AUTOIMMUNE PROGESTERONE DERMATITIS:

CASE OF A PROGRESSIVELY WORSENING CYCLIC RASH

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ABSTRACT

Autoimmune Progesterone Dermatitis (AIPD) is a NIH classified rare condition\(^1\) in which allergic dermatitis to endogenous progesterone manifests in a wide spectrum of cyclic cutaneous eruptions. Rashes or even systemic anaphylaxis begin in the premenstrual period during the luteal phase when progesterone levels peak. The rash subsides a few days into menses, with the decline of progesterone levels or with suppression of ovulation by medical intervention. We present a classic case of Autoimmune Progesterone Dermatitis in a patient who presented with a progressively worsening cyclic rash; the severity, of which, was beginning to affect the patient’s quality of life. After clinical suspicion, the patient tested positive on a controlled intradermal injection test of progesterone, which is the standard method of diagnosis of Autoimmune Progesterone Dermatitis to date since clinical history alone can be equivocal\(^{2-4}\). In this case report, we propose an approach and clinical considerations for any woman of reproductive age presenting with cyclic dermatitis related to menses. Most recent documentation states that only 70 cases of Autoimmune Progesterone Dermatitis have ever been reported\(^2\). We propose that Autoimmune Progesterone Dermatitis is a highly under-diagnosed disease due the uncertainty of its pathogenesis and vague clinical presentations. However, with a standard diagnostic procedure and treatment options for this relatively debilitating disease, APD should be a considered differential in the minds of every physician in a primary care or emergency setting.
With cases of autoimmune progesterone dermatitis reported since 1921, a wide variety of symptoms have been associated with the disease. AIPD is an autoimmune phenomenon to endogenous progesterone that occurs in women of reproductive age, with or without a history of exogenous synthetic progestin exposure, and characterized by cyclical premenstrual flares of polymorphous dermatologic manifestations such as erythema multiforme, eczema, urticaria, and papulovesicular eruptions. Pregnancy has been associated with both worsening and relief of symptoms. Some case reports of AIPD have demonstrated a progression of the disease to an anaphylactic cycle of reactions, referred to as “progesterone-induced anaphylaxis”, requiring monthly EpiPen injections. Diagnosis is best conferred with high scrutiny of the clinical history, and confirmation by a standardized and controlled intradermal injection of progesterone (of any formulation). Clinical history alone to diagnose may be unhelpful in patients with a history of irregular menses or absent uterus. Reported treatment options vary from symptomatic control to suppression or elimination of ovulation by medical or surgical interventions. Both options, of which, have had successful results in most patients with AIPD. The providing physicians should individualize patient’s treatment plans with the ultimate goal being symptomatic control, prevention of life-threatening disease progression, and improvement in the patient’s quality of life. With only a few cases of AIPD reported since its discovery, the precise pathophysiology and management for the disease is widely unknown. Understandably, it is difficult for clinicians to know how to proceed with a patient presenting with symptoms of AIPD, since very few people are familiar with the disease and there is no consensus on management thus far. It is therefore very important to report cases of AIPD to the medical community. Finding commonalities in AIPD patients’ histories and treatment successes will hopefully induce further research on this disease and help aid patients with undiagnosed or diagnosed AIPD achieve relief sooner.

