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CASE REPORT

Autoimmune estrogen dermatitis in an infertile femaleGonca Elcin¹, Duygu Gülseren¹, Miyase Bayraktar², Serdar Gunalp³, and Timur Gurgan³

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Abstract

Autoimmune estrogen dermatitis is a cyclical cutaneous eruption that occurs premenstrually and goes to the rapid resolution within a few days of menstrual cycles. The disorder has variable clinical manifestations consisting of macules, papules, vesicles, urticarial lesions, bullae, eczematous plaques, and erythema multiforme-like lesions. Herein, we present a case of a 30-year-old woman with attacks of edema and erosions involving the oral and genital mucosal sites on every first day of her menstruation period. She had also multiple endocrinological problems such as hypotroidism and infertility. To determine the sex hormone sensitivity, intradermal skin tests were performed. Based on her personal history and skin test findings, a diagnosis of autoimmune estrogen dermatitis was made. After the oophorectomy, she was free from the skin and mucosal symptoms. We propose that it is important to suspect the diagnosis of autoimmune estrogen dermatitis in patients who present with recurrent cyclic eruptions and it must be kept in mind that these patients might have a concomitant infertility.

Keywords

Estrogen, dermatitis, infertility, autoimmunity

History

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Introduction

Autoimmune estrogen dermatitis, which is in fact not a very uncommon problem, reflects the sensitivity of skin to the effects of estrogen¹. The hallmarks for diagnosis include the association of the dermatitis with the menstrual cycle and positive intradermal skin test to estrogens². Here, we describe a case of autoimmune estrogen dermatitis in an infertile female.

Case report

A 30-year-old female presented with attacks of edema and erosions involving the oral and genital mucosal sites for 2 years. She described intense pruritus and pain related to the lesions. A previous visit in a rheumatology unit resulted with a diagnosis of complex aphthosis for which she received a 4-month course of triamcinolone acetonide orabase ointment and vitamin pills including B1, B6, and B12 without any benefit. The patient then visited a dermatology department where she had a skin biopsy, the histopathology of which revealed a suprabasal detachment suggestive of pemphigus vulgaris albeit direct immunofluorescence was negative. She disagreed to a repeat skin biopsy and visited another dermatology department, where she received a 6-month course of oral valacyclovir 500mg twice a day with a diagnosis of herpes-associated erythema multiforme without any benefit.

On admission to our hospital, dermatological examination revealed circumscribed perioral erythematous to brown discoloration and marked edema of the lips with widespread oral mucosal erosions (Figures 1 and 2). A brown to purple plaque of 2.5 × 3.0 cm diameter with a bright erythematous edematous rim was noticed on her mons pubis (Figure 3).

Labia majora and minora were swollen without any noticeable erosion, which interfered with her walking. She had difficulty in urination. On the day of examination, she was at the first day of her menstrual cycle and she also had difficulty in using a sanitary pad for her bleeding. In her personal history, she stated having more than 3 oral aphthous ulcers per year for more than 15 years without any significant discomfort. Her history for other symptoms of Behçet's disease, including genital ulceration and/or scars, erythema nodosum like skin lesions, papulopustular skin lesions, signs or symptoms related to the eye, pathergy reaction and thrombophlebitis was negative. A detailed personal history revealed that she got married with no child at the age of 14 years; she applied to infertility treatments as *in utero* insemination multiple times and controlled ovarian hyperstimulation between 1997 and 2009 without any success. She stated that her symptoms started after the fertilization treatment in 2010 and since then, they have been appearing on every first day of her menstruation period, diminishing during the menstruation and recovering after the menstruation. Before her last visit to the dermatology department, she had hypermenorrhea for which she received a 15-day course of oral contraceptive pills. However, she had to discontinue the drugs because of

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Figure 1. Perioral discoloration and edema of the lips.



Figure 2. Mucosal erosions on the lower lip.



Figure 3. Brown-purple plaque with an erythematous rim on mons pubis.

severe nausea and vomiting. She also had a diagnosis of hypothyroidism in her personal history and she has been taking levothyroxine containing tablets.

