

## Autoimmune Progesterone Dermatitis Diagnosed by Lymphocyte Transformation Test and Progesterone Provocation Test

Autoimmune progesterone dermatitis (APD) is a rare autoimmune response to endogenous progesterone or to earlier exposure to exogenous progesterone (1). Skin lesions typically occur due to increases in progesterone during the luteal phase of the menstrual cycle (2).

A 31-year-old mother of two children presented to our Department with a 5-year history of pruritic and painful erythematous macules, papules, and patches on her neck, pectoral region, and face, which appeared 2-3 days before the onset of menses and gradually resolved 7-10 days later (Figure 1). The lesions first appeared 10 months after her second pregnancy and a few months after she had started using oral contraceptive pills (OCP) containing gestodene combined with ethinyloestradiol. A few months before presenting to us, the lesions had started spreading on her forearms, elbows, and pretibial areas. Since one year prior to our visit she had complained of occasional urticaria with angioedema one week prior to menses, which resolved after menses. The lesions were accompanied by malaise, headache, and fatigue. The patient was asymptomatic between the



**Figure 1.** Erythematous, indurated patchy skin eruptions on the face.

outbreaks. She reported that she had been using various local corticosteroids, peroral antihistamines, and prednisone for the treatment of her skin lesions, but this treatment had not improved her symptoms. She suffered from mild seasonal rhinoconjunctivitis.

We performed multiple laboratory tests that were unremarkable. Histopathological examination of a biopsy taken from a lesion on the neck showed epidermal hyperplasia and nonspecific mild dermal inflammation. Since progesterone was not available in aqueous solution in our country, we did not perform an intradermal test, but we performed a lymphocyte transformation test (LTT) to medroxyprogesterone and estradiol. The patient's lymphocytes showed markedly enhanced proliferation to medroxyprogesterone *in vitro*, while being negative to estradiol. We had performed control LTT in 10 healthy controls and 10 patients with atopy, and such hyperactivity was not observed in any of them. We performed an oral provocation test with OCP containing gestodene combined with ethinyloestradiol. Two days after commencing treatment, the patient developed widespread dermatitis (Figure 2) with nausea, malaise, and angioedema. The patient was informed about treatment options and possible side-effects. She started



**Figure 2.** Papular and urticarial patches on the arms a few days after oral provocation test with oral contraceptive pills (OCP) containing gestodene combined with ethinyloestradiol.

with OCP with the lowest amount of progesterone, containing ethinyloestradiol and drospirenone for treatment of APD, but terminated treatment after the second cycle due to a worsening of the skin lesions and urticaria accompanied with angioedema. At the time of writing, our patient continues to have premenstrual flares.

The typical symptoms of APD are skin lesions such as eczema, erythema multiforme, prurigo, stomatitis, papulopustular lesions, folliculitis, urticaria, angioedema, and rarely anaphylaxis (2) that develop 3-10 days before and subside 1-2 days after menses, with recurrent cyclic aggravation (1,3,4). Frequently, patients have a history of exogenous progesterone intake (1,5,6), as in our patient, which could have resulted in antibody formation. The diagnosis of APD is established by an appropriate clinical history (premenstrual flare of skin lesions), a progesterone intradermal test, an intramuscular (7), oral (8), or intravaginal (1, 6) progesterone challenge test, and circulating antibodies to progesterone. Progesterone testing has not been standardized. Most of the sex hormones are not suitable for testing since they contain an oily component that can produce an irritant test reaction. Gestodene, which was used for the oral provocation test in our patient, is a potent progesterone (9). The LTT shows reactions to circulating lymphocytes and reflects immune reactions within the body. The goal of treatment is suppression of ovulation. Currently, the first-line choice of therapy is a combination oral contraceptive (3). We believe that OCP have a limited effect because all of them contain a progesterone component. If this treatment is ineffective, patients have been treated with danazol, gonadotropin releasing hormone analogs (3,4,6), conjugated estrogens (7), tamoxifen, oophorectomy (8), and progestogen desensitization (10) with varying success.

### References:

1. Le K, Wood G. A case of autoimmune progesterone dermatitis diagnosed by progesterone pearsy. *Australas J Dermatol.* 2011;52(2):139-41.
2. Snyder JL, Krishnaswamy G. Autoimmune progesterone dermatitis and its manifestation as anaphylaxis: a case report and literature review. *Ann Allergy Asthma Immunol.* 2003;90(5):469-77.
3. Baptist AP, Baldwin JL. Autoimmune progesterone dermatitis in a patient with endometriosis: case report and review of the literature. *Clin Mol Allergy.* 2004;2(1):10.
4. Wingate-Saul L, Rymer J, Greaves MW. Chronic urticaria due to autoreactivity to progesterone. *Clin Exp Dermatol.* 2015;40(6):644-6.

5. Herzberg AJ, Strohmeyer CR, Cirillo-Hyland VA. Autoimmune progesterone dermatitis. *J Am Acad Dermatol.* 1995;32:333-8.
6. Németh H, Kovács E, Gödény S, Simics E, Pfliegler G. Autoimmune progesterone dermatitis diagnosed by intravaginal progesterone provocation in a hysterectomised woman. *Gynecol Endocrinol.* 2009;25(6):410-2.
7. Oskay T, Kutluay L, Kaptanoğlu A, Karabacak O. Autoimmune progesterone dermatitis. *Eur J Dermatol.* 2002;12(6):589-91.
8. Shelley Wb, Preucel Rw, Spooon SS. Autoimmune progesterone dermatitis. Cure by oophorectomy. *JAMA.* 1964;190:35-8.
9. Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, Schweppe KW, Thijssen JH. Classification and pharmacology of progestins. *Maturitas* 2003;46 (Suppl 1):S7-S16.
10. Foer D, Buchheit KM, Gargiulo AR, Lynch DM, Castells M, Wickner PG. Progestogen Hypersensitivity in 24 Cases: Diagnosis, Management, and Proposed Renaming and Classification. *J Allergy Clin Immunol Pract.* 2016;4(4):723-9.

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