

REVIEW

Human seminal plasma allergy: a review of a rare phenomenon

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Introduction

Human seminal plasma allergy (HSPA), in women, is an exceptionally rare phenomenon. This little known disorder was initially reported by the Dutch gynaecologist Specken [1] in 1958. It is usually caused by sensitization to proteins present in the seminal fluid, leading to immediate hypersensitivity manifestations during or soon after coitus. Symptoms can range from local pruritis to life-threatening anaphylaxis. This rare disorder is most commonly thought to be mediated by the classical IgE-mediated pathophysiological mechanism. We present a review of the 80 cases of HSPA found in the English literature.

Data sources

The MEDLINE database was used to search for articles that had been published in the literature (1966 to present) with the key words 'human seminal plasma allergy' and 'seminal fluid hypersensitivity'. Bibliographies of all papers thus located were searched for further relevant articles. All articles/abstracts published in English were included in this review. We were able to trace 80 cases in the English literature, which also included three abstracts translated in English.

History

Although Specken [1] gave the first clear description of HSPA, an earlier report by James [2], in 1945, documented an enigmatic case of an 18-year-old primigravida woman who experienced pernicious nausea and vomiting of pregnancy that was later found to be due to sensitivity to semen. Curiously, Dr James states 'Although work has been done and reports have appeared in the literature on semen allergy....' but no reference was cited nor were we able to locate any prior reports.

After the Dutch report, the first case in the English language was described 9 years later from France by Halpern et al. [3]. Since then sporadic cases have documented the existence of this extremely rare disorder. A majority of the cases (42) reported were from Europe, while 28 were from USA, two from Australia, one from New Zealand and seven from Asia, three of which were documented by us from India. There were two case reports from Japan, and one each from

Israel and Korea. The first report from the Asian continent was documented by us in 1988 [4]. There were no cases documented from Africa, Central and South America, or even Canada.

Age of onset

Information regarding age of onset was available in 56 patients (Table 1). The third decade of life was found to be the commonest period of presentation with 34 (61%) in the age group of 20–30 years. Nine (16%) patients reported the onset of symptoms during their teens. In five (9%) patients, HSPA manifested for the first time after the age of 40 years. Surprisingly, four of these five patients were more than 50 years when they first had symptoms. The index case, reported by Specken [1], described a 65-year-old woman who developed generalized urticaria after intercourse. The skin reaction, sometimes associated with asthma, disappeared after 3 h. Skin testing with human seminal plasma was reported to be positive.

Presentation

An immense diversity of reactions may be encountered in female patients with hypersensitivity to seminal fluid. The classical IgE-mediated pathophysiological reaction appears to be the most common mechanism to explain the symptomatology. Type III immune responses and cell-mediated immunological reactions have also been documented, albeit rarely.

Symptomatology

The varied presentation of HSPA can be classified as local or systemic depending on the symptom complex. Among the 80 cases reviewed, information on symptomatology was available in 74 patients (Table 2). Systemic symptoms were present in 52 (70%) patients, of whom 29 also had associated local symptoms. Twenty-one (28%) patients manifested local reactions only, while one (1%) patient presented with fixed cutaneous eruptions. Information in this regard was not available in six reports.

Systemic symptoms

The systemic features reported include generalized pruritis, urticaria and angioedema of the face, tongue, lips and throat.

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Table 1. Patient profile

<i>Age of onset</i>	
Information available in	56
No information available	24
Age (years)	Number of patients (56)
< 20	9 (16%)
20–30	34 (61%)
30–40	8 (14%)
40–50	1 (2%)
> 50	4 (7%)
<i>Symptoms at first intercourse</i>	
Information available in	56
No information available	24
First intercourse	23 (41%)
Subsequent intercourse	32 (57%)
Never had intercourse	1 (2%)
<i>Coitus after a time gap</i>	
	8 patients
Pregnancy	4
Menopause	1
Hysterectomy	1
Insertion of an intrauterine device	1
Partial prostatectomy in male partner	1
<i>History of atopy</i>	
Information available in	49
No information available	31
Present	41 (84%)
Absent	8 (16%)
Personal history only	15
Family history only	2
Both personal and family	24

Respiratory manifestations in the form of shortness of breath, wheezing, chest tightness, stridor and cough have been documented. Nasal complaints like rhinorrhoea and sneezing have also been recorded. Other features described were nausea, vomiting, diarrhoea and generalized malaise. Life-threatening anaphylactic reactions presenting as hypotension, dizziness and circulatory collapse requiring emergency intervention have been recorded in 16 patients. The symptoms culminated in loss of consciousness in only one patient [3]. However, fatality as a consequence of HSPA is yet to be recorded.

Local symptoms

The local symptoms of HSPA recorded were vulvar and vaginal itching, burning, pain, erythema (redness), swelling and blister formation. These have often been misdiagnosed as chronic vulvovaginitis and have frequently gone unrecognized. Four cases of familial allergic seminal vulvovaginitis have been described in one family of a mother and her three daughters [5]. All the four women had experienced local discomfort from contact with seminal fluid, beginning from their first sexual intercourse. One of the daughters had experienced a severe systemic reaction during coitus on one occasion. A personal history of atopy was elicited in all of them.

Fixed cutaneous eruptions

Fixed cutaneous eruptions after each unprotected intercourse have been reported in a 33-year-old married woman with two children [6]. The reaction started as pruritic erythematous

Table 2. Symptom profile

<i>Symptomatology</i>	
Information available in	74
No information available	6
Systemic symptoms only	23 (31%)
Both systemic and local	29 (39%)
Local symptoms only	21 (28%)
Fixed cutaneous eruptions	1 (1%)
<i>Time of onset of symptoms</i>	
Information available in	56
No information available	24
During coitus	12 (21%)
Immediately after coitus	17 (30%)
Within/up to 5 min	10 (18%)
5–30 min after coitus	10 (18%)
30 min–1 h	–
More than 1 h	7 (13%)
<i>Resolution of symptoms</i>	
Information available in	44
No information available	36
Only by visits to the ER	7 (16%)
Spontaneous resolution always	28 (64%)
Both spontaneously and by ER visits	9 (20%)
<i>Time for spontaneous resolution</i>	
Within 3 h	8
3–24 h	9
1–7 days	11
No information available	9

macules developing into vesicles and bullae, progressing to a purpuric, hyperpigmented macular lesion. The areas involved were the vagina, vulva, hip, breast, ear and a single spot on one finger. Remarkably, this patient did not experience any systemic or local symptoms as described above.

