of this unique evolutionary event, estimated to have occurred about 28 million years ago (Koike et al., 2007), lies in the ability of the immunocompetent crown catarrhines to generate antibodies to α-Gal (Galili et al., 1984), which may also be protective against pathogens carrying α-Gal on their surface (Yilmaz et al., 2014; Cabezas-Cruz and de la Fuente, 2017). By contrast, these antibodies (predominately IgG2 and IgM) are involved in the hyperacute rejection of xenotransplants in humans (Sandrin and McKenzie, 1994).

Nevertheless, the production of anti-α-Gal IgE has recently been associated with potentially fatal anaphylactic reactions to mammalian red meat consumption (Commins et al., 2009). Unlike other typical IgE-mediated food hypersensitivities, the α-Gal syndrome is characterized by a delay in onset of symptoms that usually occurs 3–6 hours following consumption of mammalian meat (e.g. beef, pork, lamb) or other α-Gal-containing products (e.g. gelatin, dairy) (Wilson et al., 2017). In 2007, van Nunen et al. (2007) described the association between tick bites and the anaphylaxis to mammalian meat. The strong correlation between this novel type of allergy and tick bites has further been demonstrated by a recent detection of glycoproteins with terminal α-Gal moieties in the saliva of certain ixodid tick species (Araujo et al., 2016; Chinuki et al., 2016; Mateos-Hernández et al., 2017; Cabezas-Cruz et al., 2018; Crispell et al., 2019). Although α-Gal syndrome has increasingly been reported all over the globe (van Nunen, 2018), it is still quite unknown in primary care settings in Europe, and due to the atypical long delay in the onset of the systemic allergic reaction and the unspecific clinical symptoms, this tick-acquired mammalian meat allergy often remains undiagnosed (Brestoff et al., 2017; Crispell et al., 2019).

Herein, we report a clinical case of a French patient who experienced recurrent anaphylactic reactions to mammalian meat consumption for five years before the final diagnosis of the α-Gal syndrome was made. The possible implication of *Ixodes ricinus* ticks in inducing the production of IgE antibodies to α-Gal and consequent development of the α-Gal syndrome is also discussed.

2. Clinical case presentation

In August 2018, a 44-year-old female living near Dole, a small village in eastern France, was presented to an urgent care center with an allergic reaction that occurred approximately 3–4 hours after having a barbecue. The symptoms included generalized urticaria, malaise, fatigue, dyspnoea, tachycardia, hypotension, nausea, and severe

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abdominal pain. The patient reported multiple tick bites in the past few years and the last one was acquired in July 2018 while she was walking with her dog. Skin-prick test was slightly positive for histamine but negative for other commercial food extracts including beef, pork, lamb, chicken, turkey, and cow's milk. Basal serum tryptase test performed in November 2018 was normal (5.13 μg/L; reference range < 11.4 μg/L), so the mast cell activation syndrome (MCAS) was ruled out. Finally, laboratory testing (ImmunoCAP™, Thermo Fisher Scientific, Phadia, Uppsala, Sweden) indicated significantly high levels of IgE against α-Gal (1.75 kUA/L) and beef (1.17 kUA/L), and slightly elevated IgE titers to lamb (0.72 kUA/L) and pork (0.64 kUA/L). The reference range of IgE titers for these allergens was < 0.35 kUA/L. Based on the presented results the diagnosis of the α-Gal syndrome was made and the patient was prescribed prednisolone, antihistamines, bronchodilators and an adrenalin autoinjector. In addition, the patient was advised to avoid mammalian meat, innards, and other products containing α-Gal. Prevention of tick exposure was also recommended. By following these recommendations, no further reactions or clinical signs had been reported in the patient.

However, before the final diagnosis was established, the patient was hospitalized several times in the last five years after displaying similar clinical symptoms and always following consumption of red meat. In some cases, usually after eating sausages or innards, the allergic reactions developed more rapidly and the symptoms appeared within 1 h following the allergen exposure. In 2017, she was presented to the emergency department after a brief loss of consciousness, vomiting, diarrhoea and abdominal pain, where she was treated for an idiopathic hypersensitivity reaction. Prior to the symptom onset, ticks bit the patient on several occasions and thus infection by tick-borne pathogens was initially suspected. Therewith, serological testing for *Borrelia burgdorferi* sensu lato (s.l.), spotted and typhus group rickettsiae, *Bartonella* spp., *Francisella tularensis*, *Coxiella burnetii*, *Brucella* spp. and *Babesia divergens* was performed. The immunofluorescence antibody test for *B. divergens* was positive (antibody titer 1/120; cut-off value ≥1/60), while the exposure to other pathogens could not be confirmed. Specific treatment involved an oral combination of atovaquone with proguanil hydrochloride and azithromycin. Since the patient spent some time in Guyana, South America (1999–2000), an additional test for *Trypanosoma cruzi* was performed and it returned a negative result.