**Case 1**

A 45-year-old G0P0 presents to the clinic with two chief complaints: a concern about her hormone levels and a long history of a cyclic rash. The patient, “LD”, complains of many new symptoms including fatigue, weight gain, menstrual cramps and depression; all of which have begun in the past two years and have been getting progressively worse. She would like her hormone levels checked and to possibly discuss hormone replacement therapy (HRT). LD also states to be very concerned with a long-standing history of cutaneous hives. The rash is described as pink, pruritic, maculopapular and excoriated. It began 10 months ago after the patient’s gynecologist had started her on combination oral contraceptive pills to address painful menstrual cramps. Since that time, the patient began having monthly eruptions of cutaneous hives on her abdomen, upper extremities, legs and ankles. It begins every month, 6-10 days prior to menses and resolves 2-3 days after the start of menses. The patient saw her gynecologist after the development of the rash and was told that it was unrelated to her oral contraceptive pills (OCPs). The patient’s dermatitis had been getting progressively worse and more painful each month, and has begun to interfere with her normal daily functioning; causing her to miss work on occasion. LD has had an extensive work up by many specialists; including an internist, dermatologist and allergist. None of these professionals have been able to figure out the exact etiology of her rash. Frustrated and discouraged, the patient made one last appointment with DeRosa Medical for a final evaluation of her hormones and rash.
The patient’s past medical history includes seasonal allergies, food allergies to vanilla, chocolate, turkey, tomatoes and corn, osteoarthritis, and depression. No known drug allergies. In LD’s gynecologic history, she has never been pregnant and has had no pelvic surgeries. Patient’s menarche occurred at the age of 14, periods have always been regular, but are associated with painful cramps. Her last Papanicolaou smear was 04/2013 and normal; her last mammogram was 06/2013 and also normal. Her last menstrual period was 3 weeks ago. Preventative health maintenance is up to date: including a vaginal and rectal exam, chest x-ray, EKG, and Flu vaccine. All other immunizations are up to date. Past surgeries include tonsillectomy and adenoidectomy 1986, cholecystectomy 1999, and appendectomy 1981; all were uncomplicated procedures. The patient is taking the following medications: Zyrtec 10mg tab and Flonase Nasal Spray for allergies, Pamprin for menstrual cramps, Hydroxyzine HCl 10 mg for pruritus, Loestrin OCP, Aleve and Ibuprofen 200mg for osteoarthritis pain, Multivitamins, Vitamin C-1000mg and Calcium tablets.

In a review of the patient’s constitutional symptoms, LD is positive for: fatigue, changes in memory, unintentional weight gain, generalized hives, and painful menstrual cramps. She does not have any change in vision, hearing, or speaking. She denies recent illness, chest pain, shortness of breath, abdominal pain, nausea, vomiting or changes in bowel or bladder habits. LD describes new onset of low libido and vaginal dryness. She has been having muscle aches and joint pain related to her history of osteoarthritis. Psychologically, patient states to have new feelings of depression with drastic mood swings and feelings of not enjoying life. LD denies any feelings of hopelessness or suicidal ideation and has never been hospitalized for psychological related illness.

Vital signs for LD were: height of 65 inches, weight of 234.2 lbs., BMI 39.9, Temperature (tympanic) 99.2 F, blood pressure of 120/80 mm Hg (Left arm, sitting), pulse of 82 bpm (finger clip, sitting) and respiratory rate of 15 bpm. In physical exam, LD was a mildly obese woman in no apparent distress, appearing well developed and nourished. Neck is supple with full range of motion, thyroid exam reveals mild enlargement without nodules. Normal respiratory rate and pattern with no distress appreciated. Normal breath sounds with no rales, rhonchi, wheezes or rubs. Heart sounds are regular in rhythm with normal S1 and S2. There is normal PMI placement and no murmurs heard. LD does have trace pedal edema bilaterally without pitting. The dorsalis pedis pulses are appreciated 2+ in both left and right feet. She also has mild venous stasis ulcers present on the anterior aspect of both legs. Bowel sounds are heard in all quadrants, no masses or tenderness appreciated. There is no evidence of ischemia or infection on exam: no clubbing of digits, cyanosis. Cranial nerves II-XII are grossly intact with both motor and sensory dermatomes in upper and lower extremities intact bilaterally. Patient’s gait is normal and no evidence of neurologic dysfunction is found. On osteopathic exam, lymphatic congestion is noticed in all extremities, neck and abdomen. Mild tissue ropiness is felt at levels T2-4 bilaterally and there is tenderness to palpation. There is increased lumbar lordosis with mild anteriorly rotated pelvis on the left. There is no limited range of motion in cervical, thoracic or lumbar spine. A rash is noted across the abdomen, on the upper extremities and on the lower extremities bilaterally. The color of the rash is mainly pink and best characterized as maculopapular and excoriated. LD’s mental status is alert and oriented to person, place and time. Her recent and remote memory is intact and she retains good insight and judgment.

