

Autoimmune progesterone urticaria

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ABSTRACT

Autoimmune progesterone dermatitis is a rare cutaneous disorder characterized by recurrent and cyclic skin eruption with variable morphology, occurring during the luteal phase. A case of autoimmune progesterone urticaria in a 47-year-old woman is reported. An intradermal progestin test revealed a strong reactivity against this hormone. Treatment with tamoxifen and leuprolide acetate induced only a partial remission of urticaria. Bilateral oophorectomy was performed with absolute clearing of cutaneous lesions.

INTRODUCTION

Autoimmune progesterone dermatitis is an uncommon skin disease characterized by the occurrence of cyclical eruptions during each menstrual period. Many chronic dermatoses transiently worsen premenstrually, but the term autoimmune is reserved for the few cases in which progesterone allergy can be demonstrated. A case of autoimmune progesterone urticaria in a 47-year-old woman is reported.

CASE REPORT

A 47-year-old woman presented with a 5-year history of recurrent pruritic widespread edematous papules. This cutaneous eruption appeared every

month, 1 week premenstrually, fading 1 to 2 days after the menstrual period.

The patient had been treated for several years with numerous antihistamines, doxepin and oral corticosteroids, which failed to suppress cutaneous lesions. She had never used hormonal contraception and her last pregnancy was 17 years ago.

Several laboratory examinations were performed, including antinuclear antibody, anti-DNA, Sm, Ssa, SSb and RNP auto-antibodies, C3, C4, CH100 and C1INH, serum triiodothyronine and thyroxine, thyroid-stimulating hormone, IgG, IgM, IgA, IgE and antigen-antibody complexes, which were all normal or negative.

Skin biopsy revealed edema involving the superficial portion of the dermis and a sparse inflammatory infiltrate with an eosinophilic predominance.

Basal body charts revealed that the recurrence of cutaneous lesions followed the basal body temperature rise in mid-cycle and that they faded by day 3 of the menstrual period. Hormonal analysis revealed normal serum estradiol levels on day 3 and day 21 of the menstrual cycle, but serum progesterone levels were below the normal lower limit on day 3 (0.01 ng/ml compared to a normal 0.3–2.6 ng/ml) and normal on day 21.

An intradermal test with 0.1 ml aqueous medroxyprogesterone acetate suspension (0.1, 1

and 10 mg/ml) was performed on the seventh day of the cycle while the patient was free of urticaria. A positive reaction was observed within 6 hours for 0.1 and 1 mg/ml, remaining positive for about 48 hours. We could not detect serum anti-progesterone antibodies using indirect immunofluorescence technique.

Oral challenge with progestin was not performed in our patient; however, she reported an exacerbation of urticaria while being previously treated with oral medroxyprogesterone acetate for menorrhagia.

The patient was initially treated with tamoxifen (Tamoxan®) 40 mg/day during a 4-month period, which was unsuccessful in clearing the urticaria despite a mild improvement in symptoms. Later, a gonadotropin-releasing hormone (GnRH) analog was tried for another 6 months. Leuprolide acetate (Lucrine depot®) was administered at a monthly dose of 3.75 mg as an i.m. injection, offering only a partial benefit with the recurrence of lesions in a less frequent, random fashion.

Bilateral oophorectomy was carried out and, 2 weeks later, the lesions disappeared. The uterus and both ovaries were normal in gross and histological examination. Immediately after surgery, she began estrogen therapy with a 17 β -estradiol transdermal patch and no cutaneous lesions were noticed. Six months later, the patient remains free of urticaria.

DISCUSSION

The term autoimmune progesterone dermatitis (AIPD) describes a variety of skin diseases characterized by cyclical premenstrual exacerbations related to fluctuations in serum progesterone levels, in which sensitivity to this hormone can be demonstrated. The first case report of a cyclical eruption with an allergy to endogenous sex hormones was suggested by Geber, who in 1921 reported a case of menstrual urticaria in which the eruption could be reproduced by autoinjection of premenstrual serum¹. Urticaria appears to be only part of the spectrum of AIPD, which includes eczematous eruptions, often with pompholyx^{2,3}, erythema multiforme⁴, papulopustular lesions⁵ and even dermatitis herpetiformis-like rash⁶.

