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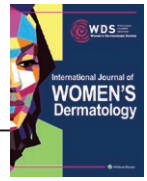

Autoimmune progesterone dermatitis: a retrospective case series

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Abstract

Background: Autoimmune progesterone dermatitis (APD) is a rare hypersensitivity disorder characterized by recurring dermatologic manifestations during the luteal phase of the menstrual cycle in women. Well-defined clinical and diagnostic criteria, outcomes measurements, and standard treatments are lacking.

Methods: We performed a single-institution retrospective review of adult patients (older than 20 years at the time of diagnosis) with APD.

Results: Fourteen patients were included with mean age of clinical onset of 34.3±7.7 (range 24-54) years. There was a delay of 3.9±5.5 (range 0.4-20) years between the onset of disease symptoms and diagnosis. The onset of APD was after exposure to exogenous progesterone in 9 of 14 patients. Progesterone skin test was performed in 9 patients and 6 were positive. Patients frequently presented with urticaria (9/14, 64.3%) and dermatitis (4/14, 28.6%). Continuous combined oral contraceptives (4/14, 28.6%), gonadotropin-releasing hormone agonist (3/14, 21.4%), and hysterectomy with bilateral salpingo-oophorectomy (2/14, 14.3%) were the most common attempted treatments with reliable outcomes.

Conclusions: APD is a rare disorder which lacks universal diagnostic measures and criteria, contributing to a significant delay in diagnosis. Large-scale multicenter studies are needed to develop accurate tests, establish diagnostic criteria, and define treatment outcomes.

Keywords: autoimmune, cyclic, dermatitis, hypersensitivity, progesterone, urticaria

Introduction

Autoimmune progesterone dermatitis

Autoimmune progesterone dermatitis (APD) is a rare hypersensitivity disorder presenting with a variety of dermatologic and allergic signs and symptoms. APD manifests recurringly during the luteal phase of the menstrual cycle coinciding with the peak of endogenous progesterone production.[1,2] APD has been reported to be triggered by exogenous progesterone exposure or pregnancy in some women.[1,2] Patients most commonly present with urticaria with or without angioedema, anaphylaxis, and pruritus.[1,2] Other presentations include vesiculobullous disorders, erythema multiforme, fixed drug eruptions, aphthous stomatitis, maculopapular rash, and recalcitrant dermatitis.[1–3] Unfortunately, there are no well-defined and universally agreed-upon diagnostic criteria for APD. There are no specific histological features on skin biopsy. Intradermal progesterone testing often shows variable results and the diagnostic accuracy is not well studied.[1,2] As such, APD is often considered a diagnosis of exclusion. Treatments are often aimed at inhibition of endogenous progesterone production from hormonal suppression of ovulation to surgical hysterectomy with bilateral salpingo-oophorectomy (BSO). Other treatments such as progesterone desensitization are being increasingly utilized.[1,2]

Objectives

Most of the published papers on APD are limited to case reports. Our group previously published the first series of cases on adolescent-onset APD.[1] In this single-center, retrospective review, we

What is known about this subject in regard to women and their families?

- Autoimmune progesterone dermatitis (APD) is a rare hypersensitivity disorder that affects women during the luteal phase of menstrual cycle.
- It can have many different presentations including recurrent and cyclical urticaria, anaphylaxis, dermatitis, and other skin manifestations.
- Diagnosis is difficult and often made based on the exclusion of all possible differential diagnoses.

What is new from this article as messages for women and their families?

- Diagnosis of APD is often delayed in women.
- Continuous combined oral contraceptives and gonadotropin-releasing hormone agonist may be effective treatments for APD.
- Future large studies are needed to establish diagnostic criteria and evaluate the treatments of APD.

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aim to review the clinical presentations, risk factors, diagnostic features, and attempted treatments and outcomes in a series of adult-onset APD.

Methods

APD diagnosis

We included all adult patients (defined as 20 years and above) diagnosed with APD between January 1, 1997, and April 30, 2021, at Mayo Clinic, Rochester, Minnesota. This study was approved by the Mayo Clinic Institutional Review Board. The diagnosis of APD was made based on clinical symptoms suggestive of APD recurring during the luteal phase of the menstrual cycle or after exposure to exogenous progesterone, with either positive progesterone skin test or complete or partial resolution of symptoms with ovulation suppression therapies, and exclusion of other differential diagnoses. The consensus between dermatologists, allergists, and gynecologists was used for confirmation of diagnosis.