Routine labs were ordered on the patient: including estradiol, testosterone, FSH, LH TSH, T4, T3, reverse T3, Prolactin, RF, ANA titer, IgA titers, CBC, CRP, and DHEA. All lab results were within normal range except for suboptimal thyroid levels (TSH 2.640 ulU/mL, Free T3 2.9 pg/mL, Free direct
T4 1.26 ng/dL) and testosterone deficiency (29 ng/dL). Testosterone was subsequently treated with hormone replacements and LD was given a prescription for Armour Thyroid 60mg. She was told to follow-up in 3 months for evaluation of her thyroid and hormone treatments. For the work-up of LD’s cyclic rash: the negative ancillary lab results along with the history of a new cyclic rash with recent OCP use, the diagnosis of Autoimmune Progesterone Dermatitis was suspected.

The diagnosis was confirmed after administering 0.1cc intradermal progesterone, which elicited an immediate reaction with induration and redness on LD’s forearm. The in-office skin prick test was also performed with normal saline and histamine for controls: of which histamine elicited a similar reaction to progesterone. A validity and control test was done on two office staff volunteers (including one male volunteer) with another 0.1cc intradermal injection of progesterone. Both test results were negative in these control subjects. At her follow up appointment we discussed the potential treatment options and the daunting possibility of progression of symptoms. LD elected for referral to a surgeon for possible oophorectomy to stop the cyclic rash and eradicate the possibility of anaphylactic reaction in the future.

**DISCUSSION**

**Presentation** - Enormous variability in patient presentations and lack of clinical education makes the diagnosis of AIPD challenging. The most indicative sign that should lead clinicians to suspect AIPD is the theme of 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)\(^4, 8, 11, 17\). A case from Wintzen et al\(^9\) describes a unique patient presenting with cyclic puerperal lesions reported to progress to a state of recurrent anaphylaxis\(^8\). The most severe symptoms in this progesterone-induced anaphylaxis being episodes of fixed drug eruptions with stomatitis and angioedema\(^8\).

Onset of AIPD symptoms can occur at any age and in any clinical scenario. In 2004, Rasi et al\(^17\) demonstrated cases where symptoms of AIPD began shortly after synthetic hormone therapy or in the post-partum period shortly after delivery. No commonality in age or clinical scenario for onset of symptoms has been demonstrated. Clinicians should be aware of the following: the disease may begin with or without exogenous progesterone use, there are possible relations to pregnancy or the post-partum period, and AIPD may be idiopathic or spontaneous\(^2, 17\). Once clinical suspicion is present, the diagnosis of AIPD must be confirmed with the progesterone challenge test.

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\(^{i*}\) Please note: this was not done under a controlled study format and is not recommended for standard AIPD patient diagnoses. Two office staff volunteered for 0.1cc intradermal injections of progesterone for comparison to the patient’s solely out of curiosity and for verifying the validity of the study altogether. One volunteer was female and close in age to patient, and the other volunteer was male.
**Pathogenesis**- There have been several theories proposed for the pathogenesis behind autoimmune progesterone dermatitis. The exact pathophysiology of the disease is unknown, only some commonalities in the few cases ever reported may give clues into this potentially life-threatening disease.

In a 1977 study by Hart et al\textsuperscript{14}, it was proposed that synthetic progesterone with their modified side chains can possibly induce antibody formation and subsequent cross-reactivity to endogenous progesterone- not dissimilar to the etiology of circulating autologous antibodies developed in systemic lupus erythematosus \textsuperscript{11, 14, 15}. In other cases, it has been suggested that prolonged progesterone therapy (like with oral contraceptive use), may result in antigen-presentation to T-helper cells which could lead to IgE synthesis and systemic allergy to endogenous progesterone as it cycles in a young woman\textsuperscript{4, 15}.

In a recent study of a patient with AIPD, Cristaudo et al\textsuperscript{13} demonstrated IFN-γ release upon progesterone stimulation using ELISpot techniques. This finding, along with evidence by Halevy et al\textsuperscript{12}, demonstrates the role of allergic and inflammatory reactions of the body in response to sensitized antibodies to progesterone. These studies and others have also indicated the presence of both immediate and delayed type (type I and type IV) hypersensitivity reactions \textsuperscript{4, 12, 14, 16, 18}, which is also demonstrated in the diagnostic progesterone sensitivity injection tests. Relative eosinophilia presents in cutaneous symptoms in many patients reported through the years, as well as suggestions that progesterone may induce mast cell degranulation by its nature \textsuperscript{4, 15}. Whether the eosinophilia is a random correlation with the disease or a direct cause is unknown\textsuperscript{4}.

