Intralymphatic Immunotherapy With Autologous Semen in a Korean Man With Post-Orgasmic Illness Syndrome

Tae Beom Kim, MD, PhD,1,* Young Sup Shim, MD, PhD,2,* Sang Min Lee, MD, PhD,3 Eun Suk Son, PhD,3 Jung Woo Shim, MD,3 and Sang Pyo Lee, MD, PhD3

ABSTRACT

Post-orgasmic illness syndrome (POIS) is a very rare disease characterized by local allergic symptoms and transient flu-like illness that nearly always occur after ejaculation and last for 2 to 7 days. In a previous case report, 2 patients with POIS received hyposensitization therapy composed of multiple subcutaneous injections of autologous semen that resulted in a gradual decrease of symptoms. However, this procedure requires patients to endure pain and discomfort during frequent subcutaneous injections and preceding masturbations to obtain the autologous semen used for therapy. Recent studies have suggested that intralymphatic immunotherapy is a promising new method of allergen-specific immunotherapy against allergic diseases, showing a faster onset and longer duration of therapeutic effects after only several intralymphatic injections. We report on a case of a Korean man with POIS who received intralymphatic immunotherapy that alleviated POIS-related symptoms and in whom the existence of semen-specific immunoglobulin E was confirmed using immunoglobulin E immunoblotting and enzyme-linked immunosorbent assay. Kim TB, Shim YS, Lee, SM, et al. Intralymphatic Immunotherapy With Autologous Semen in a Korean Man With Post-Orgasmic Illness Syndrome. Sex Med 2018;6:174–179.

INTRODUCTION

Post-orgasmic illness syndrome (POIS) is a very rare disease characterized by local allergic symptoms and a transient flu-like illness that nearly always occur after ejaculation and last for 2 to 7 days.1,2

Waldinger and Schweitzer1 1st reported on 2 cases of POIS in 2002; that study summarized the characteristics of 45 POIS cases and subcutaneous immunotherapy (SCIT) with autologous semen was performed for 2 patients. This treatment led to a gradual decrease of complaints, resulting in 90% and 60% amelioration of POIS complaints at 15 and 31 months, respectively.2,3 However, this procedure requires patients to endure pain and discomfort during frequent subcutaneous injections and preceding masturbations to obtain the autologous semen used for therapy.

Recently, intralymphatic immunotherapy (ILIT), a new method of allergen-specific immunotherapy (AIT) that requires only 3 to 6 injections into the inguinal lymph nodes at 4-week intervals, yielded symptom relief that occurred more rapidly than that associated with SCIT and lasted up to 3 years in patients with allergic rhinitis.4–7

We report on a case of a Korean man with POIS who received ILIT that alleviated his POIS-related symptoms and in whom the existence of semen-specific immunoglobulin E was confirmed using IgE immunoblotting and enzyme-linked immunosorbent assay (ELISA).

CASE REPORT

A 30-year-old Korean man visited the university hospital complaining of flu-like symptoms that occurred after masturbation. He 1st masturbated 9 years previously and had various symptoms, including a sore throat, sputum, malaise, myalgia, arthralgia, rhinorrhea, sneezing, weakness, fatigue, fever, feverishness, chill, anorexia, residual urine sensation, voiding difficulty, weak urinary stream, postvoiding dribbling, depression,
anxiety, and irritability, that nearly always occurred 3 to 4 hours after ejaculation and lasted for 48 hours with spontaneous regression. He was diagnosed with POIS, because his symptoms were consistent with the 5 diagnostic criteria. He also had food allergies and complained of lip edema after ingestion of shrimp. Serum IgE level, which was measured using the ImmunoCAP system (ThermoFisher Scientific, Uppsala, Sweden), was 403 U/mL and levels of crab- and shrimp-specific IgE were 6.58 U/mL (class 3) and 20.0 U/mL (class 4), respectively. Prostate-specific antigen levels were normal (0.52 ng/mL). Serum total IgA, IgM, IgG, IgG1, IgG2, and IgG4 levels were within normal limits, whereas IgG3 was somewhat decreased (eTable 1). For sex hormones, estradiol was increased, prolactin and testosterone were decreased, and luteinizing hormone and follicle-stimulating hormone were within normal limits.

We proposed abstinence, scheduled masturbation during holidays, and prescription drugs, including non-steroidal anti-inflammatories, antihistamine, and mucolytic drugs, to relieve POIS-related symptoms. We also suggested SCIT or ILIT with autologous semen as a causative treatment against POIS and provided all references on POIS and ILIT with sufficient explanation and discussion. The patient eventually decided to undergo ILIT with autologous semen and provided informed consent.

