



Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Autoimmune progesterone dermatitis: Update and insights☆☆☆

Tegan Nguyen, A. Razzaque Ahmed *

Center for Blistering Diseases, Department of Dermatology, Tufts University School of Medicine, Boston, MA, USA

ARTICLE INFO

Article history:

Received 1 November 2015

Accepted 6 November 2015

Available online xxxx

ABSTRACT

Autoimmune progesterone dermatitis (APD) is rare autoimmune hypersensitivity reaction to the fluctuations of endogenous progesterone during a woman's menstrual cycle. It has a wide spectrum of clinical presentations including urticaria, eczema and vesiculobullous eruptions. The disease course depends on treatment modality. The pathogenic mechanisms of APD remain to be elucidated.

Objective: We aim to review the literature on APD and evaluate the different theories of pathogenesis and treatments for this condition.

Methods: A review of the English literature on APD was performed using PubMed, EMBASE and MEDLINE.

Results: 89 patients are included in this review. Initial symptom development in association with the menstrual cycle was reported in 65 (73%) patients. In some patients, it occurred shortly after hormone therapy (8.9%) or in relation to a pregnancy (14.6%). Associated factors were not defined in three patients (3.4%). Nearly 45% had a history of exposure to exogenous progesterone. Diagnosis of APD was usually confirmed with an intradermal progesterone sensitivity test. The goal of treatment was to suppress progesterone secretion through anovulation. Some cases were controlled with oral contraceptives or conjugated estrogen, while some patients had complete resolution post-hysterectomy.

Conclusion: The wide spectrum of clinical presentations, histology, and response to therapy would suggest that there are multiple subsets in APD. The increase in the levels of progesterone may also influence the clinical profile and the corresponding immunological response. Further research on the pathogenesis of APD is required to provide a satisfactory treatment modality.

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☆ There are no funding sources.

☆☆ The authors have no conflict of interest to disclose.

* Corresponding author at: Center for Blistering Diseases, 697 Cambridge St, Suite 302, Boston, MA 02135, USA. Tel.: +1 617 562 1045; fax: +1 617 562 1047.

E-mail address: arahmedmd@msn.com (A. Razzaque Ahmed).<http://dx.doi.org/10.1016/j.autrev.2015.11.003>

1568–9972/© 2015 Published by Elsevier B.V.

Please cite this article as: Nguyen T, Razzaque Ahmed A, Autoimmune progesterone dermatitis: Update and insights, Autoimmun Rev (2015), <http://dx.doi.org/10.1016/j.autrev.2015.11.003>

1. Introduction

Autoimmune progesterone dermatitis (APD) is a rare skin reaction to progesterone that occurs exclusively in women of childbearing age. Symptoms appear 3–10 days prior to menses, coinciding with the luteal phase of the menstrual cycle, and remit shortly after menstruation [1]. APD has also been reported in women undergoing in-vitro fertilization (IVF) [1,2]. Clinical presentations include urticaria, erythema multiforme, vesicular and bullous eruptions and anaphylaxis [3]. The histopathologic findings are non-specific and often correlate with the lesion morphology [4]. The diagnosis of APD is based on correlations of symptoms with the menstrual cycle and confirmed with either an immediate or delayed skin and/or systemic reaction to an intradermal progesterone (IDP) injection.

The pathogenetic mechanisms of APD are not known. It is hypothesized that prior exposure to exogenous progesterone may have sensitized some patients in such a manner that subsequent exposure produces an immune reaction. Cross-sensitivity to different steroid groups had been suggested as the mechanism in patients with no prior exposure [5].

This review discusses the clinical presentation, diagnosis, theories on the pathogenesis, and treatments of APD based on published cases in the English literature.

2. Materials & methods

A search of English language publications was performed using PubMed, EMBASE and MEDLINE with the following key words: autoimmune progesterone dermatitis, cyclical urticaria, progesterone allergy, and cyclic autoimmune hypersensitivity.

The following inclusion criteria were used: 1) female patients with recurring dermatitis, coincident with the luteal phase of the menstrual cycle; 2) positive skin or systemic reaction to a progesterone challenge; and 3) clinical resolution with ovulation suppression therapies.

The following information was obtained from the cases present in the literature: 1) age at onset of clinical disease; 2) previous and/or current oral intake or injections of hormone therapy; 3) clinical features; and 4) treatments and clinical outcomes at time of reporting.