After almost 90 years of research on the disease, it is evident that many possibilities exist in the etiology of this disease. The commonality of allergy to endogenous progesterone remains the most basic component of AIPD, and is the basis for diagnosis and treatment of every patient presenting with these cyclic dermatologic symptoms. There is a noticeable void in the overall knowledge of AIPD. It is important to promote further investigation of this disease in order to know how to properly identify and treat it in the future.

**Diagnosis**- In 2002, Halevy et al\textsuperscript{12} and similarly in 2007 Cristaudo et al\textsuperscript{13} revealed in a study of AIPD that using in-vitro ELISA lymphocytic IFN-γ release induced by culture with progesterone supported the presence of delayed-type hypersensitivity or Th1-cell-mediated immunity in the pathogenesis of the disease. This has been a useful diagnostic tool in the study of AIPD as well as demonstrating immediate or delayed-type reactions to progesterone in-vivo with intradermal sensitivity tests (often referred to as skin-prick tests). The later method is more readily used in medical practice to diagnose Autoimmune Progesterone Dermatitis due to its cost-effectiveness and availability of tools. The intradermal sensitivity test is often performed.

![Figure 2](https://example.com) (See Graphic Elements page)
with saline or histamine injection controls at the same time. Saline should not elicit a hypersensitivity reaction, while histamine might demonstrate a similar reaction to the progesterone injection on a patient with AIPD. Due to its rarity, it is important to first rule out other more serious causes of recurrent anaphylaxis or erythema multiforme before AIPD can be considered.

Treatment- AIPD may be treated in a variety of ways, both medical and surgical. Antihistamines and topical anti-inflammatory agents, such as hydrocortisone, may be initially helpful for mild cases. Although this non-aggressive approach is typically unsuccessful and only high doses of steroids will typically suppress symptoms, it should still be the initial plan in a patient presenting with non-threatening symptoms of AIPD. As symptoms progress, however, they may become more debilitating, and more aggressive methods, such as ovulation suppression may be indicated. An injection of a GNRH agonist (such as Buserelin or Lupron) has been successful in suppressing ovulation in the past and may even be used as a test treatment to see if symptoms abate with cessation of progesterone peaks. Treatment with these agents is limited because of concerns of premature menopause and relative osteoporosis.

A less aggressive, reversible suppression may be accomplished by using low or medium dose oral contraceptive agents, as long as no cross reacting antibodies to synthetic progesterone exist. Although use of OCP’s has been linked to causality of AIPD, the patients are usually sensitized only to endogenous progesterone hormone. Until sensitivity to progestins is determined, however, use of long-term progestin suppression (such as Depo-Provera) should be avoided, since it is not easily reversible. Likewise, some reports suggest utilizing conjugated estrogens alone if the patient does not require progesterone balancing as in women who have undergone a hysterectomy.

Treatment with Danazol has been demonstrated to effectively reduce symptomatology of AIPD, and prophylactically reduce outbreaks by means of altering immune complex-induced vasculitic reactions. In addition, Stephens et al and other sources suggest the use of Tamoxifen to reportedly reduced severity of Autoimmune Progesterone Dermatitis. The later two methods have a high incidence of adverse side effects (especially Tamoxifen’s effect on menopausal symptoms and Danazol’s anti-estrogen effect on bone metabolism) and are not recommended for long-term use.

For more severe cases of AIPD, such as those with cyclic anaphylactic symptoms, bilateral oophorectomy should be considered. As reported in the study by Ródenas et al, therapeutic oophorectomy for this condition should be done in cases where conservative therapeutic measures of failed. Oophorectomy is ultimately the definitive treatment of AIPD, but is only considered in patients who do not wish to retain fertility and are good candidates for surgery.

