Case report

Seminal plasma anaphylaxis: successful pregnancy after intravaginal desensitization and immunodetection of allergens

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Date:
Accepted for publication 4 May 1999

To cite this article:
Jung Won Park, Si Hwan Ko, Cheol Woo Kim, Sang Wook Bae & Chein-Soo Hong. Seminal plasma anaphylaxis: successful pregnancy after intravaginal desensitization and immunodetection of allergens.
Allergy 1999, **54**, 990–993.

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ISSN 0105-4538

Key words: seminal plasma anaphylaxis.

For seminal plasma-allergic patients to achieve pregnancy, immunotherapy or artificial insemination is recommended. However, these modalities require complicated procedures. We recently treated a patient with human seminal plasma anaphylaxis who was successfully desensitized after intravaginal rush desensitization and became spontaneously pregnant. She had a healthy full-term infant. With immunoblotting, we identified multiple allergens in her husband's seminal plasma, with molecular masses such as 100, 75, 65, 50, 40, 38, 33, 20, and 18 kDa, and the pattern of immunoblotting did not change after desensitization. We found not only specific antibodies to the seminal plasma of the patient's partner, but also common antibodies to both the partner's and the control specimen. Our results suggest that intravaginal desensitization might be an effective and convenient initial approach for patients who want to achieve pregnancy, and also confirm the presence of both the specific and shared common allergens in the seminal plasmas of the patient's partner and the control subject.

Human seminal fluid allergies are rarely diagnosed diseases, and the allergens of seminal plasma have not yet been well characterized. Sexual abstinence or condoms have been recommended for the prevention of allergic reactions. However, these modalities are not acceptable to couples who want to achieve pregnancy. Immunotherapy or artificial insemination has been reported as an effective modality for that purpose (1–5). Recently, good results with local intravaginal desensitization have been reported (6, 7), and we treated a patient with human seminal plasma anaphylaxis who became spontaneously pregnant after intravaginal rush desensitization and subsequently had a healthy infant.

In this study, we also identified both the specific and shared common allergens in the seminal plasma of the patient's partner and a control subject with immunoblotting, and we compared the immunoblotting features before and after desensitization.

Case report

A 25-year-old, married nulligravida was referred for evaluation of a 2-month history of postcoital perivaginal swelling, systemic urticaria, facial edema, and dyspnea. These symptoms occurred immediately after ejaculation during intercourse, and on several occasions they required emergency treatment with epinephrine and antihistamine at the hospital. The patient had had only one sexual partner, and this couple did not take any medication at the time of sexual intercourse. The concentration of total serum IgE was 129 IU/ml, and she was not responsive to 108 common inhalant and food allergens in the skin prick test. Skin prick tests with her husband's fresh 10^{-1} (mean wheal diameter, 11 mm/mean flare diameter 31 mm), 10^{-2} (10 mm/27 mm), and 10^{-3} (7 mm/19 mm) v/v diluted semen demonstrated positive skin responses. Positive histamine control (1 mg/ml) showed skin response (8 mm/21 mm) and no response to 0.02% human serum albumin-0.4% phenol saline, which was used for dilution of semen. The husband was not reactive to his own fresh semen in the skin prick test. As the patient wanted to achieve pregnancy, intravaginal rush desensitization was done by depositing 2 ml of 10^{-5} v/v of the husband's diluted semen with 10-fold increments in concentration to undiluted semen at 45-min intervals. No allergic reactions occurred during the immunotherapy. The patient was instructed to have intercourse every 2 or 3 days to maintain the desensitization state, and she complied by having frequent intercourse for 3 months. A hiatus of about 5 days in this routine resulted in the return of mild perivaginal itching and swelling. The couple then resumed intercourse as recommended, and the patient did not subsequently experience any allergic symptoms. After 6 months, she was spontaneously pregnant and subsequently had a healthy full-term female baby.

Material and methods

Serum and seminal plasma

We collected the patient's serum before and 6 months after intravaginal desensitization and stored the samples at –20°C until use. Seminal fluid was collected exclusively by condom from the patient's husband and from another unrelated man for control. The samples were centrifuged at 4000 rpm for 10 min at room temperature, and the supernatant was used for SDS–PAGE and immunoblotting. The protein content of seminal plasma was determined by protein assay kit (Bio-Rad, Hercules, CA, USA).

SDS–PAGE of seminal plasma

SDS–PAGE was carried out under reducing conditions. For allergen isolation, seminal plasma antigen was dissolved in sample buffer (60 mM Tris-HCl, 25% glycerol, 2% SDS, 14.4 mM 2-mercaptoethanol, 0.1% bromophenol blue) and boiled for 5 min. An amount of 100 μg of seminal plasma antigen was applied to 4% acrylamide stacking gels (80 mm preparative slots), and the proteins were separated with 10% acrylamide gels (Mighty Small Electrophoresis Unit; Hoeffer, San Francisco, CA, USA) at 50 V for 30 min and 180 V for 2 h.

IgE immunoblotting

Proteins were transferred onto nitrocellulose (NC) membranes (pore size, 0.45 μm; Amersham, Buckinghamshire, UK) on a Transpor TE 42 Unit (Hoeffer, San Francisco, CA, USA) in transfer buffer (25 mM Tris, 192 mM glycine, and 20% [v/v] methanol, pH 8.3) at 350 mA for 80 min. The NC membrane was sliced at 5-mm widths. The strip was blocked by 1% bovine serum albumin (BSA) in TBS-T (50 mM Tris with 0.1% Tween, pH 7.5) and then incubated with patient serum (1:10 diluted in 1% BSA-TBS-T and 0.02% NaN_3) at 4°C for 18 h and washed with TBS-T. Alkaline phosphatase-conjugated polyclonal antihuman IgE (goat origin, 1:2000 diluted in 1% BSA-TBS-T, Sigma, St Louis, MO, USA) was added and incubated with the membrane at room temperature for 1 h. After washing with TBS-T, the membranes were developed with a BCIP/NBT system (Promega, Madison, WI, USA).

