

Unusual manifestations of hypersensitivity after a tick bite: report of two cases

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Background: Ticks are able to transmit, through biting, various viral, parasitic, and bacterial diseases, the best known being Lyme disease due to *Borrelia burgdorferi*. In addition, ticks may also induce allergic reactions.

Objective: A study of immediate and delayed skin reactions are undertaken to give evidence of an IgE-dependent mechanism.

Methods: Two lumbermen reported having had skin reactions following bites by ticks. Skin prick tests and intradermal tests were performed with what was most probably *Ixodes ricinus* extract in one case. Specific IgE to whole body extract of wood tick were assayed by radioimmunoassay. Histological and immunohistologic examinations of skin biopsy obtained from a pruriginous skin lesion and from a delayed reaction following the intradermal test, were performed.

Results: One of them had positive immediate reactions to a prick test and an intradermal test with the same extract. Both patients had significant levels of wood tick-specific IgE antibody as well as elevated serum total IgE levels. Histologic examinations of a pruriginous lesion revealed lymphocytic dermal and perivascular infiltration, with evidence of CD8+ T lymphocytes and Langerhans' cells in the perivascular infiltrates. A biopsy of the place of the delayed reaction following the intradermal skin test also showed the presence of dermal and perivascular lymphocytic infiltrates.

Conclusion: IgE-dependent allergy to *Ixodes ricinus* can explain allergic reactions. Standardized extracts have to be prepared with sufficient amounts of the relevant tick salivary antigens to permit diagnosis by skin and serologic tests of patients, especially lumbermen who may be allergic to *Ixodes ricinus*.

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INTRODUCTION

Ticks are able to transmit various viral, bacterial, and parasitic diseases to man.^{1,2} Allergic reactions after tick bites have also been reported but they are not so well-known, and most such observations have not been well-documented.³⁻⁷ Recently, the existence of IgE antibodies specific for a salivary gland extract was demonstrated in patients who had developed an immediate hypersensitivity reaction after hav-

ing been bitten by an Australian paralysis tick *Ixodes holocyclus*.⁵ We now report two cases in which local skin reactions following bites by the common European wood tick *Ixodes ricinus* were associated with an immediate and/or a delayed hypersensitivity.

METHODS

Tick extract

An extract was prepared by grinding the whole bodies of 27 wood ticks (most likely *Ixodes ricinus*) weighing 97 mg that had been collected by patient number 1. The ticks were put into 2 mL of normal saline solution and ground with a mortar in a glass pestle. The resulting suspension was sterilized by heating at 100 °C for 15 minutes and then passing it through a millipore filter (diameter 0.22 to 0.45 μ) after centrifugation. Because of the small

number of ticks used, the protein concentration of the extract was below the limit of detection of the Bradford assay.

Skin tests

With the informed consent of the patient, a skin prick test was done on the forearm with the tick filtrate undiluted, by pricking through a drop of the extract. An intradermal test was done on the external side of the arm with wood tick extract. To investigate the patients' atopic status, skin prick tests to various aeroallergens were done with the following allergenic extracts (Stallergènes, Fresnes, France): *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria*, *Aspergillus*, *Penicillium*, cat and dog epithelia, and Bermuda grass, timothy, birch, cypress, olive, *Parietaria*, mugwort, and plantain pollens. A reaction was considered positive when the diameter of the resulting wheal was equal to at least half the diameter obtained with a positive control (9% co-deine phosphate).

Serologic assays

Blood was collected from each of the patients and the serum separated for the immunoassays. IgE antibodies specific for the whole body extract of *Ixodes ricinus* were assayed by radioimmunoassay with allergen disks prepared as follows by Allerbio (Varennnes en Argonne, France). First, a whole body extract was obtained by stirring ticks for 12 hours in coca's solution at a ratio of 1/15 (wt/vol) at 4 °C. The extract was then purified by centrifugation and the supernatant was immediately fixed onto cellulose disks activated with cyanogen bromide. The radioimmunoassay was carried out according to the method of Grassi et al.⁸ The results were compared to ten sera

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of atopic and nonatopic patients. Total IgE was assayed by the PRIST method (Pharmacia, Uppsala Sweden). IgG antibodies specific for *Borrelia burgdorferi* were assayed by a commercial ELISA technique.

Histologic and immunohistologic examinations of skin biopsies

A small biopsy was obtained from a pruriginous skin lesion (Fig 1) of the first patient and examined by light microscopy after fixation in Boin's solution and staining with hematoxylin-eosin stain. Another skin biopsy, performed at the site of the delayed reaction that followed the intradermal test was examined in the same way. The first biopsy was also studied by immunofluorescence microscopy using antisera specific for human IgA, IgG, IgM, Clq, C3 and the lymphocyte membrane markers CD1, CD3, CD4, and CD8.

CASES AND RESULTS

Two lumbermen, both 39 years old, were seen in consultation in the Allergy Clinic of our hospital complaining of skin reactions that followed wood tick bites.

