

Progressively Worsening Cyclic Rash: Diagnosis and Approach to Care

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Autoimmune progesterone dermatitis (AIPD) is an uncommon condition in which allergic dermatitis to endogenous progesterone manifests in cyclic cutaneous eruptions. In this case series, we present 3 patients with AIPD, each with unique presentations and medical histories emblematic of the disease. Cyclic dermatitis related to menses in a premenopausal woman should raise high clinical suspicion for AIPD, especially in the primary care or emergency setting. Because of the rarity of this disorder, this case series seeks to describe AIPD to medical providers of young women, as well as present relevant literature related to the disease. We propose clinical considerations for women of reproductive age with AIPD.

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Autoimmune progesterone dermatitis (AIPD) is classified as a rare condition by the National Institutes of Health.¹ According to a 2003 review, approximately 50 cases of AIPD had been reported in literature since 1921.² It is an autoimmune phenomenon to endogenous progesterone that occurs in women of reproductive age, with or without a history of exogenous synthetic progestin exposure.²⁻⁷ Autoimmune progesterone dermatitis is typically characterized by cyclical premenstrual flares of polymorphous dermatologic manifestations that begin during the luteal phase of the menstrual cycle when progesterone levels peak, and it subsides a few days into menses with the decline of progesterone levels. Previous case reports have documented patient disease progression to a life-threatening anaphylactic cycle of reactions, which has been referred to as “progesterone-induced anaphylaxis.”²

Definitive management strategies for this possibly debilitating disease have not been well studied. However, successful diagnostic and treatment modalities exist. Once diagnosed, patients with AIPD have a favorable prognosis, with improved quality of life. However, most patients with AIPD endure their symptoms for years without effective workup, primarily a result of lack of disease awareness in the medical community.

The present case series seeks to describe AIPD to medical providers of premenopausal women so that patients may be appropriately treated. This knowledge is especially important considering AIPD’s potential to progress to life-threatening anaphylaxis.

Report of Cases

Case 1

A nulliparous 45-year-old woman presented to the clinic to discuss hormone replacement therapy (HRT) and to investigate a longstanding history of chronic cutaneous hives. Ten months earlier, the patient's gynecologist prescribed combination oral contraceptives to manage painful menstrual cramps. Since that time, the patient began having monthly eruptions of cutaneous hives on her abdomen, upper extremities, legs, and ankles. The rash was pink, pruritic, maculopapular, and excoriated. Symptoms began every month, 6 to 10 days before her menses, and resolved 2 to 3 days after the start of her menstrual cycle. The patient's dermatitis had been getting progressively worse each month and was beginning to interfere with her normal daily functioning, requiring her to miss several days of work each month.

The patient's medical history included seasonal allergies, food allergies, osteoarthritis, and depression. The patient was taking the following medications: cetirizine (5 mg per day), acetaminophen/pamabrom/pyrilamine (500 mg/25 mg/15 mg tablets, 2 tablets every 4-6 hours), hydroxyzine (25 mg every 6-8 hours), norethindrone/ethinyl estradiol (1 mg/20 µg per day), and fluticasone propionate nasal spray (50 µg per spray, 1-2 sprays in each nostril per day). Menarche was at age 14 years, and the patient described a long history of regular but painfully crampy periods. Laboratory results for autoimmune disease and allergies were all unremarkable for explanation of the rash. With negative laboratory results and a history of new-onset cyclic rash with combined oral contraceptive use, the diagnosis of AIPD was suspected.

An in-office progesterone sensitivity injection test was performed on the patient's forearm with intradermal progesterone (0.1 cm³) and saline and histamine as controls. Progesterone and histamine elicited an immediate reaction, with induration and redness, thus confirming a diagnosis of AIPD. At her follow-up appointment, the potential treatment options and possible progression of symptoms were discussed. The patient elected for re-

ferred to a surgeon for possible oophorectomy to stop the cyclic rash and eradicate the possibility of anaphylactic reaction in the future.

