

# Pigeon tick bite: A neglected cause of idiopathic nocturnal anaphylaxis

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## Abstract

Anaphylaxis is a serious systemic allergic reaction with rapid onset and potentially life-threatening. We report in detail a case of severe nocturnal anaphylaxis due to pigeon tick bite showing the diagnostic value of the extract and the recombinant allergen in the diagnostic procedures (basophil activation test, IgE immunoblot, and experimental ImmunoCAP). Apart from the presented case, we describe that during the last 10 years, we have collected 28 cases of allergy to *Argas reflexus* from several European countries. We suspect that this allergy is underdiagnosed because of the lack of diagnostic reagents. Because of the growing number of pigeons in Middle and Southern Europe cities, some cases of idiopathic anaphylaxis could potentially be caused by *A. reflexus* in those countries. The identification of pigeon ticks as a trigger of anaphylaxis would greatly improve medical care and advice for these patients as the parasite can be exterminated by eradication measures to avoid further incidents.

## KEYWORDS

anaphylaxis, *Argas reflexus*, basophil activation test, IgE, pigeon tick

## 1 | BRIEF REPORT

Anaphylaxis is a serious systemic allergic reaction that is rapid in onset and potentially life-threatening. Most anaphylaxis episodes are IgE-mediated, with foods being the most common cause in children, and drugs and insect stings the more common causes in adults. A

thorough history is probably the most important element of the workup of anaphylaxis, because it will guide subsequent testing. Idiopathic anaphylaxis is diagnosed when no specific trigger can be identified after an appropriate evaluation. Presentation of anaphylaxis which awakens the patient from sleep is rarely seen and should prompt consideration of delayed anaphylaxis due to red meat eaten

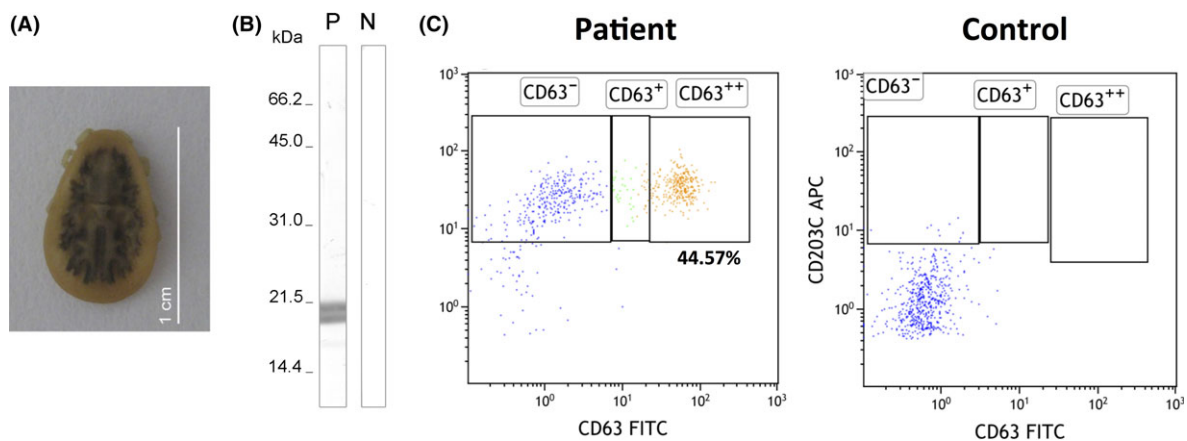
for dinner in patients sensitized to alpha-gal<sup>1</sup> and bites from insects with nocturnal habits. In Western and Southern United States, Central and South America, and Mexico, *Triatoma* species, the so-called kissing bugs, have been reported to be the cause of allergic reactions, which occur during the night, in people living in homes that have cracks and crevices in the walls and thatched roofs.<sup>2</sup>

In this report, we present a case of nocturnal anaphylaxis which was triggered by a bite of the pigeon tick *Argas reflexus*. Additional single cases with similar characteristics were collected from several European countries, showing evidence for an urgent need in diagnosis.

A 44-year-old man was admitted to the emergency department in June, 2015, following emergency medical intervention at his house, called by his spouse, because he awoke early in the morning with diffuse erythematous rash, nausea, dyspnea, and suffered later loss of consciousness. First-aid team found him confused, with diffuse erythema with wheals as well angioedema involving his lips and eyelids. His heart rate was 120/min, systolic blood pressure 70 mm Hg, and SaO<sub>2</sub> 90% in ambient air. He received on site two intramuscular injections of 0.3 mL 1:1000 epinephrine, 100% oxygen by mask with a reservoir, rapid infusion of normal saline, intravenous methylprednisolone 80 mg, and chlorpheniramine 10 mg and was transferred to a near hospital, where his symptoms gradually improved with full recovery after 4 hours. When his rash waned, an indurated and swollen red area was noticed on his hand, which was itching. He could remember some itching papules on his arms in the previous months, suspicious of insect bites, always occurring during nighttime, but he had not noticed any insect. He was not taking any drugs and he had had his usual supper 8 hours before. Tryptase level was increased at 16.2 µg/L (ImmunoCAP, Thermo Fisher California, USA, normal values <11.4 µg/L) and decreased to normal value (9.1 µg/L) 24 hours after. The case scenario of our patient with a sudden onset of cutaneous, as well two other organ systems involvement, including the respiratory and cardiovascular systems, was promptly recognized as severe anaphylaxis<sup>3</sup> and treated