Initial occurrence of symptoms

Symptoms associated with first intercourse

Information about the occurrence of HSPA at the time of first coitus was available in 56 of the 80 recorded cases (Table 1). Twenty-three (41%) of these 56 patients experienced symptoms during/after the first intercourse, while one (2%) patient never had intercourse since she developed symptoms on topical contact with seminal fluid. The remaining 32 (57%) patients did not manifest HSPA during/after the first coitus. Halpern et al. [3] proposed that in patients manifesting HSPA after the very first sexual intercourse, sensitization might have been caused by exposure to unknown antigens that cross-reacted with those in human seminal plasma. The authors state that, 'there was evidence of gestation with a twin brother.' It has also been postulated that naturally occurring antisperm antibodies may be produced as a result of infection by microorganisms carrying cross-reacting antigens [7]. It seems that after onset, symptoms usually recur with every coitus.

Symptoms after a gap of time

There have been instances when hypersensitivity reactions to seminal plasma have manifested for the first time on resuming intercourse after a gap of time (Table 1). Occurrence of HSPA

after a time gap attributable to pregnancy was identified in four patients. A 25-year-old woman complained of postcoital itching of the genital areas that started between the first and second pregnancies but after the birth of the second child, the local symptoms worsened considerably. Subsequently systemic manifestations also occurred [8]. Another 26-year-old married woman experienced severe anaphylactic symptoms immediately following unprotected intercourse during the second trimester of her third pregnancy [9].

Bernstein et al. [10, 11] reported a patient who had her initial episode of postcoital anaphylaxis 6 weeks after childbirth and 10 weeks after the last coitus during pregnancy. The fourth patient who had a temporal association of HSPA with pregnancy noticed urticaria and pruritis on a few occasions prior to her second pregnancy [12]. However, on resuming intercourse after the birth of her second child, both local as well as systemic symptoms occurred within 5 min after ejaculation and emergency treatment with epinephrine was needed. Thereafter, manifestations of HSPA recurred consistently and the patient each time required treatment with subcutaneous epinephrine.

During pregnancy, disruption of maternal immune responses has been demonstrated by the presence of naturally occurring immunosuppressive agents and enhancement of T cell suppressor activity. Bernstein et al. [10] postulated that 'this physiological impairment of immunomodulation, especially if it preferentially involves IgE-specific suppressor T cells, could disappear suddenly after pregnancy and lead to a state of rebound or exaggerated IgE responsiveness to naturally occurring or cross-reactive seminal fluid antigenic determinants in genetically susceptible women'.

A temporal relationship between HSPA and insertion of an intrauterine device [13], partial prostatectomy in the male partner [14], menopause [15] and hysterectomy [16] has been noted in one patient each. Reunala et al. [13] described a 31-year-old married woman who developed local symptoms soon after insertion of an intrauterine device after her second pregnancy. A 30-year-old married lady, with two children, suffered a sudden postcoital episode of dyspnoea and wheezing shortly after her husband had undergone a partial prostatectomy [14]. However, 3 months prior to this episode the patient thought that she had perineal irritation and swelling after intercourse, but was not certain. A 57-year-old married woman with two children, reported in a series of six cases from Denmark, noticed postcoital attacks of urticaria on legs and arms after attaining menopause [15]. It was however, mentioned that her husband had used a condom during intercourse until her menopause. Another woman, at 44 years of age, experienced episodes of dry cough following intercourse with her husband [16]. Six months later, she underwent hysterectomy for uterine fibroids. Six weeks after surgery, on resumption of sexual intercourse, she developed systemic allergic manifestations 30 min after ejaculation. Subsequently her symptoms progressed to a stage where she eventually required medical intervention.

Symptoms on topical contact only

Features of HSPA following topical contact with seminal fluid not related to intercourse have been reported in one patient [17]. The patient, a 20-year-old woman, developed a

severe generalized systemic reaction after topical contact with seminal fluid. Emergency administration of adrenaline and systemic corticosteroids were needed to treat the symptoms. The patient had never experienced vaginal intercourse.

Time of onset of symptoms

The time of onset of symptoms was mentioned in 56 patients (Table 2). The symptoms occurred either immediately during/after coitus or ranged up to 15 h later. Of the 56 patients recorded, the symptoms occurred during coitus in 12 (21%) patients, while in 17 (30%) others HSPA developed immediately after. In 10 (18%) patients, the symptoms occurred within 5 min, and in another 10 (18%) patients the symptoms manifested between 5 and 30 min. In seven (13%) patients, HSPA developed anytime between 1 and 15 h of sexual intercourse. No information regarding the time of onset of symptoms was available in the remaining 24 patients.

While on honeymoon, a previously fit 19-year-old woman developed mucoid diarrhoea with some blood followed a day later by a painful pruritic rash affecting the scalp and limbs [18]. 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, and at 12 h pains developed in the proximal interphalangeal joints, wrists and elbows. Periorbital oedema appeared at 16 h and by 24 h, the urticaria became generalized. Over the ensuing 24 h, she would have diarrhoea with occasional blood accompanied by breathlessness without wheezing. The symptoms persisted for 4–5 days before subsiding.