Progesterone skin testing protocol

Progesterone skin testing was conducted using Hydroxyprogesterone Caproate. Skin prick tests were performed on the volar surface of the forearm using histamine 6 mg/mL, diluent, and Benzyl Alcohol 10% as the controls and Hydroxyprogesterone Caproate 50 mg/mL in Benzyl Alcohol 10% (Neat Prick) for the progesterone antigen. If the skin prick test showed good histamine control response and the Hydroxyprogesterone Caproate was negative, then we proceeded to intradermal (ID) skin testing. A positive skin prick test result was defined as a wheal of 3 × 3 mm or greater with a surrounding zone of erythema in the hydroxyprogesterone above the negative control.

ID skin testing was also performed on the volar surface of the forearm using ID control of diluent and Benzyl Alcohol 10% (diluted 1:5 or 2%). If the ID controls were negative, continued with ID's of Hydroxyprogesterone starting with the most dilute (0.05 mg/mL) and increasing the concentration (0.5 and 5 mg/mL) until reaching the final concentration of Hydroxyprogesterone 10 mg/mL every 15 minutes until a positive result or reaching the final concentration. A positive ID test result was defined as a wheal of 3 × 3 mm or greater with a surrounding zone of erythema in the hydroxyprogesterone above the negative control.

Data collection

We reviewed data on age of onset and diagnosis, clinical presentation, potential risk factors, diagnostic test results, and attempted treatments, treatment outcomes, and follow-up. A complete treatment response was defined as absence of APD signs and symptoms. Partial responses required more than 50% reduction in the severity of APD symptoms and signs. No response meant the APD clinical presentation worsened, did not change with therapy, or improved minimally or transiently (<50%).

Results

Demographics and delay to diagnosis

Fourteen adults with APD were included, 14 (100%) identified as female and 14 (100%) as white. The mean age of APD clinical onset was 34.3 ± 7.7 (24-54) years, while mean age at APD diagnosis was 37.8 ± 7.8 (25-55) years. The mean delay from APD onset to diagnosis was 3.9 ± 5.5 (0.4-20) years.

Clinical presentation

The most common clinical presentation of APD was urticaria (9/14) (Fig. 1) followed by dermatitis (4/14), with erythema multiforme-like (Fig. 2) and fixed drug-like eruption in one patient each (Table 1). Most patients (13/14, 92.9%) had previous history of pregnancy and 9 of 14 (64.3%) had history of exogenous progesterone exposure. Two patients had peripartum disease onset. The progesterone intradermal test was performed in nine patients (in 7 patients presenting with urticaria and 2 with dermatitis) with a positive result in 6 (including 5 patients with urticaria and 1 with dermatitis).

Treatment

The most common attempted therapy in our patient series was a combined oral contraceptive pill (OCP) (4/14), resulting in partial response for 3 of 4 patients. A variety of other hormonal treatments including intrauterine device removal, hysterectomy with BSO, progesterone desensitization, gonadotropin-releasing hormone agonists (leuprolide), androgenic hormone (danazol), estrogen modulator (tamoxifen), and spironolactone were attempted with variable results (Table 2). Colchicine and omalizumab were tried in 1 patient each for urticarial APD with unsatisfactory outcomes.

Discussion

Delay in APD diagnosis

We presented the clinical, pathologic, diagnostic, and therapeutic features of 14 adult female patients with APD. We found a significant delay of 3.9 years between the APD symptoms onset and the diagnosis. We previously showed APD is associated with 1.1 year diagnosis delay in the pediatric and adolescent population.[1] This delay may be due to a variety of reasons; APD is rare. The signs and symptoms may be vague and variable. Patients and clinicians may not be aware of this condition. No rigorous diagnostic criteria exist for APD. Patients often need to go through a wide array of tests and diagnostic measures, as the diagnosis is often made based on exclusion, potentially leading to diagnostic delay of years. We do not know of any APD cases in transgender women, though it is a possibility and should be considered for patients for similar presentations after starting exogenous progesterone.

Clinical presentation

Our cohort most commonly presented with urticaria with or without angioedema, anaphylaxis, and aphthous ulcers, which

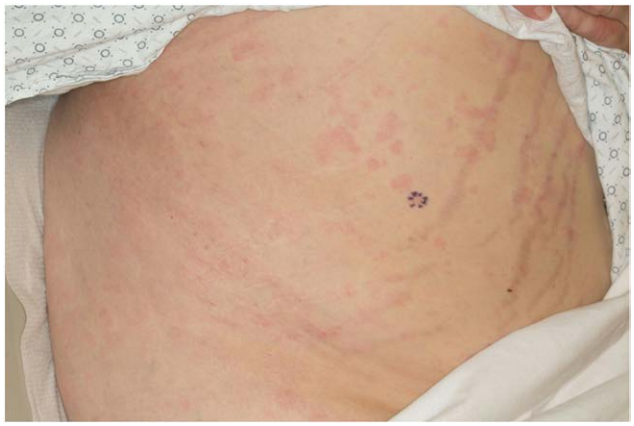

Fig. 1. Patient with APD presenting with diffuse urticaria.