Case 2

A nulliparous 41-year-old woman presented for initial consultation regarding possible diagnosis of AIPD. The patient was an obstetrician-gynecologist and reported a cyclic rash that started 2 months ago after switching from conventional combined oral contraceptives to progestin-only contraceptives. The generalized maculopapular rash began 1 week before her menses and resolved 2 to 3 days after the start of her periods. The patient stated that the rash was interfering with her work schedule. She was self-treating with diphenhydramine (25 µg), additional over-the-counter allergy medications (including loratadine, 10 mg), and steroid preparations (hydrocortisone 1% cream) during the episodes as needed. The treatments relieved some symptoms but did not eradicate the rash. The patient switched back to combination oral contraceptives (norethindrone/ethinyl estradiol, 1 mg/20 µg) 2 weeks before consultation without any resolution of symptoms.

The patient's medical history included polycystic ovarian syndrome, sulfonamide drug allergy (which elicited hives), hypothyroidism, and hormone-related migraines. The polycystic ovarian syndrome was diagnosed as a teenager by ultrasonography and had been managed with oral contraceptives. The patient's menarche occurred at age 16 years, and she experienced regular menstrual cycles as a result of her combined oral contraceptives.

A progesterone sensitivity injection test was performed on the left forearm. Three 0.1 cm³ sterile injections of saline, progesterone, and histamine were administered. A positive reading of induration was recorded by 15 minutes at both the histamine and progesterone sites. The patient was advised to stop her current combined oral contraceptives, and the various treatment options for her diagnosis were discussed at length. The patient expressed interest in obtaining symptomatic con-

trol of her disease, but she wanted to take some time to consider her treatment options. Her symptoms slowly resolved over time with continued use of combined oral contraceptives and symptomatic control using antihistamines and occasional systemic or topical steroids during more severe breakouts. More invasive treatment options have not yet been indicated.

Case 3

A 41-year-old woman (gravida 5, para 3) presented with ongoing water retention, unintentional weight gain, and edema that occurred cyclically for 2 weeks every month. The patient described severe swelling consisting of upper and lower extremity edema that had been progressively worsening. She could no longer take off her rings and had to prop her feet up on a wall at night for pain relief. At presentation, the cycles of swelling began to include a feeling of her throat closing, making it difficult to swallow, and the patient complained of periodic anaphylactic-like dyspnea. She had also been complaining of increasing headaches, acne, and abdominal bloating. The patient had previously been tested for food allergies, celiac disease, rheumatoid arthritis, and other autoimmune syndromes, the results of which were negative. The patient was amenorrheic due to a hysterectomy 6 years earlier. Before her hysterectomy, the patient described a history of regular menstrual cycles since age 14 years. Physical examination showed normal-appearing skin with generalized anasarca and 3+ pedal edema. The patient denied taking any medications regularly and reported occasional use of acetaminophen (325 mg) as needed.

Despite not having monthly menstrual cycles or a classic dermatologic manifestation, the diagnosis of AIPD was suspected because the patient's symptoms seemed to be cyclic in nature and possibly representative of an adverse reaction to progesterone from her intact ovaries. A progesterone sensitivity injection test was done in the office to confirm this diagnosis. The patient's forearm was injected in 3 separate areas, with 0.1 cm³

each of histamine, progesterone, and normal saline. The reactions were recorded within 5 minutes of injection: histamine produced a 3- to 4-cm wheal with erythema and progesterone produced a 1.5-cm wheal. The site of normal saline produced no effect or reaction. This testing indicated an allergic reaction to progesterone, thus confirming the diagnosis of AIPD.

Disease management was subsequently discussed with the patient. Because the patient's symptoms had progressed to the more concerning anaphylactoid reaction, she immediately began taking daily norethindrone acetate to suppress the hormonal ovulation cycle while she considered long-term management options. She tolerated this therapy well, with lack of cross-reactivity between synthetic and human progesterone. The patient was given a prescription for an epinephrine auto-injector to carry with her at all times in the event of life-threatening anaphylaxis and respiratory compromise. Bilateral oophorectomy was suggested to the patient for ultimate treatment vs long-term suppression of ovulation with medical management.