A patient described by Schimkat et al. [19] developed contact dermatitis that occurred 15 h after coitus. This patient had a positive vulvovaginal provocation test with sperm and a positive lymphocyte transformation test for specific seminal plasma fractions.

In another patient, the onset of systemic and local symptoms occurred at different times. The patient who became allergic to her husband's seminal fluid shortly after he had had a partial prostatectomy reported that systemic symptoms in the form of wheezing and shortness of breath generally appeared almost instantaneously after her husband's ejaculation, but localized swelling and oedema occurred 10–15 min later [14].

Gradual reduction in time of onset of symptoms

A gradual reduction in the time of onset of symptoms was noted in three patients. A 29-year-old married woman initially developed itchy and severely swollen eyes, nasal congestion and sneezing within an hour after intercourse. However, 10 days later when she again engaged in sexual intercourse, the symptoms occurred within 5 min [20]. In the patient who had developed fixed cutaneous eruptions after each unprotected intercourse, the time from exposure to onset of symptoms decreased from 2 days to 2 h over a period of 2 years [6]. In a 37-year-old lady with a 5-year-old child, symptoms of HSPA started only 6 months prior to referral. Initially she had urticaria of her hands and face 15–30 min after sexual intercourse. Later her symptoms worsened

progressively and she developed generalized urticaria with shortness of breath immediately after coitus [21].

Progression of symptoms

A gradual worsening of symptoms over the course of time has also been reported. Progression of postcoital symptoms has been recorded in 21 patients. The progression may either be from local to systemic manifestations or there may be an increase in the intensity/severity of the systemic or local symptoms.

The insidious progression from local to systemic symptoms has been reported twice. A patient described by Reunala et al. [13] noticed vaginal itching, swelling and local urticaria on the abdomen following intercourse soon after insertion of an intrauterine device. The symptoms gradually became more severe and the patient experienced swelling in her throat as well as difficulty in breathing. One-and-a-half years later, she exhibited a severe postcoital anaphylactoid reaction needing emergency intervention.

We have earlier reported the first case of HSPA from India [4]. An 18-year-old non-atopic married woman experienced, ever since her first intercourse, an intense burning and irritation of the vagina immediately after her husband's ejaculation. This was associated with pruritis, erythema and swelling of the genital region. These symptoms slowly subsided within a couple of hours, but steadily increased in severity with time. She also suffered from severe itching and burning whenever her husband's seminal fluid came in contact with her skin. Five months after marriage, in addition to local symptoms, the patient started experiencing wheezing dyspnoea and tightness of the chest after every intercourse. These episodes, however, lasted for 10 min only.

Variation of severity of reactions with time has also been reported. Among the patients with familial allergic seminal vulvovaginitis [5], one of the daughters experienced a severe systemic reaction during coitus on one occasion. She lay motionless for about half an hour and felt dizzy, but never lost consciousness. Mikkelsen et al. [22] reported a patient who had allergic manifestations with multiple partners since her first intercourse. The reactions varied in severity with all three partners. The investigators classified these reactions as minor, moderate and major. The minor reactions occurred 10–30 min after every intercourse and chiefly comprised local manifestations with occasional generalized pruritis. The moderate reactions occurred from 0.5–1 h after coitus and included periorbital swelling and sacral urticaria. The patient had had two such reactions in the last 6 months prior to examination. She had also experienced three major reactions in 6 years. These occurred immediately following coitus and encompassed generalized wheezing, dyspnoea, periorbital oedema and a sensation of impending syncope. The authors felt that her history was remarkable and there was 'great temporal variation in the frequency of reactions' and her degree of sensitivity waxed and waned.

Resolution of symptoms

Data on resolution of symptoms was given in 44 patients (Table 2). Spontaneous resolution of symptoms was recorded

in 37 (84%) patients. Of these 37 patients, nine also required emergency intervention at one time or the other for symptomatic relief. The symptoms subsided within 3 h in eight patients, between 3 and 24 h in nine and within a week in 11 patients. However, in the other nine patients whose symptoms abated spontaneously, the time required for abolition of symptoms was not stated. In seven (16%) other patients, symptoms could only be abolished after emergency medical intervention. In the remaining 36 patients, information on this score was not available.

Four patients have also reported mitigation of symptoms after a shower. In the report of familial allergic seminal vulvovaginitis [5], the youngest of the three sisters felt the need to rush to the shower immediately following coitus to wash off the ejaculate. The eldest sister, who responded to a questionnaire, informed that her discomfort due to HSPA also persisted until shower. A 28-year-old married woman reported that warm baths immediately after intercourse helped to accelerate resolution of her local symptoms that included postcoital vaginal and perivaginal swelling associated with severe itching and burning [23]. The reactions were not associated with other symptoms of systemic anaphylaxis. In another 23-year-old married woman, vulvar burning and throbbing after coitus improved upon taking a shower [24].

Occurrence of HSPA with specific partner

In three patients, HSPA occurred only with a particular partner and not with other men. A 32-year-old married woman, who had three children by a previous husband, complained of intense vulval and vaginal irritation 5 min after intercourse with her new husband [25, 26]. This was followed by a generalized irritation of the body, particularly involving the palms of her hands and feet. She also experienced generalized urticaria, pelvic pain and difficulty in breathing on a few occasions. Topical contact with her husband's semen also caused an acute irritation on her skin. The authors mention, 'her main complaint is that she remains sterile.'

Another 20-year-old female presented with a rash covering most of her body along with considerable itching and discomfort in the vaginal area following sexual intercourse with her current partner [27]. The rash increased in severity after the second coitus. None of her prior sexual experiences produced such a reaction. A 41-year-old woman developed vaginal and perivaginal pruritis, urticaria and angioedema within 5 min of intercourse [28]. Repeated episodes of coitus were associated with a progressive increase of anaphylactic symptoms with angioedema of the face and lips, bronchospasm, and documented hypotension. Contact of semen with the skin resulted immediately in local itching, burning and wealing. Detailed history revealed an atopic background, tubal sterilization in the recent past and vasectomy in her current partner. Intercourse with two former partners had never induced such symptoms. The authors postulated that the combination of the exposure to seminal plasma from a vasectomized man and the susceptibility of an atopic and recently sterilized woman might have provided the basis for the allergic phenomenon.