3. Results

Eighty-nine patients reported in 66 publications were found to fulfill the inclusion criteria [1–4,6–67]. The mean age of onset was 27.3 years (range 12–47). The initial onset and continuing development of symptoms in relation to different factors are as follows.

3.1. Relationship to the menstrual cycle

65 out of 89 (73.03%) patients had recurring symptoms on a monthly basis in relation to the menstrual cycle. Specifically 54 out of the 65 (83.08%) developed new lesions less than ten days before the onset of menstruation. Symptoms occurred on day one of menstruation in four patients (6.15%) [2,20,33,42], mid-cycle in four patients (6.15%) [10,24,27,66] and continuously with exacerbation prior to menses in three patients (4.62%) [19,21,34].

3.2. Relationship to pregnancy

Onset of APD was initially reported in 13 out of 89 (14.61%) patients in relation to a pregnancy. Disease occurred postpartum in seven [2,15,17,18,28,30,31]. In six patients, it occurred intrapartum [14,16,32,37,46]. No specific time during the pregnancy was specified.

3.3. Relationship to hormone therapy

Symptoms of APD presented shortly after the initiation of progesterone therapy in eight patients (8.99%). Progesterone based therapy

included combination estrogen–progesterone oral contraceptives in four patients [9,21,47,63] and progesterone injections for IVF treatments in three patients [1,2].

3.4. No defined relationship

The onset of symptoms, in relation to the menstrual cycle, was not mentioned in three patients (3.37%).

3.5. History of exogenous progesterone

40 out of 89 (44.94%) patients had previous exposure to exogenous progesterone therapy. 17 (19.1%) patients were unaware of previous exposure. In 32 (35.96%) patients, previous history was not mentioned.

3.6. Clinical presentations

Patients presented with a wide spectrum of cutaneous manifestations in APD (Table 1). 43 (48.31%) patients had varying severity and extent of urticaria. Other frequently reported clinical presentations included vesiculobullous eruptions in 15 (16.85%), erythema multiforme in 10 (11.24%), eczema in nine (10.11%), maculopapular eruptions in eight (8.99%), purpura/petechiae in two (2.25%), and fixed drug eruption and stomatitis in one each (1.12% each). Some of the different clinical presentations of APD are presented in Fig. 1 (A–C).

Patients consistently experienced the same symptoms with each flare (Table 2). Symptoms were not mentioned in 31 (34.83%) patients. The most common symptom was pruritus reported in 37 (41.57%) patients followed by respiratory distress in 12 (13.48%) patients. Angioedema and/or edema of the extremities were reported in five (5.62%) patients, all of whom had urticarial lesions. Three (3.37%) patients complained of soreness with burning and pain at the site of the cutaneous lesions. One (1.12%) patient had weight loss with diarrhea [24].

3.7. Distribution of lesions

The clinical presentation was relatively constant with each recurrence in the majority of patients. One patient who initially had recurring urticaria and respiratory symptoms developed fixed drug eruption-like erythema after an IDP challenge [67]. Extensive lesions that involved three or more anatomical areas of the body are considered generalized. 41 (46.07%) patients were reported to have a generalized distribution of skin lesions. In 11 of the 41 patients with generalized disease, involvement of the oral, genital or perineal mucosae was reported. Clinical disease observed in less than three different anatomical sites of the body is considered localized. Localized distribution was reported in 43 (48.31%) patients, 10 of whom had mucosal lesions in addition to cutaneous lesions. Distribution was not mentioned in five (5.62%) cases.

3.8. Diagnostic tests

The diagnosis of APD is based on clinical history and often confirmed by evidence of a skin reaction to a progesterone intradermal or

Table 1
Clinical presentations of autoimmune progesterone dermatitis.

Morphological types	Patients n = 89
Urticaria	43
Vesiculobullous eruptions	15
Erythema multiforme	10
Eczema	9
Maculopapular eruptions	8
Purpura/petechiae	2
Fixed drug eruption	1
Stomatitis	1



Fig. 1. The clinical features of autoimmune progesterone dermatitis. (A) Erosions of the oral mucosa and (B) erythematous plaques on the forearm and wrist of a patient with features of erythema multiforme. (C) Urticaria on the upper right thigh. (D) Intradermal study with serial dilutions of progesterone in an aqueous suspension. A positive test demonstrated erythema and induration at the site of injection labeled P.