Discussion

Presentation

Enormous variability in patient presentations and lack of clinical suspicion make the diagnosis of AIPD challenging. The most indicative sign that should lead clinicians to suspect AIPD is dermatologic manifestations presenting in a cyclic fashion around a woman's menstrual cycle. These cutaneous lesions vary morphologically, the most common descriptions being urticarial lesions, eczema, and erythema multiforme-like eruptions (with or without mucosal or perineal involvement).^{2,8-10} Maculopapular, papulovesicular, vesiculopustular, and vesiculobullous lesions, as well as lesions mimicking dermatitis herpetiformis and erythema annulare centrifugum, have been described.^{5,10,11} Wintzen et al⁶ described a unique patient presentation of cyclic petechial and puerperal lesions precipitated

by progesterone injections. Like in the patient from the current case 3, the progesterone-induced anaphylaxis can be described as cyclic episodes of fixed drug eruptions, stomatitis, and urticarial lesions, with or without angioedema.²

Onset of symptoms can occur at any age and in any clinical scenario. In 2004, Rasi and Khatami¹⁰ demonstrated cases where symptoms of AIPD began shortly after synthetic hormone therapy or in the postpartum period shortly after delivery. Clinicians should be aware that the disease may begin with or without exogenous progesterone use; possible relations to pregnancy or postpartum status may be idiopathic and spontaneous.²⁻¹⁶ Once clinical suspicion is present, the diagnosis of AIPD must be confirmed with the progesterone sensitivity injection test.

Pathogenesis

Many theories have been proposed for the pathogenesis behind AIPD. The exact pathophysiologic process of the disease is unknown, but commonalities have been demonstrated that may lead to the discovery of the cause. In a 1977 study, Hart¹⁴ proposed that synthetic progesterone with modified side chains could induce antibody formation and subsequent cross-reactivity to endogenous progesterone—a theory not dissimilar to the etiologic process of circulating autologous antibodies developed in lupus erythematosus.^{9,14,15} In other cases, it was suggested that prolonged progesterone therapy (like in oral contraceptive use) may result in antigen presentation to T-helper cells, which could lead to immunoglobulin E synthesis and systemic allergy to endogenous progesterone as it cycles in a young woman.^{8,15} These definitive antibodies to progesterone have been demonstrated using techniques such as immunofluorescence and basophil degranulation tests; however, negative results have also been reported.^{8,17} Cristaudo et al¹³ demonstrated interferon γ release upon progesterone stimulation using ELISpot techniques. This study,¹³ along with evidence by Halevy et al,¹¹ demonstrates the role of allergic and

inflammatory reactions of the body in response to sensitized antibodies to progesterone.

Relative eosinophilia presents in cutaneous symptoms in many patients reported through the years, and reports suggest that progesterone may induce mast cell degranulation by its nature.^{8,15} Whether the eosinophilia is a random correlation with the disease or a direct cause is unknown.⁸ In investigation of the disease's cutaneous histopathology, superficial perivascular mixed inflammation is the most consistent histologic evidence,^{9,10} with other findings ranging from nonspecific changes to specific dermatoses like erythema multiforme.¹⁰ Infiltration of the dermis in cutaneous lesions may also consist of lymphocytic or mixed eosinophil, neutrophil, or mast cellularity.¹⁰

Diagnosis

Clinical history alone may be an indicator of the presence of AIPD, but with variability in presentation, confirmation of the diagnosis is necessary. The presence of both immediate and delayed type (type I and type IV) hypersensitive reactions have been demonstrated in multiple studies of AIPD,^{8,11,14,16,17} which used the standard diagnostic test for AIPD, the progesterone sensitivity injection tests. Halevy et al¹¹ and Cristaudo et al¹³ supported the presence of delayed type or Th1-cell-mediated hypersensitivity using in vitro enzyme-linked immunosorbent assay (ELISA) to show lymphocytic interferon γ release. The in vitro ELISA has been a useful diagnostic tool in the study of AIPD. However, the sensitivity injection tests are more readily used in medical practice to diagnose AIPD because of the cost-effectiveness and availability of tools. Because of its rarity, AIPD may also be a diagnosis of exclusion after all other etiologic processes have been ruled out,⁷ especially other causes of recurrent anaphylaxis or erythema multiforme.

In all 3 of our patients, AIPD was diagnosed after indicative clinical history and subsequent testing with



Figure. Intradermal testing with progesterone (1:10, 1:1) was positive for autoimmune progesterone dermatitis after 15 minutes. Reprinted with permission from Lee MK, Lee WY, Yong SJ, et al. A case of autoimmune progesterone dermatitis misdiagnosed as allergic contact dermatitis. *Allergy Asthma Immunol Res.* 2011;3(2):141-144. doi:10.4168/aaair.2011.3.2.141.

the standardized intradermal progesterone sensitivity test and verified with controlled injections of saline or histamine (Figure). We used an aqueous solution of bioidentical progesterone, 50 mg/mL, for the sensitivity tests, and it elicited immediate or delayed-type reactions in all 3 of our cases. This method demonstrated the patient's sensitivity to endogenous or human progesterone and did not indicate the possibility of cross-reactivity with synthetic progestins that has been described in the literature. The patient in case 3, however, did not have cross-sensitivity to exogenous progesterone.

