

# Autoimmune Progesterone Dermatitis

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## PRACTICE POINTS

- Autoimmune progesterone dermatitis (APD) is a hypersensitivity reaction to the progesterone surge during a woman's menstrual cycle.
- Patients with APD often are misdiagnosed for years due to the variability of each woman's menstrual cycle, making the correlation difficult.
- It is important to keep APD in mind for any recalcitrant or recurrent rash in females. A thorough history is critical when formulating a diagnosis.

To the Editor:

Autoimmune progesterone dermatitis (APD) is a rare dermatologic condition that can be challenging to diagnose. The associated skin lesions are not only variable in physical presentation but also in the timing of the outbreak. The skin disorder stems from an internal reaction to elevated levels of progesterone during the luteal phase of the menstrual cycle. Autoimmune progesterone dermatitis can be difficult to detect; although the typical menstrual cycle is 28 days, many women have longer or shorter hormonal phases, leading to cyclical irregularity that can cause the lesions to appear sporadic in nature when in fact they are not.<sup>1</sup>

A 34-year-old woman with a history of endometriosis, psoriasis, and malignant melanoma presented to our dermatology clinic 2 days after a brief hospitalization during which she was diagnosed with a hypersensitivity reaction. Two days prior to her hospital admission, the patient developed a rash on the lower back with associated myalgia. The rash progressively worsened, spreading laterally to the flanks, which prompted her to seek medical attention. Blood work included a complete blood cell count with differential, complete metabolic panel, antinuclear antibody test, and erythrocyte sedimentation rate, which all were within reference range.

A 4-mm punch biopsy from the left lateral flank was performed and was consistent with a neutrophilic dermatosis. The patient's symptoms diminished and she was discharged the next day with instructions to follow up with a dermatologist.

Physical examination at our clinic revealed multiple minimally indurated, erythematous plaques with superficial scaling along the left lower back and upper buttock (Figure 1). No other skin lesions were present, and palpation of the cervical, axillary, and inguinal lymph nodes was unremarkable. A repeat 6-mm punch biopsy was performed and she was sent for fasting blood work.

Histologic examination of the punch biopsy revealed a superficial and deep perivascular and interstitial dermatitis with scattered neutrophils and eosinophils. Findings were described as nonspecific, possibly representing a dermal hypersensitivity or urticarial reaction.

Glucose-6-phosphate dehydrogenase testing was within reference range, and therapy was initiated with oral dapsone 50 mg once daily as well as fexofenadine 180 mg once daily. The patient initially responded well to the oral therapy, but she experienced recurrence of the skin eruption at infrequent intervals over the next few months, requiring escalating doses of dapsone to control the symptoms. After further questioning at a subsequent visit a few months later, it was discovered that the eruption occurred near the onset of the patient's irregular menstrual cycle.

Approximately 1 year after her initial presentation, the patient returned for intradermal hormone injections to test for hormonally induced hypersensitivities. An injection of 0.1 mL of a 50-mg/mL progesterone solution was administered in the right forearm as well as 0.1 mL of a 5-mg/mL estradiol solution and 0.1 mL of saline in the left forearm as a control. One hour after the injections, a strong positive reaction consisting of a 15-mm indurated plaque with surrounding wheal was noted at the site of the progesterone injection. The estradiol and saline control sites were clear of any dermal reaction (Figure 2).

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The authors report no conflict of interest.

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**FIGURE 1.** Numerous erythematous plaques with minimal induration and superficial scaling involving the left flank (A), lower back, and upper buttock (B) in a patient with autoimmune progesterone dermatitis.



**FIGURE 2.** No erythema or induration was present at the estradiol (E) and saline (S) control sites 1 hour after injection (A). The progesterone (P) site displayed a 15-mm erythematous wheal with notable induration at the same timepoint (B).

A diagnosis of APD was established, and the patient was referred to her gynecologist for treatment.

Due to the aggressive nature of her endometriosis, the gonadotropin-releasing hormone agonist leuprolide acetate was the first-line treatment prescribed by her gynecologist; however, after 8 months of therapy with leuprolide acetate, she was still experiencing breakthrough myalgia with her menstrual cycle and opted for a hysterectomy with a bilateral salpingo-oophorectomy. Within weeks of surgery, the myalgia ceased and the patient was completely asymptomatic.

Autoimmune progesterone dermatitis was first described in 1921.<sup>2</sup> In affected women, the body reacts to the progesterone hormone surge during the luteal phase of the menstrual cycle. Symptoms begin approximately 3 to 4 days prior to menses and resolve 2 to 3 days after onset of flow. These progesterone hypersensitivity reactions can present within a spectrum of morphologies and severities. The lesions can appear eczematous, urticarial, as an angioedemalike reaction, as an erythema multiforme-like reaction with targetoid lesions, or in other nonspecific ways.<sup>1,3</sup> Some patients experience a very mild, almost asymptomatic reaction, while others have a profound

reaction progressing to anaphylaxis. Originally it was thought that exogenous exposure to progesterone led to a cross-reaction or hypersensitivity to the hormone; however, there have been cases reported in females as young as 12 years of age with no prior exposure.<sup>3,4</sup> Reactions also can vary during pregnancy. There have been reports of spontaneous abortion in some affected females, but symptoms may dissipate in others, possibly due to a slow rise in progesterone causing a desensitization reaction.<sup>3,5</sup>

According to Bandino et al,<sup>6</sup> there are 3 criteria for diagnosis of APD: (1) skin lesions related to the menstrual cycle, (2) positive response to intradermal testing with progesterone, and (3) symptomatic improvement after inhibiting progesterone secretions by suppressing ovulation. Areas checked with intradermal testing need to be evaluated 24 and 48 hours later for possible immediate or delayed-type hypersensitivity reactions. Biopsy typically is not helpful in this diagnosis because results usually are nonspecific.

Treatment of APD is targeted toward suppressing the internal hormonal surge. By suppressing the progesterone hormone, the symptoms are alleviated. The discomfort from the skin reaction typically is unresponsive to steroids

or antihistamines. Oral contraceptives are first line in most cases because they suppress ovulation. Gonadotropin-releasing hormone analogues and tamoxifen also have been successful. For patients with severe disease that is recalcitrant to standard therapy or those who are postmenopausal, an oophorectomy is a curative option.<sup>2,4,5,7</sup>

Autoimmune progesterone dermatitis is a rare cyclical dermatologic condition in which the body responds to a surge of the patient's own progesterone hormone. The disorder is difficult to diagnose because it can present with differing morphologies and biopsy is nonspecific. It also can be increasingly difficult to diagnose in women who do not have a typical 28-day menstrual cycle. In our patient, her irregular menstrual cycle may have caused a delay in diagnosis. Although the condition is rare, APD should be included in the differential diagnosis in females with a recurrent, cyclical, or recalcitrant cutaneous eruption.

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