L. Kofler[1], H. Kofler[1], L. Mattsson[2], J. Lidholm[2]

A case of dog-related human seminal plasma allergy

[1]Allergieambulatorium Hall i.T, Austria - E-mail: heinz.kofler@kofler-haut.at
[2]Phadia AB, Research & Development, Uppsala, Sweden.

Key words

Can f 5, dog, dander, dog prostatic kallikrein (DPK), prostate specific antigen (PSA), seminal plasma, Type I allergy, Human Seminal Plasma (HSP)

Corresponding author
Dr. Lukas Kofler
Allergieambulatorium Hall i.T, Austria
E-mail: heinz.kofler@kofler-haut.at

Summary

Allergy to human seminal plasma (HSP) is rare. It presents with a variety of symptoms, ranging from localized changes to generalized reactions or even anaphylactic shock. Symptoms typically start within minutes to one hour after exposure. Diagnosis is based on history, evidence of specific IgE antibodies and skin prick testing (SPT). A 25-year-old Caucasian woman presented with eyelid swelling, generalized urticaria and dyspnea immediately after unprotected coitus with her partner. No symptoms occurred when barrier contraception was used. SPT and IgE testing (ImmunoCAP) demonstrated sensitization to HSP and dog dander. The patient's self-designed desensitization protocol, consisting of H1 blocker premedication followed by unprotected sexual intercourse, ameliorated her systemic reactions gradually and reduced the frequency of emergency hospital visits. She had a known allergy to male but not female dogs, and was highly sensitized to dog allergen Can f 5, a protein homologous to human prostate-specific antigen (PSA), suggesting a possible link to her HSP allergy.

Introduction

The first published case of a hypersensitivity reaction to HSP was that of Specken in 1958 (1) and a number of cases of HSP allergy have since been described in the literature (2-4). The diagnosis of HSP allergy is first and foremost based on a careful history, corroborated by the presence of specific IgE-antibodies as well as positive prick test reaction. The complete absence of symptoms when using a condom is highly supportive of the clinical diagnosis. Aside from avoiding the offending allergen, the only treatment is desensitization such as intravaginal seminal graded challenge (ISGC) or even subcutaneous injection of increasing doses of seminal fluid proteins (5).
Although type I immediate hypersensitivity appears to be the most common mechanism of HSP allergy, also type-III and cell-mediated reactions have been reported (6-7).
Symptoms of HSP allergy range from localized skin reactions like vaginal erythema, vulvovaginitis-like symptoms, pruritus or burning sensations (8-9) to systemic reactions such as dyspnea, gastrointestinal upset, angioedema, generalized urticaria or even anaphylactic shock (8-10). They usually appear within minutes to one hour after coitus (8, 11-12). In about 50% of cases, localized and generalized reactions appear after first sexual intercourse without barrier contraception (5). Women aged between 20 and 30 years are most frequently affected (6); they often have a personal or family history of atopy (8). Differential diagnostic considerations include allergic reactions to latex (as part of condoms), as well as to lubricants, spermicidal

substances or their components. On rare occasions, women sensitized to drugs or food have reported allergic reactions ("connubial allergy") after coitus because of allergen transmission from their partner via seminal fluid (12-14). The uterine muscular contraction reaction to prostaglandin contained in semen is an example of a non-allergic reaction triggered by seminal fluid (15).

Case presentation

A 25-year-old Caucasian woman presented with a history of eyelid swelling, generalized urticaria, airway constriction and dyspnea after coitus. Her problem had started about 18 months ago, after three years of relationship with her then partner and continued with a new partner as soon as they stopped using barrier contraception. Her symptoms only appeared after sexual intercourse. She recently experienced moderate urticaria after coitus, rather than the previously predominant respiratory symptoms.
The patient had a longstanding seasonal rhinoconjunctivitis caused by grass pollen and a history of dog dander allergy with asthma after contact with her partners' male dogs. Contact with the female dogs of her parents never resulted in any allergic symptoms. Her father had allergic rhinitis while her mother suffered from dust mite allergy.
The patient uses salbutamol-aerosol as well as 10 mg rupatadine (Rupafin® fumarate; Rupafin® Merckle-Recordati) against pollen allergy and has received an emergency package including cetirizine (Zyrtec® UCB Pharma Vienna), 50 mg prednisolone; (Aprednislon® Merck) and an epinephrine autoinjector-pen (Epipen®).
We performed SPT using a standardized test kit (ALK-Abelló, Austria) and prick-to-prick-testing with her partner's seminal fluid and seminal plasma prepared by centrifugation (5 min at 1600 g), as well as with the supernatants of the first and the third sequential spermatozoal washings with Dulbecco PBS-buffer solution (Ca^{2+} and Mg^{2+} free; PAA Laboratories), performed with centrifugation as above. As negative controls we used 0.9% saline solution and Dulbecco PBS-solution whereas 1% histamine dihydrochloride solution (Pangramin Positivkontrolle, ALK-Abello) was used as positive control. The skin testing (Tab. 1) showed a strong reaction to house dust mite (*D. pteronyssinus*) and pollen of early-flowering trees (birch, alder and hazel) and grasses, as well as a reaction to dog dander.
Total IgE and specific IgE antibodies to dust mite, latex, human seminal plasma and dog dander were measured by ImmunoCAP® (Phadia, Sweden). The results of the IgE testing are shown in Table 2. The patient displayed significant sensitization to dog dander (19.1 kU_A/L) and dust mite (5.6 kU_A/L), as well as sensitization to seminal fluid (0.96 kU_A/L). No IgE to latex was detected. Total IgE was 142 kU/L
The patient's conspicuous allergy to male but not female dogs prompted an investigation of her sensitization pattern to dog allergens. Her serum was tested for IgE antibodies to rCan f 1 (lipocalin), rCan f 2 (lipocalin), nCan f 3 (albumin), rCan f 4 (lipocalin) and rCan f 5 (arginine esterase, prostatic kallikrein), the latter two using experimental ImmunoCAP tests. The results are shown in Table 2. The analysis revealed that the patient was monosensitized to Can f 5 (22.4 kU_A/L), a protein related and in part cross-reactive to human PSA (16). Analysis of IgE binding to PSA (experimental ImmunoCAP test) (Tab. 2) demonstrated IgE recognition of this human protein (0.79 kU_A/L), which is abundant in seminal plasma.
To examine the potential relationship between sensitiza-