appropriately. The diagnosis was also supported by the increased levels of serum tryptase. Meticulous history, skin tests, and measurement of allergen-specific IgE levels are recommended in each case of anaphylaxis to ascertain the trigger, so that future episodes may be prevented. In our case, the history and the physical finding pointed to an unidentified insect bite as trigger of anaphylaxis. Skin prick tests and specific IgE to common inhalant, food, and hymenoptera allergens were negative. The patient was living under the roof of an old building, where urban pigeons had their nests. Suspecting an anaphylactic reaction caused by a bite of the pigeon tick, *A. reflexus* (Figure 1A), IgE antibodies to *A. reflexus* whole body extract were searched for by IgE immunoblot as described.<sup>4</sup> Two bands were found to migrate at about 19–21 kDa (Figure 1B), corresponding to Arg r 1, the major allergen of the pigeon tick.<sup>4,5</sup> Specific IgE was quantified at 60.8 kU<sub>A</sub>/L using biotinylated recombinant Arg r 1 (rArg r 1) bound to Streptavidin ImmunoCAPs.<sup>4,6</sup> The details of the BAT procedure have been reported previously.<sup>7</sup> Briefly, 100 µL aliquots of heparinized whole blood were stimulated with dilution buffer as a negative control, anti-IgE (10 mg/mL; Pharmingen, BD Biosciences, San Jose, CA, USA) as a positive control, protein extract at 0.1 µg/mL, and rArg r 1 at 0.1 µg/mL. Basophils were gated as low side scatter and anti-IgE<sup>+</sup>/CD203c<sup>+</sup> staining, and we applied to gate out at least 500 basophils. Basophils were stained with anti-human FcεR1α-Pacific Blue (BioLegend, San Diego, CA, USA), anti-human CD63-FITC (clone H5C6, BD Biosciences), and anti-human CD203c-APC (clone NP4D6 BioLegend), and upregulation of CD63 and CD203c was measured as an activation marker. The flow cytometric analyses were performed on a Navios Beckman Coulter Cytometer. Basophils were activated by the extract (Appendix S1) and rArg r 1 (Figure 1C), as indicated by upregulation of CD63 and CD203c on the patient's basophil membrane, while the assay was negative on healthy controls.

On-site intervention was undertaken in the patient's apartment by a professional pest control service and some ticks, identified as pigeon ticks, were found. Several cracks in the masonry that



**FIGURE 1** A, Pigeon tick *Argas reflexus*, B, immunoblot showing IgE-reactive bands at 19–21 kDa in tick extract with patient serum no. 6 (P), no signal with a healthy control serum (N), (C) basophil activation test. Scattered dot plots after stimulation with rArg r 1 at 0.1 µg/mL, showing upregulation of CD63 and CD203c on patient's basophil membrane. No upregulation was seen in a healthy control