HSPA with multiple partners

The occurrence of HSPA following coitus with more than one sexual partner has been documented in six patients [13, 15, 22, 29, 30]. A 30-year-old woman, who encountered symptoms ever since she first engaged in sexual intercourse at the age of 18 years, had noticed reactions with three partners [22]. Among a presentation of six cases from Denmark, patients 1 and 6 experienced symptoms with five and four different partners, respectively [15].

HSPA and difficulty in conception

A history of inability to conceive in such patients has been regarded as an important clue for the diagnosis of HSPA [31]. The first patient reported by us had not conceived in spite of unprotected coitus since her marriage 2½ years prior to referral [4]. Another patient recently reported by us had symptoms of HSPA since her first coitus after marriage 1½ years prior to referral [32]. The couple had had unprotected coitus that resulted in three first trimester abortions. At one point of time, it was thought that pregnancy was not recorded after the identification of HSPA [31]. However, review of the literature revealed five patients [5, 32–34] who, without treatment, became pregnant after the onset of HSPA. Induction of pregnancy by artificial insemination of spermatozoa (washed off semen) was successfully done in two patients [31, 35]. In addition, there were four more patients [18, 36–38] who conceived spontaneously after treatment for HSPA. The literature also revealed that there were a total of 14 patients [6, 8–15, 20, 21, 26, 33, 39] who had borne children prior to the onset of HSPA. In four [8–12] of these 14 patients, HSPA occurred for the first time on resuming intercourse after a gap of time due to pregnancy.

Pregnancy before HSPA

Levine et al. [20] had described a patient who had a past gynaecologic history of one full-term induced delivery and three abortions before the onset of HSPA. Another 32-year-old married woman had three children by a previous husband [26]. Systemic and local symptoms of HSPA started after intercourse with her second husband. Although this patient was shown to be ovulating, she was unable to conceive with her second husband.

Blair and Parish [33] reported a woman who had four pregnancies before the occurrence of HSPA. The first pregnancy terminated in a miscarriage at 2 months, the second was a normal delivery, the third an incomplete abortion at 3 months, and the fourth a full-term delivery followed by post-partum haemorrhage. Four months after the fourth pregnancy, the patient developed asthma for the first time and another 14 months later, manifestations of HSPA appeared. More than a year later, a fifth pregnancy culminated in a full-term normal delivery, but the infant became asthmatic.

Spontaneous pregnancy after HSPA without treatment

In the report of familial allergic vulvovaginitis by Chang [5], all four women in the family had experienced discomfort

from contact with seminal fluid beginning from their first sexual intercourse. The eldest daughter, who was then 33, had borne two children.

In the patient reported by Blair and Parish [33], HSPA occurred after the fourth pregnancy but she had a successful full-term normal delivery subsequently. Kint et al. [34] described a patient with combined allergy to human seminal plasma and latex who became pregnant after the onset of HSPA.

In our recent report [32], patient 2 presented with a 5-year history of HSPA dating back to her first intercourse since her marriage. Two years after the onset of symptoms, she delivered a boy and then had an elective abortion an year later. A third conception, 1 year prior to referral, resulted in a child who died 22 days after birth.

Pregnancy achieved by artificial insemination

Shapiro et al. [31] reported the first successful induction of pregnancy in a woman with systemic allergic sensitivity to semen. The husband's semen was processed such that it was devoid of allergenic components and artificial insemination was carried out with the prepared spermatozoa-rich specimen. Seven cycles of artificial insemination were performed during a 9-month duration. This resulted in the delivery of normal-appearing twins (one male and one female). In a recent report by investigators from Japan [35], pregnancy was achieved after six inseminations with washed sperm that resulted in the birth of a healthy male infant.

Successful pregnancy after treatment

A patient who exhibited an immune complex (type III) hypersensitivity to seminal fluid was treated with tranexamic acid [18]. Two years later, she had a normal pregnancy and delivered a healthy daughter. A 30-year-old woman with local symptoms became pregnant; 1 year after rapid immunotherapy had led to complete alleviation of her symptoms [36]. Another patient conceived naturally a few months after immunotherapy and gave birth to a healthy child [37]. Investigators from Korea [38] successfully treated a 25-year-old married nulligravida patient by means of intravaginal immunotherapy. The patient conceived spontaneously after 6 months and subsequently delivered a healthy full-term female baby.

Concurrent allergy to latex

Two patients have been described in the literature with allergy to both semen and latex. Kint et al. [34] reported a 32-year-old atopic woman who experienced local symptoms immediately after coitus with or without a condom. A generalized eczema then developed 6–24 h later. Prick tests for latex and human seminal plasma were positive in this patient. Another 29-year-old health care worker stated that she developed urticaria over the hands and face, and angioedema of the hands on using powdered gloves [40]. She also experienced vulvar angioedema when her husband used latex condoms. For at least 5 years, she had noted that semen caused contact urticaria and vulvar angioedema. Serum IgE antibodies to

both seminal fluid and latex rubber glove extract were elevated.

Atopic background

Information regarding history of atopy was available in 49 patients, 41 (84%) of whom had a strong atopic background (Table 1). Thirty-nine of these 41 patients were themselves atopic, 24 of whom also had a family history of atopy. There were only two patients who were not atopic but had a family history of atopy. Eight (16%) patients were neither atopic nor had any family history suggestive of allergic disorders. No information about the atopic status was available in the remaining 31 patients.