Results

We identified nine allergens of the husband's seminal plasma in the patient's serum, including those of 100, 75, 65, 50, 40, 38, 33, 20, and 18 kDa, and we could not find any difference in immunoblotting patterns after desensitization (Fig. 1 – lanes 1 and 2). To investigate whether or not the patient's specific antibodies reacted to the husband's

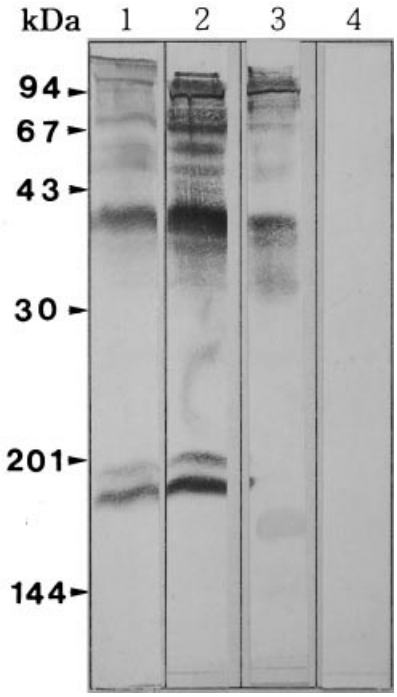

Figure 1. IgE immunoblotting features of husband's seminal plasma before (lane 1) and after desensitization (lane 2). Lane 3 shows immunoblotting features of seminal plasma of unrelated man. Lane 4 is nonatopic control.

specific antigens or a common seminal plasma antigen, we also performed immunoblotting with control seminal plasma. Except for the 18- and 20-kDa allergens, we found corresponding allergens with the same molecular masses in the immunoblotting with the control seminal plasma. In addition, we identified another 16-kDa allergen which was not found in the immunoblotting with the husband's seminal plasma (Fig. 1).

Discussion

Sperm barriers, such as condoms, are usually recommended for the prevention of allergic reactions in seminal plasma-allergic patients. For couples who want to achieve pregnancy, these modalities are an unacceptable option. Successful pregnancies have been achieved after artificial insemination with sperm washed free of seminal plasma (4, 5) or by immunotherapy with the gel-filtration chromatography fraction of seminal plasma from the male partner (1–3). These two options have been generally recommended for seminal plasma-allergic patients who want to achieve pregnancy (8). Although artificial insemination and parenteral immunotherapy may be effective, these modalities require complicated preparation. Recently, Metloff (6) reported the first case of successful local intravaginal desensitization to seminal fluid, while another case of successful pregnancy with intravaginal desensitization has subsequently been reported (7). This case is, to our knowledge, the third report of successful intravaginal rush desensitization and the second report of spontaneous pregnancy after intravaginal desensitization. We believe that our result strongly supports the clinical efficacy of intravaginal desensitization in seminal plasma-allergic patients.

The seminal plasma allergens have been characterized with gel-filtration chromatography and isoelectric focusing (3), and their molecular masses were reported to range from 12 to 75 kDa. With immunoblotting, we identified nine allergens in seminal plasma proteins, and their molecular masses were determined as 100, 75, 65, 50, 40, 38, 33, 20, and 18 kDa. Parenteral immunotherapy has generally used fractions of seminal fluid which excluded the high-molecular-mass component. Our immunoblotting features confirmed the multiple allergenicity of seminal plasma and might suggest the presence of allergenic components in the high-molecular-mass fraction of seminal fluid. These results suggest that the fractionated component of seminal fluid may delete some of the allergenic component of seminal fluid in some patients.

Our results do not suggest the superiority of the whole component of semen to the fractionated components. In practice, some patients with seminal fluid allergy were desensitized not by whole semen but by the fractionated components of semen. Marcus et al. reported high-molecular-mass immunosuppressant material for cellular immune reactions in human seminal fluid (9–11) and suggested that the inhibitory component might attenuate the efficacy of immunotherapy with whole semen (2).

The mechanism of desensitization in seminal plasma allergy is not yet known. Some patients lose their specific IgE after immunotherapy (3). In this study, we could not find any differences in the IgE-binding patterns by desensitization, and our patient was still strongly reactive to the husband's seminal plasma after delivery of her baby. Therefore, although the concentration of specific IgE was not quantified, we believe that mechanisms other than changes in the concentration of specific IgE have more important roles in desensitization.

Many seminal plasma-allergic patients were also reactive to the seminal plasma of different male partners (8). We also found that IgE-binding bands of the control seminal plasma and our data might support the clinical features of seminal plasma allergy. Although common allergens to both the husband's and control seminal plasma were found, specific

antibodies to both the husband's specimen and the control specimen were also found. This result might suggest that immunotherapy with the seminal plasma of the sexual partner might be more effective than with that of another specimen.

In general, our results suggest the clinical effectiveness of intravaginal rush desensitization in seminal plasma-allergic patients, and we believe that it may be recommended as an initial approach before resorting to more sophisticated methods for couples who want to achieve pregnancy.

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