**TABLE 1** Characteristics of patients allergic to *Argas reflexus* (A) systemic reactions and (B) local reactions

Patient no	Origin	Sex	Age	Anaphylaxis grade	Number of episodes	Occurrence of reaction		Pigeons in immediate neighbourhood	Identification of parasite	Specific IgE to rArg r 1 (kU <sub>A</sub> /L)	Atopy
						Time of day	Season				
(A)											
1	Basel	M	27	2 (UA, GI)	1	Night	Spring	Yes	Yes	308	Yes
2	Turin	F	59	2 (UA, R)	7 (previous mild)	Night	Spring	Yes	Yes	5.97	No
3	Turin	M	45	1 (UA)	1	Night	Spring	Yes	Yes	0.53	No
4	Turin	F	27	2 (UA, GI)	2	Night	Spring	Yes	Yes	2.77	No
5	Turin	M	39	3 (UA, GI, CV)	1	Night	Spring	Yes	Yes	10.6	No
6	Turin	M	44	3 (UA, GI, CV)	3 (previous mild)	Night	Spring	Yes	Yes	60.8	No
7	Turin	F	42	2 (UA,GI,R)	2 (previous mild)	Night	Summer	Yes	Yes	5.63	No
8	Turin	M	15	3 (UA,R,CV)	1 (local & systemic)	Night	Spring	Yes	No	0.63	No
9	Turin	F	26	1 (UA only)	>10 (local & systemic)	Night	Spring	Yes	No	35.3	No
10	Turin	M	51	3 (UA,R,CV)	2 (local & systemic)	Night	Winter	Yes	Yes	1.94	No
11	Turin	F	16	1 (UA)	1	Night	Winter	Yes	Yes	1.24	Yes
12	Turin	F	61	2 (UA, R)	2 (previous mild)	Night	Spring	Yes	Yes	14.5	No
13	Prague	F	22	3 (UA,GI)	2	Night	1× spring 1× winter	Yes	Yes	2.68	Yes
14	Prague	M	46	3 (UA, GI, R,CV)	3	Night	2× winter, 1× spring	Yes	Yes	261.6	No
15	Prague	F	24	3 (UA,GI,CV)	2	Night	1× spring	Yes	Yes	0.65	No
16	Prague	M	29	3 (UA,GI,R,CV)	2	Night	1× spring 1× autumn	Yes	Yes	1.9*	No
17	Brussels	M	61	2-3	9-10	Morning	NA	Yes	No	160.8	No
18	Brussels	M	58	3 (UA, R, CV)	5-8 (local & systemic)	Night	NA	Yes (in the past)	Yes	9.33	No
19	Lyon	F	42	1 (UA)	1	Night	Spring	No	Yes	64.8	NA
(B)											
Patient no	Origin	Sex	Age	Anaphylaxis grade	Number of episodes	Occurrence of reaction		Pigeons in immediate neighbourhood	Identification of parasite	Specific IgE to rArg r 1 (kU <sub>A</sub> /L)	Atopy
1	Leipzig	F	40	0 (LR)	5 (local)	Night	NA	Yes	Yes	58.1	No
2	Leipzig	M	42	0 (LR)	3 (local)	Night	NA	Yes	Yes	91.4	No
3	Leipzig	F	44	0 (LR)	10 (local)	Night	NA	Yes	Yes	62.1	No
4	Leipzig	M	8	0 (LR)	30 (local)	Night	NA	Yes	Yes	1.15	No
5	Leipzig	F	30	0 (LR)	3 (local)	Night	NA	Yes	Yes	29.9	Yes
6	Leipzig	F	51	0 (LR)	5 (local)	Night	NA	Yes	Yes	1.43	No

CV, cardiovascular; GI, gastrointestinal; LR, inflammatory local reaction; NA, not addressed; R, respiratory; UA, urticaria/angioedema; \*serum has been quantified by ELISA as no more serum was available for ImmunoCAP determination.

All sera were collected from patients coming to the clinic for analytical workup following an allergic reaction, except for patients from Leipzig, who were recruited in a study assessing reactions to *Argas reflexus* tick bites.<sup>5</sup>

would allow the passage of the ticks were repaired. The patient was provided with an epinephrine autoinjector and instructed in its use.

The European pigeon tick, *A. reflexus*, is an urban pest which parasitizes urban pigeons, but sometimes may bite humans, causing a wide range of reactions, from local (itching, edema, erythema) to

severe, IgE-mediated, systemic reactions.<sup>4,8</sup> During the last 10 years, we have collected single cases of allergy to *A. reflexus* from several European countries (Table 1). Major characteristics are severe anaphylactic reactions (grade 2-3) occurring at night during spring and summer as well as the presence of pigeons in the immediate neighborhood. In most cases, the tick could be identified and all patients had specific IgE to rArg r 1. We suspect that pigeon tick allergy is not sufficiently taken into account in the differential diagnosis of severe anaphylaxis, as allergen extracts for determination of specific IgE are not commercially available and the use of tick extracts for skin prick test harbors the potential risk of transferring infectious agents. The availability of rArg r 1 or *A. reflexus* tick extract for in vitro IgE diagnosis would greatly improve the diagnosis of patients with anaphylaxis of unknown etiology. Important clues for allergic symptoms related to *A. reflexus* bites are the occurrence of nocturnal reactions, previous local reactions on arms or legs highly suggestive of insect bites, and living in buildings where pigeons have their nests. Because of the growing number of pigeons in Middle and Southern Europe cities, infestations of pigeon breeding sites by *A. reflexus* may become an important public health problem.

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#### CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

#### AUTHOR CONTRIBUTIONS

GR and EH cared for the index patient. MB did the basophil activation test. ChH produced the recombinant Arg r 1 and performed the immunoblot. MR was responsible for the rArg r 1 Streptavidin ImmunoCAP and quantified sIgE to rArg r 1. GR, EH, VD, MM, MC, SD, JKT, and AB cared for patients listed in the table. GR, EH, and ChH wrote the manuscript, and all other authors were implicated in the final revision.

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#### SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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