A personal or family history of asthma, allergic rhinitis/rhinoconjunctivitis, allergic skin disorders or allergy to drugs and foodstuffs [33] were often elicited. The common allergic skin diseases included eczema, atopic dermatitis and urticaria. A 46-year-old woman, who presented with a history suggestive of HSPA for 6 years, had noticed that cutting her husband's hair produced intense itching and redness of her skin [39]. In addition, she experienced severe itching while peeling potatoes. She also gave a strong history of allergic rhinitis. Furthermore, she complained of vomiting and diarrhoea on eating green and yellow vegetables. Intradermal tests were positive with her husband's semen (1:10), pooled donor semen (1:1000), and her husband's and sons' sweat.

Bernstein et al. [41] conducted a questionnaire survey to determine the prevalence of HSPA in women. The questionnaire was distributed to 1073 women who suspected they had symptoms consistent with HSPA. Two hundred and sixty-six women reported symptoms 'possible' for HSPA (88 localized and 178 systemic). Of these 266 patients, the authors thought that 130 patients (46 localized and 84 systemic) had 'probable' HSPA. Furthermore, they felt that atopy was not a risk factor for HSPA. However, this was only a questionnaire-based study and none of these cases were confirmed by specific investigations, and no further details were given.

The antigen

In an attempt to determine the antigen responsible for a reagenic antibody response in HSPA, Halpern et al. [3], who reported the first case of HSPA in English literature, separated the protein constituents of human seminal fluid by zone electrophoresis and identified the sensitizing agent as a basic sialic acid-rich glycoprotein. A few years later, Levine et al. [20] fractionated pooled seminal plasma, obtained from four vasectomized men, using column chromatography and isolated a protein fraction of 20–30 kDa that they thought was responsible for the allergic phenomenon. They reported the antigen to be unaffected by enzymes degrading carbohydrates but susceptible to proteases [42]. Subsequently antigenic proteins with molecular weights ranging from 14 000 to 75 000 Da have elicited positive skin reactions in patients with HSPA [17, 22, 33, 43]. The pI of the allergenic activity was between 8.4 and 8.6 [20, 43], thereby suggesting the antigen to be basic. However, in one study lower estimates of 5.4–6.6 were observed [17].

Although the exact nature is not yet known, the seminal plasma antigen is probably of prostatic origin. Levine et al. [20] found that the filtered extract of prostatic tissue, obtained by suprapubic prostatectomy for benign prostatic hypertrophy, gave positive weal-and-flare reactions to 1:10⁶ dilution (w/v) in sensitized women. They concluded that the responsible antigen appeared to be a relatively small protein omnipresent in human prostatic secretions and were surprised by the fact that the disease was so rare. Voorhorst [8] also postulated, on the basis of skin tests, that the prostatic secretion contained the offending allergen and attributed the weaker skin reactions that were elicited by extracts of the seminal vesicles and the mucous membrane of the bladder to contamination with prostatic material during procurement of the test material. It is noteworthy that a case of HSPA following partial prostatectomy in the male partner has been described [14].

A bizarre case of anaphylactic reaction after repetitive coital exposure to canine seminal plasma has been described in a 42-year-old pregnant lady [44]. A scratch test with 'dog sperm' elicited a 4+ reaction of erythema and swelling at the site associated with a hot feeling and weakness within 10 min. Earlier, Halpern et al. [3] had obtained negative skin tests with semen from rabbit, guinea-pig, horse and bull, and also with bovine submaxillary mucin and bovine testicular hyaluronidase. The authors had postulated that the responsible allergen was species-specific.

Immunological mechanisms

Most features of HSPA are consistent with classical IgE-mediated reactions wherein reagenic humoral antibodies are produced against an antigen present in the seminal plasma. The antigen reacts with these IgE antibodies, which are bound to mast cells or circulating basophils, thereby leading to degranulation of mast cells. This results in release of vasoactive amines including histamine that mediate the immediate hypersensitivity reactions in the form of vasodilation, visceral smooth muscle contraction and mucous secretory gland stimulation.

Fixed cutaneous eruptions [6] and type III immune response [18] have also been implicated in one patient each, while evidence of cell-mediated immunity has been shown in two patients presenting with recurrent allergic vulvovaginitis [10]. In the patient who developed fixed cutaneous eruptions after each unprotected intercourse, the investigators were not able to document IgE-mediated immediate hypersensitivity responses to seminal fluid antigens. The skin biopsy too did not show any evidence of antibodies or complement in the sampled tissue [6].

In a 19-year-old woman, seminal fluid hypersensitivity appeared to have produced a type III immune response [18]. As described earlier, her symptoms were chronologically related to sexual intercourse and started 8 h after exposure to the antigen. The clinical suspicion was corroborated by intradermal testing with purified seminal fluid of her husband. The presence of circulating immune complexes in the serum also supported a type III reaction.

Bernstein et al. [10] reported two patients with history of recurrent allergic vulvovaginitis who did not develop humoral

antibodies but did have cell-mediated immunity to seminal fluid antigens. One of these patients also had significant titres of IgM and IgG sperm agglutinating antibodies to seminal plasma.

Although the seminal plasma has potential antigens in abundance, allergy to human seminal plasma is singularly uncommon. This could most probably be attributed to the complex homeostatic mechanisms that modulate immune recognition of seminal antigens in the female genital tract. In addition, this may relate to genetic polymorphism or the genetic material imprinted to recognize and respond to specific antigens [45]. Bernstein et al. [10] have demonstrated a high degree of HLA sharing between affected partners in two of their patients. It follows that disruption of normal immunomodulation in the female genital tract could explain the development of HSPA.

Diagnosis

The diagnosis of HSPA, in women, is based on a characteristic history with symptoms that can chronologically be linked to coitus. Prevention of symptoms by condom usage or by coitus interruptus points towards a definitive diagnosis. This must be confirmed by demonstration of sensitization to seminal fluid, which includes *in vivo* tests and *in vitro* immunologic methods.