We performed ILIT and evaluated POIS status before and 8 and 15 months after the 1st injection of ILIT (eFigure 1). Before ILIT, the patient was asked to score the severity of each POIS-related symptom using a visual analog scale ranging from 0 to 100 mm and to describe the duration of each. The patient also was asked to complete the Male Sexual Health Questionnaire (MSHQ) and was evaluated using the International Index of Erectile Function (IIEF). The patient’s semen and serum were obtained, and a skin prick test (SPT) and intradermal test with serially diluted autologous semen were performed before and 8 months after the 1st ILIT injection.

Using ultrasound guidance and a 25-gauge needle, autologous semen was aseptically injected into an inguinal lymph node at a dilution of 1:40,000. Then, the concentration was increased by 3-fold, as in a previous study of ILIT. The patient complained of transient mild pain and a warm and abnormal sensation at the local injection site after each injection of ILIT. After the 3rd and 4th injections, the patient also complained of flu-like symptoms, including fatigue, chill, a burning sensation in the eyes, sore throat, and parotid swelling; these symptoms persisted for 3 to 4 weeks with an intensity that remained at 50% to 60% 5 days after the 3rd injection and at 60% to 70% 5 days after 4th injection. After sufficient discussion, the patient requested that he receive the 5th injection with the full concentration of autologous semen and stated that he did not want further injections thereafter. Based on this request, we performed the 5th injection with the full concentration of autologous semen as the last dose.

At 8 and 15 months after the 1st injection of ILIT, all POIS-related symptoms except sore throat and urinary symptoms were alleviated and their durations were shortened (Table 1). In particular, sneezing completely subsided. Moreover, the patient’s responses to several questions on the MSHQ and IIEF indicated alleviation of discomfort after ejaculation and improvement in sexual function (eTable 2). His answers to other questions on the MSHQ or IIEF did not change after ILIT. Time from erection to ejaculation also remained unchanged at 5 minutes. According to the semen analysis, the amount of semen and sperm with normal motility and morphology increased 8 months after ILIT (eTable 3). Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) analysis of seminal fluid showed multiple protein bands with an apparent molecular mass ranging from 10 to 170 kD, as previously described (eFigure 2). The IgE immunoblotting of autologous seminal fluid incubated with serum from the patient and 1 healthy control showed IgE binding bands at 14, 16, 34, and 55 kD (eFigure 3). The IgE binding band at 55 kD was particularly prominent before ILIT, but it was fainter when seminal fluid was incubated with serum obtained from the patient 8 months after ILIT. In addition, ELISA analysis showed that the level of semen-specific IgE was increased in the patient’s serum before ILIT compared with the healthy control, but it had deceased to levels similar to those of the healthy control 8 months after ILIT (eFigure 4). Skin reactivity to the SPT and intradermal test with serially diluted autologous semen increased 8 months after ILIT (eTable 4).

The study was approved by our institutional review board.

DISCUSSION

Waldinger et al hypothesized that allergies could play a role in POIS and examined the allergic history and measured serum levels of total IgE in all patients and performed hyposensitization therapy in 2 patients. Their hypothesis seems reasonable because most of their subjects (87%) developed POIS-related symptoms within 30 minutes of ejaculation, which suggests an immediate hypersensitive allergic reaction. In addition, some of their subjects (22%—44%) had ocular and nasal symptoms similar to those of allergic rhinoconjunctivitis. Interestingly, POIS-related symptoms were alleviated after SCIT in 2 subjects. However, because most subjects with POIS frequently had flu-like symptoms, such as extreme fatigue, exhaustion, concentration difficulties, irritation, feverishness, extreme warmth, and perspiration, which are not typical allergic symptoms, the pathogenesis of POIS cannot be entirely explained by allergies. In addition, some but not all of their subjects had existing allergic diseases. Furthermore, although autologous semen had a positive effect in most of their subjects who underwent SPT, Jiang et al suggested that even healthy controls showed positive SPT results with autologous semen, and no semen-specific IgE was detected in the serum of patients with POIS through SDS-PAGE, Western blotting, or ELISA. It is possible that not all patients with POIS have allergies and that multiple causes exist for this syndrome.

