



## Letter

## Autoimmune progesterone dermatitis with delayed intradermal skin reaction

### A case report

A 47-year-old, gravida 3, para 2 woman presented to the allergy and immunology clinic with a recurrent, cyclical urticarial rash on the trunk and upper extremities of 1-year duration. A detailed clinical history revealed that the rash appeared approximately 10 days before menses and spontaneously remitted 2 to 3 days into her menstruation period. The lesions always commenced on the right shoulder, resolved after a few days, then reappeared at other locations. The lesions were pruritic, burning, and not associated with systemic symptoms. Previous unsuccessful medical management included a 1-time steroid injection, topical steroid creams, and histamine<sub>1</sub>- and histamine<sub>2</sub>-antagonists. Her medical history is significant for Crohn disease, and she was not taking any medications.

There were no lesions present on initial examination. A complete blood cell count revealed the following: hemoglobin, 13.0 g/dL; hematocrit, 39.5%; white blood cells, 7,500/ $\mu$ L (eosinophils, 100/ $\mu$ L) and platelets, 212,000/ $\mu$ L. Sedimentation rate, antinuclear antibody level, C4 level, tryptase level, and liver and thyroid function test results were within normal limits. A punch biopsy specimen was obtained from a lesion on the right upper arm at a subsequent visit, which revealed perivascular lymphocytic inflammation with rare eosinophils. The results of skin prick testing with progesterone (50 mg/mL in normal saline) were negative. The results of intradermal testing (50 mg/mL of progesterone at dilutions of 1:1,000, 1:100, and 1:10<sup>1</sup>) were initially negative at 20-minute intervals. A 3-mm wheal and 6-mm flare at the 1:10 injection site evolved at 24 hours (Fig 1). The patient was prescribed levonorgestrel and ethinyl estradiol (0.1 and 0.02 mg, respectively) and ethinyl estradiol (0.01 mg) with significant improvement of her symptoms.

Autoimmune progesterone dermatitis (AIPD) is an uncommon hypersensitivity reaction to endogenous or exogenous progesterone, with fewer than 100 reported cases in the literature.<sup>1</sup> It is a cyclical dermatosis that usually occurs in fertile women during the luteal phase of the menstrual cycle.<sup>2</sup> Nonetheless, it has been reported in a man and postmenopausal women receiving exogenous progesterone.<sup>3</sup> Lesions typically appear 3 to 10 days before menstrual flow and subside as progesterone levels decrease 2 to 3 days into menses.<sup>4</sup> The natural course of AIPD varies, with some patients experiencing worsening symptoms over time and others achieving spontaneous remission. However, many patients require ongoing treatment for this chronic condition.<sup>5</sup>

The clinical presentation is highly variable and nonspecific and thus can be mistaken for other skin conditions. Cutaneous manifestations include urticarial lesions, erythema multiforme,

vesiculobullous eruptions, eczematous lesions, fixed-drug eruptions, angioedema, oral lesions, and anaphylaxis.<sup>4,6,7</sup> Skin eruptions can be localized or generalized and may appear on the trunk, extremities, mucosa, lips, and palms.<sup>8</sup> The differential diagnosis is broad, and it is important to rule out other chronic dermatologic conditions, such as lupus, acne, psoriasis, angioedema, allergic and irritant contact dermatitis, and dermatitis herpetiformis.<sup>8</sup>

Increased risk factors for AIPD include fertile age, exogenous progesterone, and pregnancy.<sup>8</sup> A review by Nguyen et al<sup>7</sup> reported recurrent monthly symptoms in 65 of 89 patients (73%) in relation to their menstrual cycle, 13 of 89 (14%) in relation to pregnancy, and 8 of 89 (8.9%) shortly after the initiation of exogenous progesterone therapy. Most women with AIPD have a previous exposure to exogenous progesterone, even if many years before the onset of skin lesions.<sup>5</sup> Of note, some women report improvement during pregnancy, possibly secondary to desensitization from persistently elevated progesterone levels.<sup>2</sup>

The pathogenesis of AIPD remains unclear but likely involves multiple mechanisms, owing to the variability of the disease. In cases of exogenous progesterone, it is suggested that antigen-presenting cells ingest hormone and trigger T<sub>H</sub> cells, leading to



**Figure 1.** A 3-mm wheal and 6-mm flare at the 1:10 injection site at 24 hours.

**Disclosures:** Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2016.07.037>

1081-1206/© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

progesterone sensitization. Others have conceptualized the possibility of low progesterone tolerance and the development of an inflammatory reaction in response to increased hormone levels. This could be from peaked progesterone levels during the luteal phase or from exogenous progesterone. Another hypothesis is the cross-reactivity among various hormones, which could explain the onset of disease in patients without previous exogenous progesterone exposure.<sup>1,7,8</sup>