Condom test

The condom test is based on the fact that symptoms of HSPA can be abolished completely with condom usage [32]. Information regarding usage of condoms was available in 62 cases. Condom usage prevented symptoms in 60 patients. However, the other two were concurrently allergic to latex as well [34, 40].

In vivo skin tests

The *in vivo* skin tests include prick tests and intradermal tests, which are usually done on the volar surface of the arms. The antigen has been prepared from fresh semen, either from the patient's partner or from donors or both. However, with the advent of AIDS and other diseases transmitted through body fluids, it may no longer be ethical to prepare the antigen from a donor. Skin tests with seminal fluid antigen on control subjects too would be considered unethical [46].

Fresh semen obtained from the patient's partner was usually allowed to liquify at room temperature for 45 min prior to centrifugation at $1500 \times g$ for 30 min at 4 °C. The clear supernatant was then filtered through a Whatman no. 1 filter paper. The filtrate thus obtained was diluted 1:1 with buffered saline and subsequently sterilized by filtration through a Millipore filter membrane (0.22 µm). The skin tests were subsequently performed on the patient in serial dilutions of the seminal plasma antigen along with a negative control (buffered saline) and a positive control (histamine: 100 mcg/mL), and graded [4, 47]. Of the 80 patients reviewed, information regarding skin tests was available in 77. Sixty-six patients tested positive, five were negative, one refused, and in five patients, the test was not performed.

In the first patient that was investigated in detail [3], skin scratch tests produced positive results with whole human semen, which was obtained from the husband and other healthy donors (number not mentioned), as well as with human seminal fluid devoid of spermatozoa. The serum of the husband as well as washed human spermatozoa did not elicit any reaction.

Halpern et al. [3] effectively demonstrated that the antigen was common to men. This was subsequently confirmed in a case reported by Mikkelsen et al. [22] wherein skin tests were performed, using seminal fluids from five donors, in a 30-year-old woman presenting with HSPA. Initially the scratch test done with antigens prepared from the seminal fluids of five donors was negative. Subsequently, she was tested intradermally with the same seminal fluids in a dilution of 1:2000, which resulted in typical immediate reactions with weals of approximately 7×7 mm surrounded by erythema. Intradermal injection of the same diluted seminal fluids into control subjects caused a weal about 3 mm diameter and little if any flare.

In the only patient in whom hypersensitivity to seminal plasma appeared to have produced a type III immune response [18], scratch skin tests with purified seminal fluid (1:10 000 w/v) from her husband did not elicit any response. However, following an intradermal injection of the same antigen, a 3 mm area of induration was visible at 8 h. This also led to recurrence of all her symptoms.

Although Halpern et al. [3] had ruled out the possibility of HSPA being caused by spermatozoa, positive skin test with human spermatozoa extract has been demonstrated in one patient. Bernstein et al. [10] described one patient who had two episodes of systemic reactions prior to evaluation. The initial episode occurred 6 weeks after delivery of a normal baby, 10 weeks after the last coitus during pregnancy. Intracutaneous and scratch skin tests to both seminal plasma and spermatozoa extract were positive in this patient.

Anaphylaxis following intradermal testing has been reported in one patient [39]. This patient was allergic to her husband's sweat and semen. When intradermal test was performed with 0.05 mL of her husband's semen (diluted 1:10), she developed an anaphylactic reaction within 1 min consisting of nausea, syncope, tachycardia and sweating. Intradermal tests were also positive with pooled donor semen (1:1000) and her husband's as well as both sons' sweat. However, no anaphylaxis occurred after these tests.

Prausnitz-Kustner (PK) test

The PK reaction demonstrates the passive transfer of hypersensitivity and is based on the affinity of the reaginic antibody (IgE) to skin cells. This test was also performed in nine patients reported prior to 1985. The PK test was positive in eight of these nine patients. This is no longer advocated because of the dangers of transmitting diseases like viral hepatitis and AIDS.

As early as 1945, James [2] had reported a case of pernicious vomiting of pregnancy. An 18-year-old primigravida repeatedly developed mild morning sickness that gradually progressed over a period of 3 days to severe nausea and continuous vomiting when she was hospitalized. In spite of treatment, the vomiting persisted but it abated at the ninth

day when she was discharged. A week later, she again had vomiting and was readmitted to the hospital. The course in the hospital was almost identical to the first admission. The author then suspected that the semen of the patient's husband could be responsible for these attacks, and thus advised condom usage. Although the patient rejected this possibility, she followed the author's advice, but instead of using a condom, the couple followed coitus interruptus and the patient remained well. However, she was admitted once again when her husband inadvertently deposited his semen into her vagina. After parturition, semen sensitivity was demonstrated by a positive PK test that was performed in three non-allergic individuals.

In vitro immunologic tests

The *in vitro* immunologic tests that have been done to demonstrate sensitization include detection of raised total serum IgE levels and elevated specific IgE antibodies to seminal plasma. The semen-specific IgE antibodies were measured by RAST or by ELISA. Additional tests included leucocyte histamine release (LHR) assays and lymphocyte transformation response to seminal fluid. Although these *in vitro* tests yield positive results, they seem to be less sensitive than the *in vivo* skin tests as sensitive specific-IgE assays are not yet available [48].

The total IgE was measured in the serum of 32 patients and was raised in 19 of them. Semen-specific IgE was detected in 28 of the 46 patients tested. Histamine release assays were performed for nine patients and a positive result was obtained in eight of them. The lymphocyte transformation test was positive in one patient and negative in another.

Differential diagnosis

HSPA is a rarely considered diagnosis. Due to its varied presentation, the differential diagnoses of systemic and local manifestations have been discussed separately.