In contrast to the case report by Jiang et al, we detected the existence of serum semen-specific IgE in our patient through SDS-PAGE, Western blotting, and ELISA. Moreover, our
patient had POIS-related symptoms 3 to 4 hours after ejaculation and experienced the alleviation of most POIS-related symptoms after ILIT, which indicates that his POIS might be associated with an allergic type I hypersensitivity reaction. Sneezing, a typical symptom of allergic rhinitis, completely disappeared 15 months after ILIT, but the sore throat and urinary symptoms, including residual urine sensation, voiding difficulty, weak stream, and dribbling, remained unchanged after ILIT. We also observed lower levels of IgG3 in the patient’s serum. Variable disorders of the innate and adaptive immune systems, including T-helper cell type 1, 2, and 17 immunity, might be involved in the pathogenesis of POIS, and the roles of specific components of the immune system remain to be investigated.

Hyposensitization therapy, or AIT, can have therapeutic effects in patients with POIS in whom allergies are a dominant etiologic factor. The present patient was judged to belong to this group of patients and received ILIT, which alleviated his POIS-related symptoms. The mechanism of ILIT is not sufficiently understood, but we propose that ILIT might be mediated by plasmablasts, plasma cells, and memory B cells that are activated by allergens injected into lymph nodes and produce allergen-specific IgE, IgG4, or other antibody isotypes with or without enhanced affinity.

Waldinger et al² reported that 56% of their patients had lifelong premature ejaculation with an intravaginal ejaculation latency time shorter than 1 minute. However, none of their patients had erectile dysfunction according to the IIEF-5 criteria. The patient described by Jiang et al¹⁰ had normal erectile function and sexual desire but also complained of premature ejaculation. In this case, the patient had erectile dysfunction and other sexual dysfunctions described by the IIEF and MSQH, all of which were alleviated after ILIT. However, time from penile erection to ejaculation remained at 5 minutes before and after ILIT.

Serum levels of estradiol were increased in the present patient and in the patient described by Jiang et al¹⁰ (86.98 and 43.07 pg/mL, respectively), whereas serum levels of other sexual hormones were not consistent in the 2 studies. Additional studies are needed to determine the role of sex hormones in POIS.

### Table 1. Severity and duration of symptoms related to post-orgasmic illness syndrome before and 8 and 15 months after intralymphatic immunotherapy

| Symptom                          | Severity (VAS, mm)* | Duration (h)       |
|----------------------------------|---------------------|--------------------|
|                                  | Baseline → 8 mo → 15 mo | Baseline → 8 mo → 15 mo |
| General                          |                      |                    |
| Weakness                         | 100 → 80 → 70        | 48 → 40 → 40       |
| Fatigue                          | 100 → 80 → 70        | 48 → 40 → 40       |
| Fever                            | 100 → 50 → 20        | 48 → 24 → 12       |
| Feverishness                     | 100 → 50 → 20        | 48 → 24 → 12       |
| Chill                            | 100 → 50 → 20        | 48 → 24 → 12       |
| Malaise                          | 100 → 80 → 60        | 48 → 48 → 48       |
| Myalgia                          | 100 → 80 → 60        | 48 → 48 → 48       |
| Arthralgia                       | 100 → 80 → 60        | 48 → 48 → 48       |
| Ocular                           |                      |                    |
| Burning sensation                | 100 → 60 → 60        | 48 → 36 → 40       |
| Respiratory                      |                      |                    |
| Rhinorrhea                       | 100 → 60 → 60        | 48 → 36 → 36       |
| Sneezing                         | 100 → 60 → 0         | 48 → 36 → 0        |
| Sore throat                      | 60 → 60 → 60         | 48 → 48 → 48       |
| Sputum                           | 100 → 50 → 40        | 48 → 24 → 24       |
| Gastrointestinal                 |                      |                    |
| Anorexia                         | 100 → 70 → 70        | 48 → 40 → 24       |
| Urinary                          |                      |                    |
| Residual urine sensation         | 80 → 80 → 80         | 48 → 48 → 48       |
| Voiding difficulty               | 80 → 80 → 80         | 48 → 48 → 48       |
| Weak stream                      | 80 → 80 → 80         | 48 → 48 → 48       |
| Dribbling                        | 80 → 80 → 80         | 48 → 48 → 48       |
| Neuropsychiatric                 |                      |                    |
| Depression                       | 100 → 80 → 50        | 48 → 40 → 24       |
| Anxiety                          | 100 → 50 → 40        | 48 → 24 → 20       |
| Irritability                     | 100 → 80 → 80        | 48 → 40 → 36       |

VAS = visual analog scale.