The first patient had had tick bites on various parts of his body from June to September during the past several

years. These bites induced pruriginous local skin reactions which lasted for some hours afterwards. Brown reddish nodular lesions reminiscent of prurigo were disseminated on the trunk at the time of his first visit to this clinic. No satellite adenopathy was observed (Fig 1). He had positive immediate reactions to the wood tick extract, the skin prick test producing a 5 mm wheal (the codeine-induced wheal was 5 mm) and the intradermal test an impressive 16 mm wheal with surrounding erythema of 55 mm (Fig 2). Forty-eight hours later, the intradermal test showed a delayed reaction (Fig 3).

The assay for wood tick-specific IgE was negative in ten controls, but positive, with a titer of 5.6 kU/L. Although he had no history of previous allergic disease, he was considered to be an atopic patient on account of a positive skin prick test to birch pollen extract. This diagnosis is supported by the fact that his total IgE, 1,470 IU/L, was definitely elevated (normal limit: 150 UI/L). Serology for *Borrelia burgdorferi* was negative.

Histologic examination of this patient's pruriginous skin lesion revealed inflammation in the dermis and also perivascular lymphocytic infiltration. There were no epithelial abnormalities.

There were, however, some protein-rich, leukocyte poor vesicles at the epidermal-dermal junction. The immunohistologic examinations revealed that the perivascular infiltrates were composed essentially of CD1+ Langerhans' cells and CD8+ T suppressor lymphocytes. There were no deposits of IgG, IgA, or IgM or of Clq and C3 in any of the sections. The small section of the delayed reaction at the intradermal test site showed only a perivascular lymphocytic infiltrate.

The second patient was seen in consultation complaining of local skin reactions that began immediately after a tick bite. He also reported semi-delayed reactions that persisted for up to two days at the same site. He had no history of other previous allergic reactions and did not react to prick tests with the aeroallergen extracts. The skin was normal on the day of the visit. As he had not been bitten very frequently, skin tests were not scheduled for ethical reasons. He did, nevertheless, have a definitely positive wood tick-specific IgE antibody titer, at 26 UI/L (negative in ten controls). He had no history of previous allergic reactions and did not react to skin prick tests with the aeroallergen extracts. His total serum IgE was raised to 1000 IU/L. Serology for *Borrelia burgdorferi* was also negative in this patient. No skin biopsy was performed.

DISCUSSION

Ticks are blood-sucking arthropods of the arachnid class, which, in addition, includes spiders, scorpions, and mites. There are three families of ticks: the Nuttalliellidae, the Argasidae (soft ticks), and the Ixodidae (hard ticks). In the family Ixodidae, there are more than 800 different species distributed throughout the world.² A study done in Belgium identified 16 species there.⁹ However the common wood tick, *Ixodes ricinus*, is the most abundant species in Europe: three different studies in Belgium show that from 92% to 100% of the collected ticks belong to this species.⁹

Ixodes ricinus is characterized morphologically by a nonsegmented body covered by a rigid dorsal plaque and a



Figure 1. Typical delayed pruriginous skin lesions after tick bites (*Ixodes ricinus*) in patient 1.



Figure 2. Immediate positive intradermal test with a tick extract (*Ixodes ricinus*) in patient 1.

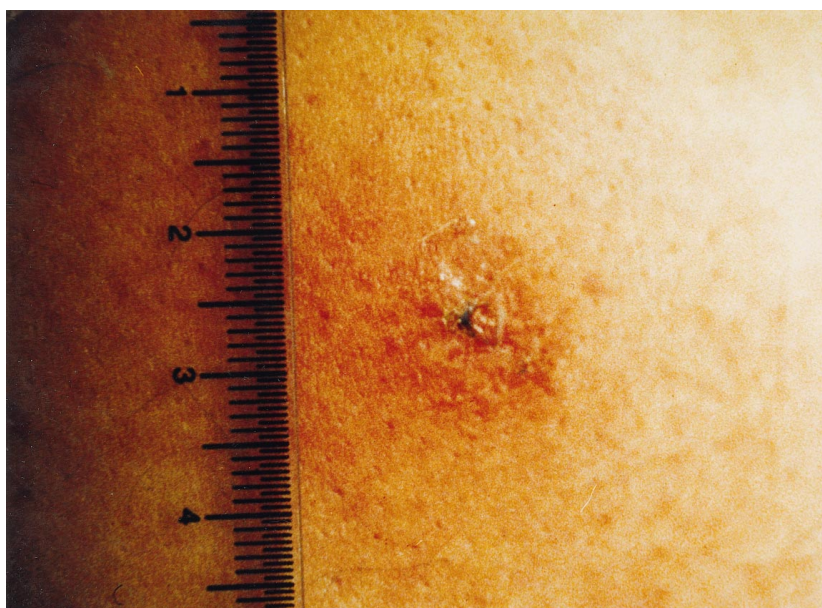


Figure 3. Delayed reaction after intradermal test with a tick extract (*Ixodes ricinus*) in patient 1.