Treatment

Because very few providers are familiar with the disease, there is no consensus on management thus far. However, both medical and surgical options are available for patients with AIPD. Antihistamines and topical anti-inflammatory agents, such as hydrocortisone, may be initially helpful for mild cases.^{2,4,8,9,15-18} Although this approach is typically unsuccessful and only high doses of steroids have been effective,¹² symptomatic control is still consid-

ered the first-line treatment in patients with non-life-threatening symptoms of AIPD.

As symptoms progress, more aggressive methods, such as ovulation suppression, may be indicated. An injection of a gonadotropin-releasing hormone agonist (such as buserelin or leuprolide) may be used^{2,5,7,8,12,17} and often provides immediate relief with cessation of the progesterone peaks. However, treatment with these agents is limited because of concerns for premature menopause and relative osteoporosis.¹² Treatment with danazol has been shown to effectively reduce symptoms of AIPD^{6,8,10,12,17} and prophylactically reduce outbreaks by means of altering immune complex-induced vasculitic reactions.¹⁸ In addition, Stephens et al,¹⁹ among others, suggest the use of tamoxifen for reducing the severity of AIPD.^{3,6-8,11,12,17} The latter 2 methods have a high incidence of adverse effects, particularly tamoxifen's effect on menopausal symptoms and danazol's antiestrogenic effect on bone metabolism.^{2,17} These drugs are not recommended for long-term use.¹¹ A less aggressive, reversible suppression may be accomplished using low- or

medium-dose oral contraceptives.^{3-5,7,8,12} Although synthetic progestins may be linked to the causation of the sensitivity, a suppressive progestin (such as the norethindrone, given in case 3) or combined oral contraceptive may also be successful in suppressing the symptoms caused by the monthly endogenous progesterone surge, as long as no cross-reacting antibodies to synthetic progesterone exist.³ Until sensitivity to progestins is determined, suppression of ovulation with long-term progesterone analogs (such as medroxyprogesterone) should be avoided, because this form is not reversible and could cause detrimental effects. Likewise, some reports suggest using conjugated estrogens alone if the patient does not require progesterone balancing, as in women who have undergone a hysterectomy.^{2-5,7,9}

For more severe cases of AIPD, such as patients with cyclic anaphylactic symptoms, bilateral oophorectomy should be considered. As reported by Ródenas et al,⁵ therapeutic oophorectomy for this condition should be considered when conservative treatment has failed. Premenopausal women may then be given oral, topical, transdermal, or pellet estrogen replacement, with monitoring of the endometrial thickness in patients with an intact uterus.

Osteopathic Considerations

Increasing lymphatic drainage and return to the venous system through manual techniques (eg, lymphatic pump) have long been practiced and are only recently documented in the practice of osteopathic medicine. Osteopathic manipulative treatment has been used to reduce pain and edema, increase range of motion and functionality, and decrease inflammation and promotion of cytokine release in patients with chronic inflammatory diseases.^{20,21} Patients who present with AIPD may benefit from lymphatic pump techniques to decrease the inflammatory response, decrease the severity of symptoms, and improve the circulating immune system.

Conclusion

Autoimmune progesterone dermatitis is a highly underdiagnosed disease most likely a result of its variable presentation and the lack of disease awareness in clinical practice. There should be a high index of suspicion among clinicians in the primary care and emergency settings, especially with young females of reproductive age with a classic presentation of a cyclic rash beginning days before the onset of menses and terminating 1 to 2 days into menstruation. However, clinicians should be aware that patients with irregular or no menses might present differently. Office testing for patients who present with these cyclic allergic symptoms should be done and, after confirmation of AIPD, appropriate treatment should be offered to the patient. Treatment plans should be individualized and tailored to best suit a woman's reproductive needs and concerns as well as address the level of severity of presentation, with the ultimate goal to improve quality of life and prevent progression of symptoms. Education and awareness of the disease is the best way to aid patients with diagnosed or undiagnosed AIPD. We encourage more case reports of AIPD to further disease research and develop more definitive management plans.

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