Systemic manifestations

Systemic manifestations of this entity, in women, need to be distinguished from other forms of coitus-linked asthma [49, 50], including postcoital asthma [51] and condom-induced asthma [52, 53]. Postcoital asthma or 'sexercise-induced asthma' [54] and postcoital 'honeymoon rhinitis' [55] can occur in both males and females [51]. Episodes of asthma and/or rhinitis, in these patients, cannot be ascribed to any cause other than sexual excitement. Anxiety and apprehension are predominant features in such patients and their partners. Condom usage too can cause asthma in both males and females due to latex allergy [52]. This is often associated with local allergic manifestations. As described earlier, two cases of HSPA with concurrent latex allergy have also been reported [34, 40].

Local reactions

The local forms of HSPA frequently go unrecognized as they are often misdiagnosed as vulvovaginitis [45, 56]. In a

majority of cases of vulvovaginitis, which are often chronic, the cause is not readily apparent [57]. Apart from semen, other allergens acting locally can also affect the vulva and vagina. Recurrent vaginitis can also be caused by IgE antibodies present in the seminal fluid. Witkin et al. [58] described three patients who reported a repeated association between coitus and vaginitis. This was found to be a result of sexual transmission of IgE antibodies that were reactive either to antigens of the female genital tract or components of semen. One of the seminal fluids had highly elevated concentrations of total IgE, while the other two semen samples contained IgE antibodies that were reactive with a particular fraction of the vaginal fluids obtained from the patients. The seminal fluid of the partner of one of these three patients also contained IgE reactive with *Candida albicans*.

Allergic vulvovaginitis [57] due to allergens such as pollens [59], dust, topical medications and chemicals present in soaps, perfumes, nail polish, sanitary napkins, textile fibres and contraceptive spermicides can simulate the local forms of HSPA. Recurrent pruritis vulvae due to irritation by printer's ink have been documented in three patients. A detailed history revealed that symptoms occurred on manual manipulation of the vulva soon after reading the newspaper. The patients responded dramatically, needing no further treatment of any kind, when their husbands either changed this habit or washed hands thoroughly after reading the newspaper [60]. In case symptoms occur with correct condom usage in patients who are not allergic to latex, primary or secondary dyspareunia should be considered [61].

Seminal transfer of antigens

Not only can the seminal fluid function as an allergen in certain female subjects, it can also be a vehicle for transfer of allergens in females allergic to those particular agents. Hypersensitivity reactions due to transfer of allergens present in the seminal fluid have been described in the literature. Such reactions need to be distinguished from HSPA. There have been case reports of allergic reactions to vinblastine [62], walnut [63], thioridazine [64] and penicillin [65].

The wife of a patient with stage III B Hodgkin's disease experienced severe vaginitis whenever the couple had sexual intercourse within the first 3 or 4 days after the husband had taken vinblastine [62]. This reaction was prevented by condom usage. Another case of postcoital anaphylaxis has been documented in which a female patient allergic to walnut experienced a severe reaction after intercourse with her husband, who had just eaten walnuts [63]. Walnut protein was isolated from the husband's seminal plasma. A 28-year-old white woman noticed severe itching and an erythematous rash on her genitals 24 h after intercourse when her husband took 100 mg of thioridazine [64]. Skin testing with this drug produced a positive weal. The rash did not occur after condom usage. A 33-year-old atopic woman developed generalized hives associated with a sensation of fullness in her throat, heaviness of her eyelids, eye burning and nausea within 30 min following intercourse on three occasions in a week [65]. Skin testing with semen and serum for semen-specific IgE antibodies were negative. Interrogation revealed that her partner had been taking dicloxacillin for a skin

infection during that particular week. The woman had a positive weal-and-flare response to intradermal testing with penicillin. Using a condom during intercourse while the male partner continued to take dicloxacillin did not produce the hypersensitivity reactions.

Treatment

Allergen avoidance remains the mainstay of management. Exposure to seminal fluid can be avoided by abstinence or coitus interruptus, but this is rarely acceptable to the patients as well as their partners [45]. Usage of condoms is the most widely advocated method but again may be unacceptable to couples who wish to start a family [37, 45]. In case the patient or the male partner is also sensitive to latex, condoms made of material other than latex viz., lambskin (made from processed sheep's intestine) or a plastic polymer (polystyrene-poly(ethylene-butylene)-polystyrene) have been advocated [34].

Immunotherapy

As in other forms of atopic disorders, immunotherapy could be contemplated. Previous reports of immunotherapy have shown variable success. Attempts to treat HSPA by immunotherapy have been reported in 25 patients (Table 3). In 14 of them [3, 9, 16, 17, 33, 66] the conventional method was adopted, while 'rush' protocol was followed in the remaining 11 patients [12, 21, 23, 36–38, 67–69].

Conventional method Halpern et al. [3] were the first to try immunotherapy in their patient. They attempted to induce the formation of 'blocking antibodies' by injecting undiluted seminal fluid. In spite of the treatment, the systemic reactions occurred regularly with a defined dose and the symptoms too recurred after sexual intercourse. The authors attributed the apparent inability of their patient to produce blocking antibodies for the seminal plasma allergen to the fact that a homologous antigen was involved.

The next attempt was reported 13 years later. On their patient's request, Mathias et al. [9] intradermally injected serial dilutions of the husband's seminal plasma twice a week. Barring aggravation of atopic dermatitis during the initial stages, the patient tolerated immunotherapy well. There was a decline in the LHR assay and RAST binding during the therapy. Approximately 6 months later, the patient was accidentally exposed to her husband's semen that led to reappearance of her usual symptoms and an increase in the LHR and RAST assays. Continuation of therapy attenuated the symptoms, but the objective parameters (LHR and RAST) remained elevated thereafter.

In the patient whose symptoms were triggered after hysterectomy [16], immunotherapy was carried out with

seminal plasma fraction showing the highest degree of skin reactivity. Subcutaneous injections were given thrice weekly, starting at an allergen concentration at least 100 times below the positive skin test threshold concentration. The maximum dose used was tenfold higher. Two weeks after the final dose of immunotherapy, intercourse was performed and no adverse symptoms were experienced by the patient. Regular and frequent sexual activity was required to maintain the tolerant state.

