

Case Report

A New Manifestation of Seminal Fluid Hypersensitivity

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SUMMARY

An immediate hypersensitivity reaction to seminal fluid is an uncommon but well recognized condition. We describe a young woman who developed haemorrhagic proctitis, arthralgia and urticaria on honeymoon. Investigations suggested an immune complex (type III) hypersensitivity. It subsequently became clear that her symptoms were temporally related to sexual intercourse. After 8 hours she developed nasal congestion and urticaria followed by migratory arthralgia and periorbital oedema. Over the ensuing 24 hours she had diarrhoea, occasionally with blood. She became breathless and had evidence of a restrictive ventilatory defect. These symptoms improved over 4–5 days. Further *in vitro* investigations were inconclusive but intradermal skin testing with seminal plasma led to recurrence of all her symptoms. Symptoms ceased with condom usage, and the condition abated over 2 years.

This patient is unique in that seminal fluid hypersensitivity appears to have produced a type III immune response.

INTRODUCTION

An allergic reaction to seminal fluid in a female was first described by Specken in 1958 [1], since when different manifestations of seminal fluid allergy, involving over 40 patients have been reported. The major features of the conditions are now well defined [2–7].

Different patients may experience local or systemic reactions in response to exposure to seminal fluid. Local responses [4, 6] consist of a stinging, burning or itching sensation in the vagina, with pain in some cases, which occurs during intercourse or soon after. The vulva and vagina become swollen and red, with urticarial lesions on the vulva. This becomes maximal at 24 hours and lasts 2–3 days.

General reactions are also fairly typically 'allergic'. Symptoms include generalized pruritus [8], dyspnoea [7], wheezing [2], sneezing [3], abdominal cramps [9], diarrhoea and vomiting [7]. These occur during or within one hour of intercourse and persist for up to 24 hours. Urticaria has been found in all of these patients [5, 8, 10], and they may also have

angio-oedema of the lips and eyelids [8], laryngeal oedema [3], respiratory obstruction requiring adrenalin [5], and anaphylaxis [4, 11].

These reactions are generally a manifestation of an immediate hypersensitivity (Gell and Coombs type 1) reaction [12], and the close temporal association with intercourse enables a diagnosis to be made rapidly. We describe a patient with hypersensitivity to seminal fluid whose illness differed from those above and arose through a different pathogenetic mechanism. The relationship with seminal plasma (intercourse) was not immediately apparent.

CASE REPORT

A previously fit 19-year-old woman developed numerous symptoms while on honeymoon. Initially there was diarrhoea with mucus and some blood, which continued for some days. The following day she had a painful pruritic rash affecting the scalp and limbs, which did not respond to treatment with antihistamines. Subsequently she developed a migratory arthralgia affecting the ankles, wrists, knees and thumbs. There was no previous or family history of allergy. Examination showed an extensive urticarial rash but no other untoward features. On sigmoidoscopic examination there were signs of mild haemorrhagic proctitis.

Initial investigations, including full blood count, biochemical profile and seromucoid, were normal. Immunoglobulin levels, including IgE, were within the normal range. The relevant abnormal findings (Table 1) were raised complement C3 (2.0 g/l), raised C1 esterase inhibitor (0.46 g/l) and the presence of circulating immune complexes detected by platelet aggregation to a titre of 1:160. Skin testing to a wide range of common allergens was negative.

She improved after in-patient treatment with steroids and antihistamines, but symptoms soon recurred on returning home. Over a period of time a temporal relationship between symptoms and sexual intercourse was observed. Eight hours after intercourse she would develop nasal stuffiness and urticaria affecting the scalp. At 12 hours pains developed in the proximal interphalangeal joints, wrists and elbows. Periorbital oedema appeared at 16 hours. By 24 hours the urticaria had become generalized.

Over the ensuing 24 hours she would have diarrhoea with occasional blood. She felt breathless, without wheezing, during this time. The symptoms persisted for 4–5 days.

She had not had sexual intercourse before marriage, and neither vaginal creams nor spermicides were used. Intercourse was by the vaginal route only. Over a period of months the symptoms became more severe, with increasing arthralgia which prevented her from performing her job as a typist. She had a persistent irritating skin rash, and increasing breathlessness. Chest radiograph was normal, but pulmonary function tests showed a mild

TABLE 1. *Abnormal initial investigations*

	Initial results	After resolution of symptoms	Normal range
C ₃ complement	2.0 g/l	0.85 g/l	0.75–1.75 g/l
C ₄ complement	0.5 g/l	0.21 g/l	0.14–0.54 g/l
C ₁ esterase inhibitor	0.46 g/l	0.26 g/l	0.18–0.26 g/l
Circulating immune complexes	1:160	Negative	Negative

TABLE 2. Results of pulmonary function tests.