Table 1 - Skin reactions after 20 minutes of applying each test solution

Allergen	Wheal diameter (mm)	Erythema diameter (mm)
Human seminal fluid, native	6	32
Human seminal plasma	7	40
Supernatant of first spermatozoal washing	5	35
Supernatant of third spermatozoal washing	2	10
1% histamine hydrochloride [positive control]	7	35
0.9% NaCl [negative control]	negative	negative
Dulbecco PBS-buffer solution [negative control]	negative	negative
Tree pollen mix (birch, alder, hazel)	7	30
Grass pollen mix	8	30
Dog dander	3	20
House dust mite	8	20

Table 2 - Specific IgE and total levels in serum

Allergen	kU_A/L
Dog dander (e5)	19.1
Seminal fluid (o70)	0.96
D. pteronyssinus (d1)	5.6
Latex (k82)	0.16
rCan f 1 (e101)	<0.1
rCan f 2 (e102)	<0.1
nCan f 3 (e221)	<0.1
rCan f 4 (experimental)	<0.1
rCan f 5 (experimental)	22.4
PSA (experimental)	0.79
Total IgE (kU/L)	142

tion to Can f 5 and HSP in this patient, an IgE inhibition experiment was performed. Serum samples were first incubated 2 hrs with either rCan f 5 (100 μg/mL final concentration) or buffer and IgE antibody binding to HSP and PSA was then measured. While Can f 5 shows no unspecific inhibitory effect on IgE antibody binding to unrelated allergens (16), it blocked this patient's IgE binding to both HSP and PSA to a level below the detection limit of the assay system. In an additional inhibition experiment, house dust mite extract, with sufficient concentration to fully inhibit IgE binding to dust mite ImmunoCAP, could not inhibit any of the patient's IgE binding to PSA (not shown), ruling out the possibility that the patient's IgE recognition of PSA was caused by sensitization to some structurally related mite protein.

Discussion

Although the original description of HSP allergy was published more than fifty years ago, it is still rarely diagnosed. However, due to presumed underreporting by patients and the diversity of symptoms, it may represent a hidden disease, with a significant number of undiagnosed cases (8, 9, 11).

The patient described here appeared to have partially desensitized herself by repeatedly having unprotected sexual intercourse, despite her allergic reactions. This might explain her change in discomfort from respiratory symptoms and generalized urticaria with angioedema to moderate urticaria. Since 1967, when Halpern et al. (2) first published immunotherapy as treatment of HSP allergy, different clinical protocols have been described, including rush protocols or intravaginal seminal graded challenge with incremental doses (ISGC) (5, 17-19). After intravaginal desensitization, patients are advised to have unprotected sexual intercourse in order to maintain tolerance (11, 17). This strategy would be similar to the actions of our patient, who stopped using barrier contraception and thereby intermittently exposed herself to the culprit allergen. The increased exposure to the relevant allergen may thus have led to induction of immunological tolerance.

Frequent IgE recognition of human PSA among Spanish dog dander sensitized individuals and cross-reactivity between dog dander extract and PSA was recently demonstrated (20) and the causative dog protein, prostatic kallikrein, was isolated and identified as a new major dog allergen, designated Can f 5 (16). Can f 5 displays structural similarity and partial cross-reactivity to human prostate-specific antigen (PSA; human kallikrein 3) (16), which has been identified as an allergen in IgE-mediated vaginal reaction to HSP (21). Thus, it has been speculated that HSP hypersensitivity might be related to sensitization to dog allergens by way of cross-reaction between PSA and Can f 5 (16).

The patient was highly sensitized to dog dander and her IgE antibodies appeared exclusively directed to Can f 5. Inhibition analysis of her IgE responses to HSP and PSA revealed that they could both be completely outcompeted by Can f 5. This observation, together with the much higher level of IgE binding to Can f 5 than to HSP and PSA, suggests that (i) PSA was the only significant determinant in HSP for this patient and (ii) sensitization dog, and specifically Can f 5, was the primary cause of immunological reactivity to HSP and presumably the reason for her HSP allergy. Unique sensitization to Can f 5, believed to be produced only in male dogs (16), would also explain the patient's reported tolerance to female dogs despite her allergic reactions to male dogs.

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