*The above photographs were obtained and reprinted by written permission of the publisher. [Jenkins J, Robinson-Bostom L, Girolomoni G, Kroumpouzou G. Autoimmune progesterone dermatitis. In: Kroumpouzou G, editor. Text Atlas of Obstetric Dermatology, Philadelphia: Lippincott Williams & Wilkins; 2014, p.57–65.]

intramuscular challenge. The test is considered positive with the development and persistence of a wheal-and-flare reaction within a 24 to 48 hour period. A positive cutaneous response to an IDP challenge in a patient with APD is presented in Fig. 1D. 67 patients underwent IDP challenge with varying concentrations of progesterone (dilution range 0.01%–1%). Wheal-and-flare reaction was noted at injection sites in 64 out of 67 patients. Three patients did not develop skin reaction. Six patients had subsequent wheal-and-flare reaction with intramuscular progesterone (IMP) injections (range 12.5–25 mg).

Eleven patients who did not undergo either IDP or IMP challenge had other laboratory studies such as progesterone skin prick test, eosinophil count, and quantitative measurements of immunoglobulin and complement. Hormone levels such as luteinizing hormone, follicular stimulating hormone, progesterone and estradiol were also measured. One patient developed erythematous papules 24 h after the insertion of a vaginal progesterone pessary [30]. Clinical improvements with ovulation suppression therapy, including conjugated estrogen and gonadotropin-releasing hormone (GnRH) therapy, supported the diagnosis of APD in two patients who did not undergo a progesterone challenge [44,66].

Diagnostic studies were not mentioned in five patients. They were diagnosed with APD based on clinical history. A summary of the diagnostic tests and findings is described in Table 3.

Table 2

Associated symptoms with autoimmune progesterone dermatitis.

Symptoms	Patients n = 89
Pruritus	37
Respiratory distress	12
Angioedema	5
Burning/soreness/pain	3
Weight loss/diarrhea	1
None/not mentioned	31

3.9. Treatments & outcomes

In the majority of patients, disease control and/or remission was achieved after several trials of different therapies. Clinical outcomes are defined as follows: disease control was the healing of old lesions with fewer and less severe new lesions/symptoms with therapy; partial remission was the absence of recurrence with therapy; and complete remission was the absence of disease off all therapy.

The final treatment and clinical outcomes at time of reporting are summarized in Table 4. Patients were advised to avoid known food and chemical allergens during treatment and follow-up periods. The majority of patients achieved remission, including 27 (30.3%) in partial remission and 27 (30.3%) in complete remission. Four out of 27 patients who achieved complete remission did not undergo any treatment and had a spontaneous remission [18,32,37]. Recurrences were observed in 11 (12.3%) patients and disease control was reported in 21 (23.6%). Treatment outcome was not reported in three (3.4%) patients, one of whom was lost to follow-up.

The majority of patients were consistent with their follow-up schedules. One patient, who failed a trial of combination OCP, was lost to follow-up after starting GnRH therapy [4]. The mean follow-up period was 22.3 months (range 1–204 months) for 71 patients. Duration of follow-up was not mentioned or specified in 18 patients.

4. Discussion

APD is a rare dermatological condition that affects women of child-bearing age. 89 female patients from the literature were found to fulfill the inclusion criteria for this review. While initial symptom onset was reported in association with different factors, all patients had recurring symptoms in relation to the menstrual cycle.

A hormone found principally in the corpus luteum, progesterone contributes to different stages of the reproductive cycle, including

Table 3
Clinical diagnostic studies of patients with autoimmune progesterone dermatitis^a.

Diagnostic findings	IDP	IMP	Other Studies						
			SPT	Menstrual fluid injection	Progesterone pessary	Oral Estrogen ^c	Ig/complement levels	Eosinophil count ^b	GnRH ^c
Positive	64	6	2	1	1	1	1	1	1
WNL	3	0					3		

IDP – intradermal progesterone; IMP – intramuscular progesterone; Ig – immunoglobulin; SPT – skin prick test to progesterone; WNL – within normal limits.

^a Diagnostic studies were not reported or performed in five patients.

^b Elevated eosinophil count (normal < 350 cells/mL).

^c Patients' symptoms improved with ovulation suppression therapy.

oocyte maturation and embryo implantation [68]. It also modulates immune functions. In-vitro experiments have demonstrated direct effects of progesterone on the functions of the cells of the immune system [68,69]. However, the mechanisms by which patients develop progesterone sensitivity and subsequently APD are not known.