	Symptomatic	In remission	Predicted values (from ref 21)
FEV ₁ (l)	2.35	2.35	2.94
FVC (l)	2.55	2.65	3.55
FEV ₁ /FVC %	92%	88%	81.8%
TLC (l)	3.5	3.75	4.75
Transfer factor TLCO (mmol/min/KPA)	7.8	8.3	9.5
Transfer coefficient KCO (mmol/min/KPA)	2.45	2.3	1.93

restrictive ventilatory defect with reduced lung volumes and preserved gas transfer (Table 2) while she was symptomatic, which improved (though not markedly) in between acute episodes.

When the association with intercourse was recognized, the use of a condom by her husband resulted in immediate improvement in her symptoms.

There was no response to a scratch skin test with purified seminal fluid from her husband (W/V 1:10,000). However, following an intradermal injection of the same antigen, a 3-mm area of induration was visible at eight hours. At this stage she developed angio-oedema, dyspnoea and multiple joint pains. The rash became more extensive over 24 hours and was followed by diarrhoea. Treatment with steroids and antihistamines had no effect, and the symptoms settled in five days. (She was not blinded during this test and was aware of the nature of the antigen.)

Her husband was unwilling to continue using condoms for long, and the original symptoms soon returned. Treatment with antihistamines, combined with H₁- and H₂-receptor blockade and non-steroidal anti-inflammatory agents was unhelpful. Because of increasingly severe symptoms Tranexamic acid treatment was started and she was asymptomatic for the next six months. The drug was slowly withdrawn and, apart from initial mild symptoms, there has been no recurrence of her illness. Two years later she has had a normal pregnancy and delivered a healthy daughter. She has remained well during this time on no specific therapy, and blood tests remain satisfactory (Table 1).

INVESTIGATIONS

Antibodies to spermatozoa were assessed by direct immunofluorescence, using standard techniques [13]. The double gel diffusion technique of Ouchterlony was used to detect precipitating antibodies to seminal fluid, using the husband's semen. Complement fixation tests with the husband's seminal fluid as antigen were performed by standard techniques. The seminal fluid was diluted to 100 µg/ml in CF diluent (veronal buffered saline 0.14 M, pH 7.4 + 0.005 M Mg²⁺ and 0.0015 M Ca²⁺). Heat-inactivated serum from the patient and two healthy controls was used at serial dilutions from 1:2 to 1:512.

Total haemolytic complement (CH₅₀) was measured by the method of Mayer [13]. The effect of the husband's seminal fluid on CH₅₀ was assessed using the method of Petersen *et al.* [14] seminal plasma and serum were diluted to 1:10 and incubated together at 30°C for 30 minutes, following which CH₅₀ titres were determined.

Specific IgE antibodies to seminal fluid were examined by the radioallergosorbent test [6] with seminal plasma coupled to cyanogen bromide-activated methyl cellulose at concentrations ranging from 20 to 70 mg protein/ml. In addition to the patient, healthy subjects and a patient known to have immediate hypersensitivity to seminal fluid were used as controls.

Cell-mediated immunity to seminal fluid was determined by the leucocyte migration inhibition test [15]. Seminal fluid was filtered through a 0.45 μ m millipore filter, then diluted in RPMI tissue culture medium at concentrations of 1:2, 1:12, 1:20. Leucocytes were separated from heparinized venous blood by Dextran sedimentation, and washed in RPMI at a concentration of 30×10^6 /ml. Six replicates were set up for each antigen concentration, and for medium alone. Leucocytes from the patient, and controls were incubated with the antigen for 18 hours, at which time the degree of leucocyte migration was measured by planimetry. The leucocyte migration index was calculated from the ratio:

$$\frac{\text{Mean migration area in presence of antigen}}{\text{Mean migration area in culture medium}}$$

A ratio of less than 0.8 was considered positive.

RESULTS

Anti-sperm antibodies were not detected by immunofluorescence. Precipitating antibodies to seminal fluid from the patient's husband were not present, and seminal fluid did not induce complement fixation. Total haemolytic complement in the patient was in the normal range, and was not significantly altered after incubation of her serum with seminal fluid. The radioallergosorbent test showed no specific IgE antibodies to seminal fluid in the patient or controls, one of whom had proven type I allergy to seminal fluid. There was a similar degree of leucocyte migration inhibition in the patient as in two unaffected, healthy controls when leucocytes were incubated with seminal fluid, at each of the four concentrations.

DISCUSSION

This patient differs in many respects from previously described patients with seminal fluid allergy. Some of her symptoms, such as urticaria and angioneurotic oedema, commonly occur in patients with seminal fluid hypersensitivity. Similarly, the appearance of her symptoms after first exposure to seminal fluid is common in other patients [2, 11]. However, arthralgia, proctitis with bloody diarrhoea and breathlessness due to a restrictive ventilatory defect has not previously been described.