*The VAS ranged from 0 to 100 mm.
Waldinger et al. also reported incoherent speech, concentration difficulties, easily irritable mood, photophobia, and depression in some patients, which is similar to symptoms of “opioid withdrawal syndrome.” The present patient also complained of irritability, anxiety, and depression that were partly alleviated after ILIT. However, the exact mechanisms underlying neuropsychiatric disorders and the effects of AIT on these disorders in patients with POIS remain unknown.

In conclusion, we performed ILIT in a Korean man with POIS. ILIT alleviated POIS-related symptoms and alleviated sexual dysfunction. However, this is a single case report, so we cannot exclude the possibility that the patient might have had spontaneous remission. More studies are needed to elucidate the pathogenesis, epidemiology, clinical manifestations, and diagnostic and therapeutic modalities for PIOS, including SCIT, ILIT, and other forms of AIT.

Corresponding Author: Sang Min Lee, MD, PhD, Division of Pulmonology and Allergy, Department of Internal Medicine, Gachon University Gil Medical Center, 21, Namdong-daero 774 beon-gil, Namdong-gu, Incheon, 21565 Republic of Korea. Tel: +82-32-458-2713; Fax: +82-32-469-4320; E-mail: sangminlee77@naver.com

Conflicts of Interest: The authors declare no conflicts of interest.

Funding: The Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (NRF-2015R1D1A1A02061943).

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Tae Beom Kim; Young Sup Shim; Sang Min Lee; Eun Suk Son
(b) Acquisition of Data
Sang Min Lee; Eun Suk Son; Jung Woo Shim; Sang Pyo Lee
(c) Analysis and Interpretation of Data
Tae Beom Kim; Sang Min Lee; Eun Suk Son; Sang Pyo Lee

Category 2

(a) Drafting the Article
Sang Min Lee; Eun Suk Son; Jung Woo Shim; Sang Pyo Lee
(b) Revising It for Intellectual Content
Tae Beom Kim; Young Sup Shim; Sang Min Lee; Eun Suk Son; Jung Woo Shim; Sang Pyo Lee

Category 3

(a) Final Approval of the Completed Article
Tae Beom Kim; Young Sup Shim; Sang Min Lee; Eun Suk Son; Jung Woo Shim; Sang Pyo Lee

REFERENCES

1. Waldinger MD, Schweitzer DH. Postorgasmic illness syndrome: two cases. J Sex Marital Ther 2002;28:251-255.
2. Waldinger MD, Meinardi MM, Zwinderman AH, et al. Postorgasmic illness syndrome (POIS) in 45 Dutch Caucasian males: clinical characteristics and evidence for an immunogenic pathogenesis (part 1). J Sex Med 2011;8:1164-1170.
3. Waldinger MD, Meinardi MM, Schweitzer DH. Hyposensitization therapy with autologous semen in two Dutch Caucasian males: beneficial effects in postorgasmic illness syndrome (POIS; part 2). J Sex Med 2011;8:1171-1176.
4. Senti G, Crameri R, Kuster D, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. J Allergy Clin Immunol 2012;129:1290-1296.
5. Schmid JM, Nezam H, Madsen HH, et al. Intralymphatic immunotherapy induces allergen-specific plasmablasts and increases tolerance to skin prick testing in a pilot study. Clin Transl Allergy 2016;6:19.
6. Lee SP, Choi SJ, Joe E, et al. A pilot study of intralymphatic immunotherapy for house dust mite, cat, and dog allergies. Allergy Asthma Immunol Res 2017;9:272-277.
7. Kim ST, Park SH, Lee SM, et al. Allergen-specific intralymphatic immunotherapy in human and animal studies. Asia Pac Allergy 2017;7:131-137.
8. Oh CY, Lee JS, Chung BH. A validation and reliability study for the Korean version of the Male Sexual Health Questionnaire. Korean J Urol 2005;46:1308-1326.
9. Chung TC, Lee TK, Chung S, et al. The Korean version of the International Index of Erectile Function (IIEF): reliability and validation study. Korean J Urol 1999;40:1334-1343.
10. Jiang N, Xi G, Li H, et al. Postorgasmic illness syndrome (POIS) in a Chinese man: no proof for IgE-mediated allergy to semen. J Sex Med 2015;12:840-845.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.esxm.2017.12.004.
eTable 1. Baseline serum levels of immunoglobulins and sexual hormones