In some patients, the onset of this condition occurs after progesterone therapy, suggesting that the synthetic progestins of contraceptive pills can

induce a cross-reaction against the endogenous hormone^{2,7-11}. AIPD can also appear or become aggravated during pregnancy^{5,7}, perhaps because the increasing progesterone levels that occur during this period can promote an immunological imbalance responsible for the autoaggression. However, in many cases, the progesterone hypersensitivity appears without any previous pregnancy or hormonal therapy¹²⁻¹⁵, as happened in our case.

The evidence for autoimmunity to progesterone is suggested by two of the following criteria: a positive intradermal test, response to anovulatory drugs, recurrence following i.m. or oral progestin challenge and demonstration of circulating antibodies to progesterone or corpus luteum¹⁶. Our patient had a strongly positive intradermal test, which persisted up to 48 hours, and cutaneous lesions also flared up with oral medroxyprogesterone acetate. Indirect immunofluorescence was negative in our case, but other negative results have also been reported^{17,18}.

There are no distinguishing morphological or histological features in AIPD, which corroborates our biopsy results showing a typical pattern of urticaria.

The majority of cases of AIPD encountered have failed to respond to conventional treatment modalities. Antihistamine therapy is unsuccessful and corticoids often offer only a little benefit even in high doses¹⁰. Some cases, however, respond well to estrogens or tamoxifen¹⁹, presumably by suppression of ovulation and hence the post-ovulatory rise in progesterone, but side-effects in both cases are of considerable importance. The GnRH analogs have also been used in the management of AIPD²⁰. Initially they stimulate the pituitary, but subsequently down-regulate pituitary gonadotropin receptors. This results in a decrease in luteinizing hormone and follicle-stimulating hormone secretion, which in turn inhibits ovulation and suppresses sex hormone production. Nevertheless, this drug should not be used for more than 6 months because of a negative impact on the bone and cardiovascular system. In severe cases, following inefficacy or side-effects of previous treatments, bilateral oophorectomy may be necessary to clear cutaneous lesions²¹.

Our patient had been treated with antihistamines, doxepin and corticoids without acceptable results. Following the diagnosis of AIPD, tamoxifen was prescribed. In our case, a

poor response to tamoxifen was noticed, probably related to incomplete suppression of ovulation since our patient maintained regular menses. We decided to suspend tamoxifen treatment, based on the propensity to side-effects with long-term therapy with this drug and because alternative therapy was still available.

Therapy with leuprolide acetate was then started. Because GnRH analogs have an initial stimulatory effect on gonadotropin receptors, there is a possibility that skin lesions may be exacerbated at the beginning of the therapy; however, this was not seen in our patient. An irregular pattern of uterine bleeding instead of amenorrhea was achieved, despite a 6-month course of GnRH analog therapy. Although there was a partial improvement with this drug, cutaneous pruritic lesions still appeared, probably because sporadic ovulation still occurred. Yee and Cunliffe²⁰

reported a case in which daily intranasal buserelin was successfully utilized and a therapy-induced amenorrhea was noticed after 2 months, with total urticaria remission. In contrast with our patient, other systemic diseases (polycystic kidney and liver disease) affected their patient. Their patient became amenorrheic and was free of urticaria during a 3-month period of aggravated illness, even before starting the GnRH analog. This fact could have modified her response to the drug.

Hysterectomy with bilateral oophorectomy was decided in our patient based on previous unsuccessful therapies. Immediately after surgery, she began estrogen therapy with a 17 β -estradiol transdermal patch and no urticaria recurrence was noticed after a 6-month follow-up. This observation agreed with our hypothesis that progesterone and not estrogen is involved in the etiology of the urticaria.

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