AIPD is a diagnosis of exclusion because laboratory and histologic findings are nonspecific. Clinical history is key and should endorse a cyclical pattern between the onset of lesions and menses. Diagnosis is confirmed by demonstrating progesterone sensitization with skin prick or intradermal testing or intramuscular or oral progesterone challenge.<sup>1,5,9</sup> Less commonly, the presence of circulating progesterone antibodies or positive immunofluorescent study results makes the diagnosis.<sup>5</sup> Furthermore, remission of progesterone-induced symptoms with ovulation suppression must be established.<sup>7–9</sup>

Our patient had progesterone sensitization with a delayed skin reaction at the intradermal injection site. Reactions after skin testing can be immediate or delayed, which may be attributable to multiple mechanisms involved in the pathogenesis of AIPD. This also may account for the diverse clinical manifestations among patients. Immediate reactions suggest a type 1 IgE-mediated hypersensitivity, whereas delayed reactions implicate a T-cell-mediated type 4 hypersensitivity.<sup>7</sup> Therefore, skin reactions may not appear until 24 to 48 hours after testing. In addition, our patient experienced significant clinical improvement after the initiation of a combined oral contraceptive (OCP). Thus, AIPD was the most likely diagnosis.

Definitive treatment of AIPD is targeted at suppressing ovulation, the time during which progesterone is at its highest. Paradoxically, OCPs with low-dose progesterone are often given as first-line therapy. Successful treatment is credited to the suppression of ovulation through synthetic estrogen and progesterone to which the patient does not react. However, complete remission is not always observed conceivably as a result of cross-reacting antibodies in some patients.<sup>6</sup> Estrogen-only OCPs offer increased remission rates but an unfavorable side effect profile, including thromboembolic events and endometrial carcinoma.<sup>7,9</sup>

Other efficacious agents include the GnRH analogs, such as buserelin and triptorelin, which subdue ovulation by suppressing the hypothalamic-pituitary axis. Use should be limited to 6 months to limit adverse effects associated with estrogen depletion, such as vaginal dryness, bone loss, and hot flashes.<sup>7</sup> Tamoxifen, a selective estrogen receptor antagonist, has been used as treatment for AIPD

but is not first-line treatment because of its association with bone resorption and increased risk of endometrial carcinoma. The use of 17- $\alpha$ -alkylated steroids, such as danazol, has also been reported in severe cases. Progesterone desensitization for patients undergoing in vitro fertilization has been documented and involves increasing doses of vaginal progesterone suppositories. Patients with recalcitrant cases who no longer desire fertility can be definitively treated with bilateral oophorectomy.<sup>1,4,7–9</sup>

AIPD is a rare, highly variable autoimmune disease elicited by endogenous or exogenous progesterone. It should be considered in patients presenting with recurrent skin lesions corresponding to the luteal phase of menstruation. Diagnosis is confirmed with positive progesterone skin test results, positive intramuscular or oral progesterone challenge results, and cessation of rash with ovulation suppression. Various treatment options exist but use should be limited as a consequence of long-term adverse effects.

Jillian Frieder, MD\*

Mohammad Younus, MD†

\*St. John Hospital and Medical Center

Grosse Pointe, Michigan

†Henry Ford Hospital

Detroit, Michigan

jhfrieder@gmail.com

## References

- [1] Prieto-Garcia A, Sloane DE, Gargiulo AR, Feldweg AM, Castells M. Autoimmune progesterone dermatitis: clinical presentation and management with progesterone desensitization for successful in vitro fertilization. *Fertil Steril*. 2011;95:1121.e9–1121.e13.
- [2] Fournier JB. Resolution of autoimmune progesterone dermatitis after treatment with oral contraceptives. *JAAD Case Rep*. 2015;1:319–320.
- [3] Chawla SV, Quirk C, Sondheimer SJ, James WD. Autoimmune progesterone dermatitis. *Arch Dermatol*. 2009;145:341–342.
- [4] Hacinecioglu F, Benar H, Gonul M, Okcu Heper A. A case of autoimmune progesterone dermatitis characterized by grouped small vesicles. *Clin Exp Dermatol*. 2016;41:681–682.
- [5] Dedeker F, Graesslin O, Quereux C, Gabriel R, Salmon-Ehr V. Autoimmune progesterone dermatitis: a rare pathology. *Eur J Obstet Gynecol Reprod Biol*. 2005;123:120–121.
- [6] Toms-Whittle LM, John LH, Griffiths DJ, Buckley DA. Autoimmune progesterone dermatitis: a diagnosis easily missed. *Clin Exp Dermatol*. 2011;36:378–380.
- [7] Nguyen T, Razzaque Ahmed A. Autoimmune progesterone dermatitis: update and insights. *Autoimmun Rev*. 2016;15:191–197.
- [8] Maguire T. Autoimmune progesterone dermatitis. *Dermatol Nurs*. 2009;21:190–192.
- [9] Kaygusuz I, Gumus II, Sarifakioglu E, Eser A, Bozkurt B, Kafali H. Autoimmune progesterone dermatitis. *Taiwan J Obstet Gynecol*. 2014;53:420–422.