3. Discussion

After the oligosaccharide α-Gal was recognized as a source of delayed anaphylaxis to mammalian meat in 2009 (Commins et al., 2009), cases of the α-Gal syndrome associated with red meat consumption have increasingly been reported worldwide including France (van Nunen, 2018). In the US, a growing body of research suggests that the IgE immune response to α-Gal is associated with bites of *Amblyomma americanum* (Commins et al., 2011; Crispell et al., 2019), while bites of other tick species, *Amblyomma sculptum, Amblyomma testudinarium* and *Haemaphysalis longicornis* have been proposed as a possible cause of red meat allergy in Brazil and Japan, respectively (Araujo et al., 2016; Chinuki et al., 2016; Hashizume et al., 2018). Given that none of the abovementioned tick species is present in Europe, the possible implication of *I. ricinus* in α-Gal syndrome development has often been discussed (Hamsten et al., 2013a; van Nunen, 2018). The previous study demonstrated the occurrence of α-Gal epitopes in the gastrointestinal tract of *I. ricinus*, which are presumably exposed to the host during blood feeding (Hamsten et al., 2013a). The presence of α-Gal-containing proteins in other tick species found in Europe (i.e. *Hyalomma marginatum*, *Rhipicephalus bursa*) does not exclude the possible implication of these ticks in the α-Gal syndrome (Mateos-Hernández et al., 2017).

However, the origin of α-Gal in ticks was uncharacterized until recently, and the possible epitope sources included the residual mammalian glycoconjugates from a previous blood meal and tick midgut bacteria that carry α-Gal on the outer membrane (Steinke et al., 2015). However, a more recent study provided strong evidence for the endogenous α-Gal production in *Ixodes* ticks (Cabezas-Cruz et al., 2018). Apart from being involved in the α-Gal synthesis, the results also suggest that tick galactosyltransferases may play a role in tick development, tick-pathogen interactions and possibly in the etiology of the α-Gal syndrome (Cabezas-Cruz et al., 2018). This outstanding discovery, however, opens further questions on whether the IgE immune response to α-Gal in humans is triggered by the α-Gal moieties present in tick saliva or IgE arises as a result of antibody class-switching after tick feeding (Crispell et al., 2019). In any case, significantly higher levels of anti-α-Gal IgE antibodies along with predominantly type 2 cytokine-producing T-cell skin infiltrations have been observed in patients after repeated bites of *A. testudinarium* ticks compared to those who acquired a single tick bite or healthy individuals (Hashizume et al., 2018). This finding is the only one to provide an insight into the potential mechanism responsible for IgE antibody production after repeated exposure to the allergen through the skin of a human patient (Hashizume et al., 2018).

In the reported case, the patient has apparently developed the α-Gal syndrome after repeated tick bites, but the species of tick(s) to which she was exposed remains unknown. However, an immunofluorescence antibody test showed that the patient was exposed to *B. divergens* likely through the bite of *I. ricinus* tick, which is a natural vector of this zoonotic pathogen (Ord and Lobo, 2015). According to literature data, *I. ricinus* is responsible for 10–40% of all human tick bites in Europe and it represents a substantial public health concern, particularly in terms of co-transmission of pathogens (Moutailler et al., 2016). Although the scientific data support the association of *I. ricinus* bites and α-Gal syndrome in Europe, the ability of this tick species to induce a specific IgE immune response to α-Gal needs to be confirmed in experimental studies using a mouse model.

All healthy individuals are able to produce anti-α-Gal antibodies regardless of tick bites, but due to structural similarity of antigen B and the α-Gal epitope, it has been suggested that those people with blood groups AB and B produce less anti-α-Gal IgE in contrast to individuals with blood group A or O who are consequently more prone to develop α-Gal syndrome (Hamsten et al., 2013b; Brestoff et al., 2018; Cabezas-Cruz et al., 2017). The result of the presented clinical case, in which the patient with blood type A has developed an anaphylactic reaction to α-Gal after recurrent tick bites, is in line with the current hypothesis.

The final diagnosis of the α-Gal syndrome in the patient was made based on the clinical history and the detection of IgE antibodies to α-Gal. The quantitative measurement of the serum IgE antibodies is currently considered the most reliable diagnostic tool (Platts-Mills et al., 2015), but with this test it is not possible to distinguish patients with the α-Gal syndrome and those with α-Gal sensitization (Mehlich et al., 2019). Therefore, the basophil activation test has been recently introduced as an additional *in vitro* diagnostic method to partially overcome this limitation (Mehlich et al., 2019). Skin-prick test using commercial meat extracts has shown to be unreliable because it often yields poor or false-negative results (Commins et al., 2009) as seen in the presented case. Prick-to-prick tests with pork kidney (contains higher concentration of the allergen) proved to be more sensitive when compared to cooked or fresh muscle meat and it should be highly preferred (Fischer et al., 2014).

In conclusion, despite the increasing number of α-Gal syndrome cases reported worldwide, it has still often been misdiagnosed as idiopathic anaphylaxis. Therefore, the presented clinical case should raise the awareness of the primary care practitioners in order to improve the early diagnosis of this tick-associated anaphylactic reaction and avoid potentially life-threatening complications.

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Ethical approval

Written informed consent for publication of this clinical case report was obtained from the patient.

Conflict of interest

The authors declare that there are no conflicts of interest.

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