| Variables                  | Serum results | Reference range |
|----------------------------|---------------|-----------------|
| **Immunoglobulins (mg/dL)**|               |                 |
| IgA                        | 166           | 84–438          |
| IgM                        | 72            | 57–288          |
| IgG                        | 1,462         | 680–1,620       |
| IgG1                       | 802           | 382–929         |
| IgG2                       | 606           | 242–700         |
| IgG3                       | 19*           | 22–176          |
| IgG4                       | 28            | 3.9–86          |
| **Sexual hormones**        |               |                 |
| E2 (pg/mL)                 | 86.98*        | 0–39.8          |
| Prolactin (ng/mL)          | 1.09*         | 2.1–17.7        |
| Testosterone (ng/dL)       | 10.49*        | 241–827         |
| LH (mIU/mL)                | 8.03          | 1.5–9.3         |
| FSH (mIU/mL)               | 17.15         | 1.4–18.1        |

E2 = estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone.
*Values outside the normal range.

eTable 2. Changes in answers to questions from the MSHQ and IIEF

| Questionnaires                      | Before ILIT                      | 8 mo after ILIT                     | 15 mo after ILIT                     |
|-------------------------------------|----------------------------------|-------------------------------------|-------------------------------------|
| MSHQ 2. In the past month, if you could get an erection without using drugs like Viagra, how often would you able to stay hard as long as you wanted to? | About half the time | Most of the time | Most of the time |
| MSHQ 9. In the past month, how would you rate the amount or volume of semen when you ejaculate? | A little less than it used to be | As much as it always was | As much as it always was |
| MSHQ 10. Compared with 1 mo ago, would you say the physical pleasure you feel when you ejaculate has ... | Neither increased nor decreased | Increased moderately | Increased moderately |
| MSHQ 11. In the past month, have you experienced any physical pain or discomfort when you ejaculated? Would you say you have ... | Extreme pain or discomfort | Moderate pain or discomfort | Slight pain or discomfort |
| MSHQ 12. In the past month, if you have had any ejaculation difficulties or have been unable to ejaculate, have you been bothered by this? | Very bothered | Moderately bothered | A little bit bothered |
| IIEF 12. How would you rate your level of sexual desire? | Low                           | Low                           | Moderate                           |
| IIEF 13. How satisfied have you been with your overall sex life? | Moderately dissatisfied | Moderately dissatisfied | Equally satisfied and dissatisfied |

IIEF = International Index of Erectile Function; ILIT = intralymphatic immunotherapy; MSHQ = Male Sexual Health Questionnaire.
**Table 3.** Semen analysis before and 8 months after ILIT

|                      | Time                  |
|----------------------|-----------------------|
|                      | Before ILIT | 8 mo after ILIT |
| Amount (mL)          | 1.0          | 1.5             |
| Sperm, n             | 4,395        | 3,185           |
| Sperm with normal    | 20           | 30              |
| motility, %          |              |                 |
| Sperm with normal    | 30           | 40              |
| morphology, %        |              |                 |
| pH                   | 8.0          | 8.5             |
| Micro RBC count/HPF  | 0 ~ 1        | 0 ~ 1           |
| Micro WBC count/HPF  | 1 ~ 3        | 0 ~ 1           |

HPF = high-power field; ILIT = intralymphatic immunotherapy; RBC = red blood cell; WBC = white blood cell.

**Table 4.** Skin prick test and intradermal test with autologous semen

| Dilution of semen | Skin prick test | Intradermal test |
|-------------------|-----------------|------------------|
|                   | Semen/histamine ratio | Semen/saline ratio |
|                   | Before ILIT | 8 mo after ILIT | Before ILIT | 8 mo after ILIT |
| 1/1 (undiluted)   | 0.58         | 0.46             | Not done   | Not done       |
| 1/4               | 0.33         | 0.38             | Not done   | Not done       |
| 1/40              | 0.33         | 0.31             | 1.06       | 1.81           |
| 1/400             | 0.33         | 0.46             | 1.00       | 1.50           |
| 1/4,000           | 0.17         | 0.38             | 0.94       | 1.75           |
| 1/40,000          | 0.17         | 0.23             | 0.72       | 1.31           |
| 1/400,000         | 0.00         | 0.23             | 0.56       | 1.50           |
| 1/4,000,000       | 0.00         | 0.31             | 0.50       | 1.38           |

ILIT = intralymphatic immunotherapy.