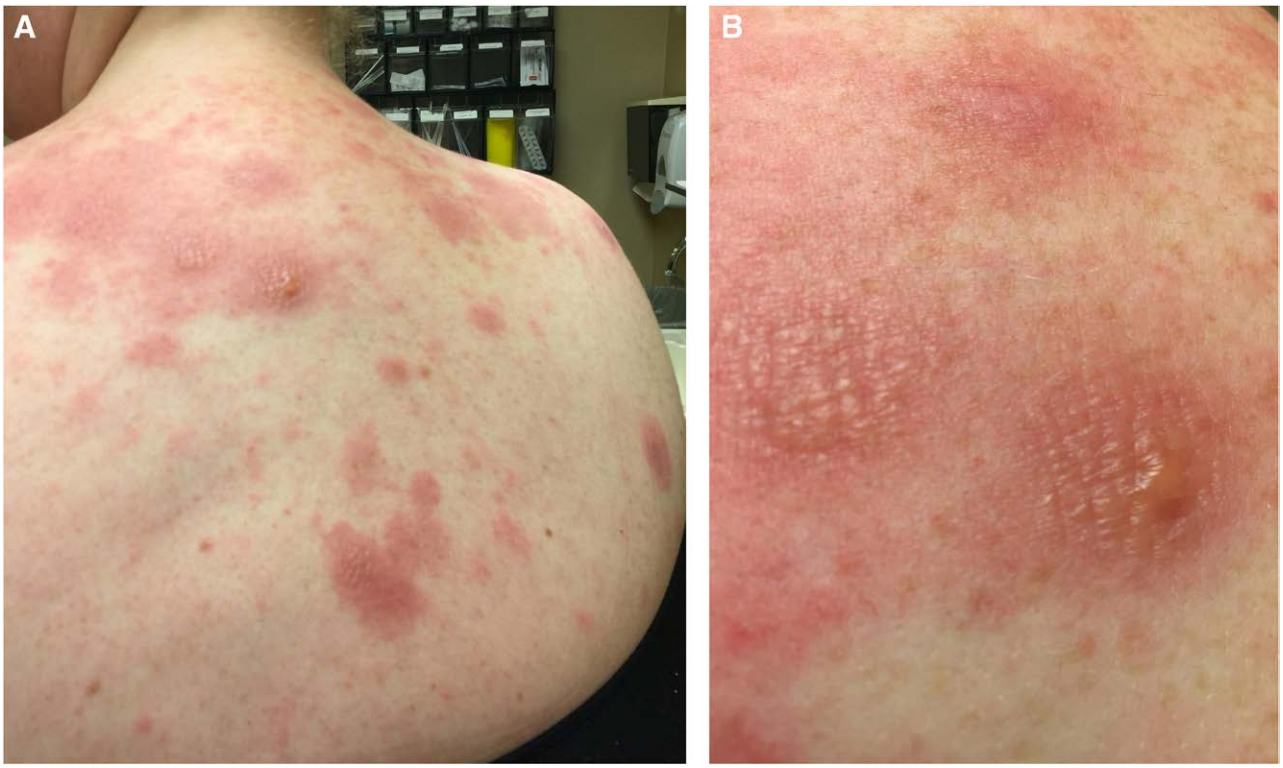

Fig. 2. (A and B) Patient with APD presenting wit recurrent erythema multiforme-like eruption.

reflects prior studies.[1,2] Our series reinforces a key aspect in diagnosing APD; the majority of patients with progesterone hypersensitivity presented after exposure to an exogenous synthetic progestogen. Interestingly, all but 1 patient in our series had a prior pregnancy. We also documented peripartum onset and flares in a subset of our patients. Pregnancy-associated APD flares may be explained by elevated progesterone levels before delivery,[4] rapid shifts in progesterone after delivery,[5] or stress of childbirth, as stress hormones can uncover or exacerbate various autoimmune diseases.[6]

Table 1.

Clinical and diagnostic features of 14 patients with APD

Clinical presentation	Number of patients (%)
Urticaria	9 (64.3)
with angioedema	5 (35.7)
with anaphylaxis	2 (14.3)
with aphthous ulcers	6 (42.9)
Dermatitis	4 (28.6)
Erythema multiforme-like	1 (7.1)
Fixed drug eruption	1 (7.1)
Association of APD with pregnancy	
History of prior pregnancy	13 (92.9)
Postpartum onset	1 (7.1)
Onset in third trimester of pregnancy	1 (7.1)
Progesterone exposure	
Prior use of external progesterone (OCPs or IUD)	9 (64.3)
Progesterone skin test	9 (64.3)
Positive	6 (42.9)
Negative	3 (21.4)
Dermatopathology	
Nonspecific dermatitis	3 (21.4)
Superficial and deep perivascular lymphocytic inflammation	2 (14.3)
Urticaria	1 (7.1)
Lichenoid interface inflammation	1 (7.1)

IUD, intrauterine device.