Osteopathic Considerations- Increasing lymphatic drainage and return to the venous system through manual techniques (lymphatic pump) have long been practiced and are only recently documented in the practice of osteopathic medicine. OMM has been used to reduce pain, edema, increased range of motion and functionality as well as decrease inflammation and promotion of cytokine release in patients with chronic inflammatory diseases. Patients who present with AIDP may benefit from lymphatic pump techniques to decrease the inflammatory response, decrease the severity of symptoms, and improve the circulating immune system.
CONCLUSION

Although the exact pathophysiology is unclear, Autoimmune Progesterone Dermatitis remains a very diagnosable and treatable disease. Clinical history alone can be an indicator of the presence of AIPD, but with variability in presentation, confirmation of the diagnosis is necessary. This may be accomplished by a number of proposed diagnostic methods, the most commonly used method being the intradermal progesterone challenge test. There should be a high index of suspicion among clinicians in the primary care and emergency setting, especially with young females of reproductive age presenting with a cyclic rash beginning days before the onset of menses and terminating 1-2 days into menstruation. Emergency physicians should be aware of the potential for AIPD to progress to a state of anaphylaxis. New onset of this cyclic rash may or may not be preceded by introduction of synthetic progestin in the patient’s clinical history. Pregnancy has also been associated with both increased severity and resolution of AIPD symptoms. Treatment plans in patients presenting with AIPD should be individualized and tailored to best suit a women’s reproductive needs and concerns, as well as to address the level of severity of presentation. The ultimate goal in diagnosis and treatment of AIPD is the improvement of the patient’s quality of life, as well as preventing progression of symptoms to a life-threatening state.

Autoimmune Progesterone Dermatitis, although termed rare, may in fact be a much more prevalent disease occurring in pre-menopausal women. Since the first diagnosis of AIPD at DeRosa Medical, two more patients have presented with similar complaints of cyclic rashes and tested positive with the intradermal progesterone challenge test. One of these patients had progression of symptoms to recurrent anaphylaxis, requiring regular Epinephrine injections for control. With treatment of symptoms and sometimes eradication of the endogenous progesterone surges by suppression of ovulation or surgery, all patients with AIPD have a favorable prognosis once diagnosis has been made. This is why medical education on this uncommon disease and promotion of further case studies are important to patients with both diagnosed and undiagnosed Autoimmune Progesterone Dermatitis. Too few cases have been reported to definitively agree on a pathophysiology or have consensus on exact management of AIPD. Considering that two more patients were diagnosed with AIPD at the DeRosa clinic within one year of our case study patient’s presentation could support our suggestions that this is a relatively under-diagnosed disease. Knowledge about this disease in the clinical setting, both outpatient and inpatient/emergency, may be the only limiting factor between helping a female patient with AIPD achieve a better quality of life.

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References

1) NIH: Genetic and Rare Diseases Information Center (GARD). Autoimmune progesterone dermatitis. www.rarediseases.info.nih.gov


*Note: No photographs were taken of the patient referenced in this case study. Please consider the cited photographs from other published cases of Autoimmune Progesterone Dermatitis in reference to the described lesions in this case study.

1 Figure 1: “Autoimmune Progesterone Dermatitis. Pruritic, erythematous, and urticarial papules and plaques on the back of a 40-year-old Iranian woman.”

- Figure 1 demonstrates a classical presentation of AIPD as a diffuse erythematous rash similar in appearance to erythema multiforme. This patient in the case above, by Rasi et al17, is of similar age and presentation to the patient in our case study.
- Autoimmune Progesterone Dermatitis may present in a wide variety of cutaneous lesions. Any cutaneous rash or allergic reaction occurring in a cyclic fashion in a pre-menopausal woman may be sufficient enough to consider the diagnosis of AIPD.
Figure 2: “Post-intradermal progesterone challenge lesion. There is a blister surrounding erythema on the arm.”


- Figure 2 is an example from Nasabzadeh et al6 AIPD case study of a patient with a positive intradermal progesterone challenge test.
- The patient in our case study had an immediate erythematous lesion with induration after injection of progesterone intradermally, similar to the reaction in Figure 2.
- The patient in our case study did not present with a blister reaction as in Figure 2.
- Progesterone challenge lesion is positive with either an immediate allergic reaction to the intradermal injection or a delayed-hypersensitivity at the injection site noted days later.
- Control injections with saline and/or histamine may be done at the same time (at different sites on the body). Saline injections should have no reaction while histamine produces an immediate erythematous lesion, often similar in appearance to an AIPD patient’s positive progesterone challenge injection.