complex anterior sucking apparatus. The adult male is 2.5 mm long, while the female varies in length from 4 to 11 mm.² The habitat of *Ixodes ricinus* is mainly in clear, leafy forests in which ferns, bramble, and grasses serve as support. Its developmental cycle begins with the egg stage and is followed by three successive parasitic stages: larval, nymphal, and adult. At each of these stages, this parasite attaches it-

self to a host and ingests a blood meal. After a variable period which can last up to several days, the blood-filled tick detaches itself from its host, falls to the ground and continues its maturation cycle and, in the case of the female, drops its eggs. The total duration of the cycle varies according to climatic conditions. It can last several months or even several years, being interrupted when the parasite does not find a con-

venient host as well as during periods of cold. The activity of *Ixodes ricinus* is thus seasonal, and the risk of being bitten is greatest during spring and autumn.^{2,9}

Ticks transmit various infectious agents when attached to their host, either through inoculation via their saliva or by regurgitation during the course of the blood meal. In France, there are six human tick-borne infectious diseases that are of epidemiologic and clinical importance: Q fever (*Coxiella burnetii*), Mediterranean spotted fever (*Rickettsia conorii*), Lyme disease (*Borrelia burgdorferi*), tularemia (*Francisella tularensis*), tick viral encephalitis (Arbovirus), and babesiosis (*Babesia divergens*).^{1,2}

The possibility of an allergic reaction following a tick bite has been noted, especially in Australia, where it has been associated with bites by the Australian paralysis tick, *Ixodes holocyclus*. Solley estimated that, in Australia ticks account for 0.5% of all allergic reactions due to insect bites or stings.⁵ The clinical manifestations of an allergic reaction to a tick bite can be (1) a more or less extensive local reaction, (2) a more generalized reaction of an urticarial or angioedematous nature, or (3) a systemic (anaphylactic) reaction. Gauci et al.⁴ suggested classifying tick bite reactions into six categories: class 1, small local reactions; class 2, extensive local reactions; class 3, anaphylactic reactions; class 4, atypical reactions; class 5, tick paralysis; and class 6, Lyme disease. According to those authors, class 1 reactions are usually nonallergic and class 5 and 6 are due, respectively, to a salivary toxin of the *Ixodes holocyclus* tick species and infectious agents.

Gauci et al demonstrated that anaphylactic and most atypical reactions (classes 3 and 4, respectively) are IgE-dependent, based on a positive skin prick test with a salivary gland extract and the presence of specific IgE detected by radioimmunoassay.^{3,4} The salivary antigens of *Ixodes holocyclus* are 28 and 55 kD proteins.¹⁰ They suggested that in individuals with large local reactions the pathogenesis may involve either delayed hypersensitiv-

ity, a late-phase IgE response, or the direct pharmacologic action of tick secretions.

In addition, atopy was recognized as a risk factor for tick allergy. The two cases we have reported are the first in which the presence of specific IgE antibodies to *Ixodes ricinus* has been established.

We found no published reports of histologic studies of reactions to tick bites in humans. In our first case, the histology of the clinically typical delayed hypersensitivity skin reaction was due to a delayed hypersensitivity mechanism; the histology of the pruriginous lesion was identical. The immunohistologic examination showed that the lymphocytic-histiocytic infiltrate contained mostly CD8+ lymphocytes and indicated that Langerhans' cells, CD1+ cells were probably participating in the reaction.

The mechanism of the reactions to cutaneous infestation by ticks has been extensively studied in laboratory animals.¹¹⁻¹⁵ For example, guinea pigs develop primarily a nonspecific inflammatory infiltrate with polymorphonuclear leukocytes (neutrophils) in response to a tick bite.¹³ After subsequent bites, a dermo-epidermal infiltration with basophils, most of which are degranulated, and eosinophils appears. It has been suggested that the liberation of chemical mediators by these cells contributes to the rapid detachment of the ticks.¹² In addition, the presence of Langerhans' cells in some sites has been noted, and it has been shown that these cells play a role in the development of resistance to ticks, first by serving as antigen-presenting cells and then by serving as a focal point for the accumulation of the leukocytes.^{12,13} In the case of tick bites in mice, the histology of the reactions is somewhat different, mast cells rather than basophils being involved.¹⁵

The present observations draw attention to the occurrence of IgE-dependent allergic reactions to the European wood tick, most likely *Ixodes ricinus*. The diagnosis is based on the wheal and flare reactions induced by the tick bites, the positive skin tests to tick extract in patient 1 and the presence of

specific IgE in both cases. In addition, a delayed hypersensitivity reaction may also be induced, as indicated by similar dermal lymphocytic infiltrates in biopsies from a pruriginous lesion and from the site of the delayed response at the site of the intradermal test. The presence of T lymphocytes in the lesion was demonstrated by the immunofluorescence study.

Although the incidence is not known, these types of reactions to *Ixodes ricinus* are probably not rare. The lack of published reports suggests, however, that they may not have been noted previously. It should be recognized that, while most tick-induced allergic reactions will not be severe, some people are nevertheless at risk for an anaphylactic reaction when they walk in the woods. The correct identification of allergy to ticks should be based on appropriate *Ixodes ricinus* extracts for diagnostic skin tests and radioimmunoassay, comparable to the preparations that are available in Australia for *Ixodes holocyclus*. The possibility of transmission of *Borrelia burgdorferi* might restrict the use of such extracts to in vitro methods.

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