Immunotherapy was successfully conducted over a 24-month period in the patient who developed HSPA after topical contact with seminal fluid [17]. A cumulative dose of 32 mg of protein was administered. No side-effects other than local swelling occurred. A year later, IgE antibody levels became unmeasurable while IgG antibody titres rose progressively during this period. Clinically the patient became less sensitive to topical contact.

Although Drouet et al. [66] reported the largest series on HSPA so far, the data presented was very brief. Of the 13 patients described, six presented with local reactions only while the remaining seven had systemic symptoms. The authors mentioned that immunotherapy was attempted in nine patients, three of whom had local reactions only. Immunotherapy was not successful in this group of three patients with local reactions only and additionally in one patient with systemic features. The other five patients, all of whom had systemic manifestations, were successfully treated by immunotherapy.

Rush immunotherapy

The 'rush' immunotherapy protocol was adopted in 11 patients. The procedure was carried out subcutaneously in six patients and intravaginally in five, and was successful in all the 11 patients.

Subcutaneous route Rush immunotherapy by the subcutaneous route was first employed by Frisch et al. [67]. They successfully desensitized a 33-year-old doctor who presented with both local and generalized symptoms within minutes after coitus. The seminal plasma was obtained from a pool of HBsAg-negative donors and subcutaneous injections were given with progressively increasing doses at half-hourly intervals for 10 h daily. After 3 days, the injections were gradually spaced out. No allergic symptoms were recorded when unprotected intercourse was tried after 7 weeks of treatment.

Mittman et al. [12] adopted a 2-day protocol of rapid immunotherapy with subcutaneous incremental doses of two human seminal plasma fractions that demonstrated the highest degree of allergenicity based on *in vitro* LHR studies. There was a one-log increase in the intracutaneous endpoint threshold concentration to both fractions after completion of the second day of rapid immunotherapy. Injections of both fractions were then continued three times weekly for the next 4 months. At that time, sexual intercourse was resumed without the use of condoms. No local or systemic reactions were reported after coitus. Immunotherapy was stopped and on maintaining a regular schedule of sexual intercourse every 2–3 days, there was no recurrence of symptoms over the next 6 months.

Table 3. Immunotherapy

Method	Attempted in	Successful in
Conventional	14	9 (64%)
'Rush' protocol	11	11 (100%)
Subcutaneous	6	6 (100%)
Intravaginal	5	5 (100%)

Boom et al. [68] attempted a 1-day rush immunotherapy procedure in a 24-year-old woman. Subsequently, two booster injections were given weekly with the highest possible dose reached at the day of the rush procedure. Apart from minor anaphylactic symptoms, no serious side-effects were noted during or after the procedure or after boosting. Five weeks after the start of immunotherapy, the patient did not experience any symptoms following unprotected coitus. However, she continued to experience itching and a local urticarial reaction when the seminal fluid came in contact with her skin. Bernstein et al. [36] also described three women who presented with localized postcoital vaginal secretions that were successfully treated with rapid immunotherapy using human seminal plasma proteins.

Intravaginal route In 1993, Matloff [23] reported the first successful attempt at intravaginal desensitization to seminal fluid in a 28-year-old married woman who noticed progressive local symptoms 2 years after she began having intercourse with her husband. No local reactions were seen with dilutions of 1:1000, 1:100 and 1:10. After the undiluted semen sample was deposited, minimal reaction occurred that lasted for only 30 min. The patient then had intercourse without condoms every 24–48 h for 2 months without experiencing any local symptoms. A 10-day hiatus resulted in return of symptoms. The procedure was repeated without adverse effects. The patient maintained the 'desensitized' state with frequent sexual intercourse thereafter.

Subsequently, immunotherapy via the intravaginal route has been described in four more patients [21, 37, 38, 69]. In two of these patients, successful pregnancy after immunotherapy has also been recorded [37, 38].

Prophylactic measures

Prophylactic usage of antihistaminics and intravaginal cromolyn cream have been reported to prevent the local forms of HSPA. Oral administration of diphenhydramine, 30 min prior to coitus, has been shown to be effective in preventing the local reactions [5, 19, 70]. Alleviation of local symptoms with intravaginal cromolyn cream has also been recorded in two patients [71, 72]. However, in one patient with local manifestations only, precoital treatment with a combination of intravaginal cromoglycate cream and antihistaminics failed to ameliorate the symptoms [73].

In the patient who developed fixed cutaneous eruptions after each unprotected intercourse, complete prevention of symptoms was achieved with mefenamic acid, 500 mg 2 h before intercourse and every 4 h thereafter as needed [6]. The drug was less effective if taken after intercourse. The authors postulated that activation of prostaglandins could possibly have caused the fixed drug eruptions and hence used mefenamic acid, a non-steroidal anti-inflammatory drug that inhibits prostaglandins.

Treatment with antihistaminics, combined with H1- and H2-receptor blockade and non-steroidal anti-inflammatory agents was unhelpful in the patient in whom hypersensitivity to seminal fluid appeared to have produced a type III immune response [18]. However, treatment with tranexamic acid abolished the symptoms and the patient remained asymptomatic

for the next 6 months. The drug was slowly withdrawn and apart from initial mild symptoms, there was no recurrence of illness.

Conclusions

This review of 80 published patients, which included three abstracts [74–76], suggests that HSPA may not be as rare as it appears to be. This could be because it is difficult to recognize, especially the local forms. Patients with episodic allergic manifestations and a history of difficulty in conceiving should be evaluated sensitively for temporal relationship of symptoms with coitus. A high index of suspicion is required as HSPA may easily be overlooked due to patient embarrassment and lack of physician awareness, especially in conservative social conditions and busy outpatient departments [77].

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