Diagnostic tests

Intradermal progesterone tests may be used to help diagnose APD.[2] However, only 6 patients in our study had a positive intradermal progesterone test. One research team performed intradermal progesterone testing on healthy controls without APD characteristics and found a 90% false-positive rate.[7] It is unclear if progesterone testing is required for diagnosis of APD: the test has unknown sensitivity and specificity, and test results do not typically change management. Progesterone allergy testing is not standardized; there are different preparations, dosages, and time delays until patients become reactive.[8] A reaction to the oil preparation may interfere with interpreting reactions to progesterone reactive.[8] In APD patients presenting with urticaria and/or anaphylaxis, the intradermal skin test may potentially be of more value. However, larger studies are needed to further clarify the utility of testing. Skin biopsy may be helpful in ruling out other diseases. Similarly, the highly variable dermatopathology findings reflect the range of clinical findings seen in APD. This reaffirms the diagnosis of APD remains a challenge, requiring further clarification of criteria and development of accurate diagnostic tests.

Treatment with OCPs

There are no well-established outcome measures for APD. The treatments have been described in a small number of patients with variable efficacies and side effects. The most common treatment attempted in our patient series was continuous combined OCPs, achieving partial control of disease activity in most patients. However, the numbers are too small to draw conclusions about the efficacy of treatment. One patient experienced flare of anaphylaxis on OCPs, so exposing patients to exogenous progestogens should be done cautiously for patients with

Table 2.

Attempted treatments and outcomes in patients with APD

Treatment (No. patients attempted)	Complete response	Partial response	No response	Side effects
Combined OCPs (4)		3[a]	1[b]	Anaphylaxis (1)
Gonadotropin-releasing hormone agonist (leuprolide) (3)	2	1		Hot flashes (1)
Hysterectomy with bilateral salpingo-oophorectomy (2)	1	1		
Progesterone desensitization (1)	1			Asthma flare during therapy (1)
Levonorgestrel IUD removal (1)	1			
Androgenic hormone (danazol) (1)		1		Virilization with smaller breasts and deeper voice (1)
Estrogen modulator (tamoxifen) (1)			1	
Spironolactone (1)			1	Palpitations (1)
Omalizumab (1)			1	
Colchicine (1)			1	

[a]Continuous type.

[b]Unknown if continuous or cyclical.

suspected APD. It is unknown if treatment outcomes depend on the exact progesterone derivative in combined OCPs.

Other treatments

Our patients also received a variety of other hormonal treatments aiming at hypothalamic-pituitary-gonadal axis suppression including gonadotropin-releasing hormone agonist (leuprolide) with satisfactory control of the disease in 3 patients. Other hormonal therapies such as danazol and tamoxifen were used in limited numbers and with variable results. Progesterone desensitization was another successful intervention although it was attempted in only 1 patient. Two similar studies note 75% and 67% complete response with progesterone desensitization.[1,2] Hysterectomy with BSO is effective treatment for APD as documented in 2 of our patients but requires shared decision-making regarding fertility and hormone replacement.[2]

Limitations

Limitations of this study include sample size and a patient cohort from a single institution. However, relative to its presumed rarity, 14 is a reasonable cohort size compared to a recent review article of 89 APD patients in the literature. We were also limited by a homogenous cohort who all identified as white, which reduces generalizability to broader populations. Additionally, our institution serves as a tertiary care referral center, so many patients have a consultative appointment and receive long-term care from a local provider. With additional follow-up, further delineation of disease course and treatment outcomes may have been elucidated.

Conclusions

In conclusion, we report the clinical, pathologic, diagnostic, and treatment outcomes of APD for 14 adult women. APD lacks universal diagnostic measures and criteria, contributing to a significant delay in diagnosis. Developing accurate tests, establishing diagnostic criteria, and treatment outcome measures in multicenter, large-scale studies are needed.

Author contributions

N.A.: Methodology, investigation, data curation, writing – revision.
N.A.B.: Investigation, formal analysis, data curation, writing – original draft.
R.R.T.: Conceptualization, writing – revision, visualization, supervision.
M.A.P.: Writing: data curation editing and revision.
D.M.R.D.: Conceptualization, methodology, writing – editing and supervision.

Conflicts of interest

None.

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Study approval

N/A.

Patient consent

Informed, written consent was received from all patients and confirmed to the journal pre-publication, stating that the patients gave consent for their photos and case history to be published.

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