Because of the cyclic pattern and flaring of her skin symptoms just before her menstruation period, we suspected sensitization to endogenous sex hormones. To determine the responsible hormone, intradermal skin test was performed with progesterone and estrogen preparates. We used medroxyprogesterone acetate suspension as progesterone. Because of



Figure 4. Reactions to low estrogen, saline and high estrogen injections (from top to bottom).

not being able to provide pure estrogen in injectable forms in Turkey, we had to use combined estrogen-progesterone prepare to confirm the estrogen sensitivity. It consisted of 50 mg norethisterone enanthate and 5 mg estradiol valerate in a 1.0-ml solution. Both progesterone and combined estrogen-progesterone prepare were diluted with saline solution and prepared in the concentration of 0.1 mg/ml medroxyprogesterone acetate, 0.1 mg/ml norethisterone enanthate and 0.01 mg/ml estradiol valerate. Each of these was injected 0.1 ml with 27 gauge intradermally. Normal saline was used as control. The test was positive on the combined estrogen-progesterone containing injection site with an urticarial response, but negative with pure progesterone after 30 minutes. At 24 hours, urticarial plaque disappeared but there was still an erythematous macule and tenderness. No reactions were observed on the other areas where pure progesterone and saline were injected. The positive test result with combined estrogen-progesterone but negative with pure progesterone suggested a diagnosis of estrogen dermatitis. To confirm this, we made another test with pure estrogen pill. It was diluted with saline into two different concentrations of 0.025 mg/ml and 1 mg/ml and injected 0.1 ml intradermally. The skin test with 1 mg/ml concentration produced an immediate urticarial wheal and persisted for two hours. The test with the lower estrogen concentration (0.025 mg/ml) and the normal saline were negative (Figure 4). Just after these two intradermal tests, the lesions of the patient flared, the pruritus, edema and erosions became more apparent on her oral and genital mucosal sites.

Based on the personal history and clinical findings which flare with menstrual cycles and positive intradermal test with estrogen, a diagnosis of autoimmune estrogen dermatitis was made. After consulting the patient to the gynecology department, in order to suppress the estrogen secretion and ovulation, gonadotropin-releasing hormone (GnRH) agonists leuprolide depot-3-month was injected intramuscularly for treatment. Unfortunately, her first menstrual period appeared timely, and all her symptoms and signs recurred. In her

second menstrual cycle, she did not get bleeding and she had no skin or mucosal lesions. In the third month, along with the lost efficiency of the depot leuprolide injection, her menstrual period appeared again with flaring of her symptoms and signs.

Upon the inefficiency of leuprolide treatment during this 3-month course, we started 1 mg/kg/day (total dose 70 mg/day) oral prednisolone treatment during her menstrual periods, discontinuing it in two weeks with gradual dose reduction. Each time when the steroid dose was reduced to 10 mg daily, she developed severe dizziness, fatigue, and nausea. In order to exclude a steroid insufficiency syndrome associated with an adrenal disorder, we consulted the patient to endocrinology and tamoxifen therapy in a daily dose of 20 mg was started to suppress ovulation. During the 6 months tamoxifen therapy, her symptoms disappeared but she developed nausea, vomiting, dizziness, depression and anxiety, which led to a dose reduction to 10 mg daily. With dose reduction, all her symptoms and lesions reappeared again.

When we reviewed her medical history, we realized that she had been suffering from multiple endocrinological problems, such as hypothyroidism and infertility and also her symptoms like steroid insufficiency during steroid dose reduction suggested us a diagnosis of adrenal insufficiency. Her tests consisted of magnetic resonance imaging of the pituitary gland and blood hormone panel including estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, prolactin, cortisol, adrenocorticotropic hormone (ACTH) and thyroid function tests, and serum electrolytes were normal. The ovarian antibody, adrenal antibodies and 21-hydroxylase antibody which were performed to exclude an autoimmunity against adrenal glands and gonads were all negative. Upon these test results she was addressed back to the gynecology department for oophorectomy. After the oophorectomy, she was free from the skin and mucosal symptoms on her monthly follow-ups during 9 months period, however her nausea and dizziness continued.

She also had follow-up in the gynecology department after oophorectomy, and herbal products were prescribed to prevent osteoporosis. On the first month of this herbal therapy, all her symptoms repeated similar to the earlier oophorectomy on the same body sites with the same severity. After discontinuation of the herbal products, she remained free of her symptoms without any flares in her fourth year of oophorectomy now.