In all previous reported cases the reaction has occurred either during intercourse or within one hour (as would be expected in an immediate hypersensitivity type I reaction) and usually resolved within 1–3 days. In our patient the reaction always appeared eight hours after intercourse (hence the initial delay in diagnosis) and resolved slowly over five days. Most of the previously described patients with this condition were atopic [2–4, 8–10] our patient was not. The disease in other patients appears to be life-long, with regular recurrence of symptoms following unprotected intercourse. It is interesting that two such patients have become tolerant of seminal plasma following careful desensitization (immunoprophylaxis) [7, 11]. Our patient appears to have developed a natural tolerance to the antigen, though it is of interest that the pulmonary function tests did not completely revert to normal.

The clinical features in our patient initially suggested a circulating immune complex, type III, hypersensitivity. Symptoms occurred eight hours after exposure to the antigen (after intercourse and skin testing) and the arthralgia, restrictive ventilatory pulmonary defect and

possibly the proctitis were also suggestive. The presence of circulating immune complexes in the serum and other evidence of complement activation also suggested this mechanism. However, the *in vitro* studies which might have confirmed this possibility were negative. The clinical and immunological findings in the previously described cases implicate a type I hypersensitivity reaction to antigen(s) present in seminal fluid rather than on spermatozoa. An immune response has been found to four of the five major fractions of seminal plasma recognized by chromatography *in vivo* and *in vitro* [3, 5, 6, 11]. Intracutaneous testing with seminal fluid or its subfactors invariably gives an immediate hypersensitivity response in affected patients, but not in healthy controls [2, 4, 6-8]. Confirmation that the reaction in these cases is mediated by IgE is shown by passive transfer of the sensitivity (Prausnitz-Kustner test) [6, 9, 11] and the detection of specific IgE antibodies by the radioallergosorbent test [5, 9]. The leucocyte migration inhibition test, an *in vitro* correlate of cell mediated immunity, gives positive responses in some affected subjects [6], as does the lymphocyte blast transformation test [16]. However, positive responses are also seen in some unaffected controls, and this may be because histocompatibility antigens expressed on sperm membranes can induce a mixed lymphocyte culture response [6].

Deposition of circulating immune complexes is the most likely explanation of the restrictive ventilatory defect in this patient. An alternative possibility is that the defect is due to direct activation of the alternate pathway. Normal seminal plasma contains an enzyme which suppresses whole complement activity (CH_{50}) [14]. This may have been absent in the husband's seminal fluid as there was no reduction in total haemolytic complement when his seminal fluid was incubated with the patient's plasma. (Normally up to 50% reduction would be expected.) Lack of this anticomplementary factor would allow activation of the alternate pathway. In other circumstances in which there is direct activation of the alternate pathway mechanism, e.g. by *Micropolyspora faeni*, the result is extrinsic allergic alveolitis with a restrictive defect [17].

Though seminal fluid proteins are the source of antigen in most cases, Green and Green [10] have described a penicillin-sensitive woman who developed urticaria related to intercourse while her partner was being treated with penicillin, presumably due to secretion of penicillin products in his semen. Our patient's husband was not taking penicillin or any other medication.

Many patients with true seminal fluid hypersensitivity develop symptoms immediately after the first admitted sexual experience, suggesting that the sensitization is caused by prior exposure to antigens that cross-react with seminal fluid antigens [2], possibly from infection with micro-organisms carrying cross-reacting antigens. Three patients have been described with vaginitis initiated by an allergic reaction to IgE antibodies present in the partner's seminal fluid [18]. These antibodies were directed against female vaginal secretions or components of semen.

None of these explanations is sufficient to account for the illness seen in our patient. She may possibly have had a short-term sensitizing IgG antibody to seminal fluid. By analogy with its action elsewhere [19] this antibody would provide a local increase in vascular permeability in the genital tract, allowing seminal antigen and other IgG antibodies to form complexes resulting in an Arthus (type III) reaction.

An alternative explanation relates to the response to tranexamic acid, an antifibrinolytic agent which competitively inhibits the activation of plasminogen to plasmin. Possibly some factor in seminal fluid was directly activating the fibrinolytic, and hence the complement system. However, this is not a property of seminal fluid *in vitro*, and the mode of action of tranexamic acid *in vitro* is obscure.

Initial diagnosis in our patient took some time because of the delayed onset of symptoms

after intercourse. Though such a situation has not been described before it is likely that other patients with a similar illness exist, but that seminal fluid hypersensitivity may not have been considered. Chronic urticaria, for example, is a common condition, and in one large series an underlying cause was found in only 21% of cases. It is probable that some such patients have seminal fluid hypersensitivity similar to that in our patient. The absence of a simple skin test or blood test may make the diagnosis difficult. We believe that this type of hypersensitivity should at least be considered in these patients, as simple and effective therapy is available if the diagnosis is confirmed.

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