Discussion

Hypersensitivity to endogenous sex hormones is a rare disorder described firstly by Zondek and Bromberg in 1945 in a woman who had symptoms related to menstrual cycle³. After that, autoimmune progesterone dermatitis was defined in another woman who developed generalized erythema multiforme lesions premenstrually and benefited from oophorectomy⁴. A relatively new and rare entity, related with menstruation cycle, was described first in 1995 as autoimmune estrogen dermatitis². This disorder has variable

clinical manifestations consisting of macules, papules, vesicles, urticarial lesions, bullae, eczematous plaques, and erythema multiforme-like lesions. Because of the lack of diagnostic laboratory and histologic findings, a diagnosis of autoimmune estrogen dermatitis should be suspected in women who present with recurrent, premenstrual skin eruptions that go to the rapid resolution within a few days of menstrual cycles².

Pathogenesis of autoimmune estrogen dermatitis is unclear. It is thought to be related to a sensitization reaction to a relatively raised level of endogenous estrogen in the premenstrual phase of the menstrual cycle⁵. The mechanism how one is sensitized to her own estrogen is not clear, however the most widely accepted hypothesis is previous exposure to exogenous estrogens. Oral contraceptive pills or even corticosteroids may lead to a cross reaction with one's own estrogen. Also, estrogen preparations themselves are suggested to induce autoantibody formation against self-estrogens^{5,6}.

Murano and Koyana reported a woman with two flares of estrogen dermatitis in each menstrual period consistent with double-peaked pattern of serum estrogen levels during ovulation and premenstrual phase⁷. It is believed that estrogen sensitivity is dose dependent. The rise and fall of the serum estrogen concentration at ovulation is abrupt, thus concentration cannot remain high enough to induce persistent allergic reactions⁷. In our patient, the positivity of the test with 1 mg/ml serum estrogen concentration despite negativity with 0.025 mg/ml concentration supports the necessity of high serum estrogen levels to develop estrogen sensitivity, too. In order to determine a positive skin reaction to estrogen, clinicians should be aware to perform the skin test with higher estrogen concentrations.

Itsekson et al. reported that hypersensitivity to sex steroids reveals in numerous clinical presentations, including dermatitis, premenstrual syndrome, dysmenorrhea, headache, arthralgia, asthma, rhinitis, acne, pruritus, mastalgia, and bullous erythema multiforme⁸. Even in pregnancy, hyperemesis gravidarum has been regarded as a hormone hypersensitivity reaction⁹. Prieto-Garcia et al. have added infertility to all these clinical presentations regarded as hormone hypersensitivity reactions¹⁰. In another study, Itsekson et al. have described an association between intolerance to sex hormones and recurrent miscarriage⁶. Our patient suffered from primary infertility, too and she received different infertility treatments so far but she could not get pregnant. Her infertility problem suggested us that even her infertility might be a result of her estrogen hypersensitivity.

Progesterone desensitization is an effective treatment option not only for patients with progesterone dermatitis and infertility, but also for patients who have oral contraceptive intolerance and for who experience dysfunctional uterine bleeding. Progesterone desensitization made us think it is likely that women who have autoimmune estrogen dermatitis or who are infertile due to estrogen hypersensitivity can be desensitized to estrogen, too. Although it is not a very commonly applied procedure and also not available in our institution, we believe that desensitization therapy to estrogen might have a chance for autoimmune estrogen dermatitis. Our patient took oral contraceptive pills containing drospirenone

and ethynil estradiol, but she could not tolerate it because of severe nausea and vomiting. Today we know from the literature that nausea and vomiting in patients with hyperemesis gravidarum are attributed to hormone hypersensitivity⁹. When 3-month-depot leuprolid was administered intramuscularly, our patient's symptoms did not regress for the whole 3-month-duration, but only for 1-month. Her skin symptoms disappeared after starting the antiestrogen drug tamoxifen at the dose of 20 mg daily with side effects, and a dose of 10 was not enough to suppress the symptoms and signs. On our patient's request, bilaterally oophorectomy was performed, lastly. All her skin symptoms were controlled with surgery but her nausea, vomiting and dizziness continued for another 9 months. She was then cured without any symptoms and signs and free of disease in the fourth year of follow-up. We could not decide whether this 9-month delay was the half-time needed for total estrogen removal or was a cross-sensitivity to other steroid hormones in the body. Being the most radical treatment oophorectomy promises permanent cure for autoimmune estrogen dermatitis as it was the case in our patient.

In conclusion, it is important to suspect the diagnosis of autoimmune estrogen dermatitis in patients who present with recurrent cyclic eruptions and it must be kept in mind that these patients might have a concomitant infertility.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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