Some researchers hypothesized that the uptake of exogenous progesterone by antigen presenting cells and subsequent stimulation of T helper cells may have resulted in sensitization [3]. Nearly 50% of patients had previous exogenous progesterone therapy. Seven patients developed symptoms shortly after exposure to exogenous progesterone. Cyclic recurrence in association with the menstrual cycle in these patients favored the diagnosis of APD.

The concept of hormone sensitivity raises several concerns since progesterone is an endogenous hormone. Investigators have presented the following hypothesis to explain the onset of APD in patients without known exposure to exogenous progesterone: It may be possible that some women can only tolerate low levels of the hormone [5]. They develop an inflammatory response as the levels rise in certain physiological states [5], with the high levels of progesterone varying from patient to patient. This may to some extent account for variations in the clinical presentations and responses to different therapeutic modalities. This hypothesis may also explain the development of the disease during pregnancy, when the levels of progesterone are 10 to 5000 times higher than the pre-pregnancy state [5].

Another mechanism for sensitization may be hormone cross sensitivity [5,70]. This could possibly explain the onset of disease in patients who did not have previous exposure to exogenous progesterone. A cutaneous patch study with hydrocortisone, 11-deoxycortisol, and 17- α -OH-progesterone, the precursor of progesterone, suggested a possible relationship between the steroid groups [70]. In the study, five out of 19 women with known hydrocortisone sensitivity had a positive cutaneous reaction to 17- α -OH-progesterone [70]. A subsequent study did not confirm such a relationship, suggesting that 17- α -OH-progesterone may be an unreliable patch test agent [71].

The expression of the progesterone receptor (PR) and the detection of PR mRNA transcripts in cultured human keratinocytes, may in part, account for the preponderance of cutaneous lesions in APD [72]. Biopsies of inflammatory skin lesions in disease entities such as pruritic urticarial papules and plaques of pregnancy, urticaria and psoriasis demonstrated the presence of the progesterone receptor in suprabasal epidermal cells [72]. The presence of the progesterone receptor was greater on keratinocytes with inflammatory cell infiltrates in the dermis [72]. These observations suggest that progesterone may directly affect the keratinocytes in patients with APD. Immunohistochemistry studies that focus on the expression of PR in patients with APD may provide some insights on its pathogenesis.

The different clinical manifestations of APD (Fig. 1A–C) may possibly be due to multiple mechanisms involved in the pathogenesis. For instance, some patients had an immediate urticarial reaction to the IDP challenge, suggesting immunological Type I IgE-mediated hypersensitivity reactions. Type IV immune reactions, which are T cell-mediated, may explain the delayed, eczematous reaction observed in some patients [73]. APD has also been described in one case series in which three sisters were affected [3]. Genetic studies

of HLA alleles may elucidate possible familial linkage disequilibrium in this disease.

While the onset of symptoms during the luteal phase favors the diagnosis of APD, differential workup should include tests to rule out disorders with prominent premenstrual flares [73]. Jenkins et al recommended testing with serial dilutions of aqueous progesterone in one arm and saline solution as the control in the contralateral arm to confirm diagnosis [73]. Intradermal tests should be used with caution in some patients as they may result in anaphylaxis reactions [33]. Some authors have recommended treating the patient with a gonadotropin releasing hormone agonist (GnRH) over a six-month period to prevent ovulation [66]. At the conclusion of GnRH therapy, a flare of the disease through an IDP challenge would provide support for progesterone sensitivity [66].

The goal in treating APD is to suppress ovulation by eliminating the surge of progesterone during the luteal phase of the menstrual cycle. Various treatments have been described but most have been published as case reports. Thus comparative analysis on the response to individual approaches to treatment is challenging.

23 (26.7%) patients were initially treated with oral H₁ and H₂ antihistamines. Only one patient achieved and maintained partial remission for eight months with H₂ antihistamine therapy, which she took only during menstruation [56]. Thus antihistamines may be of benefit in providing symptomatic relief and could be used as adjuvants with other therapies.

44.94% of patients diagnosed with APD had a history of exogenous progesterone exposure, most commonly from OCP. Nevertheless OCP was commonly used as initial treatment and seven patients had partial remission with continuing OCP therapy. Complete clinical remission was not observed possibly due to the fact that all commercially available hormone contraceptives contain progestin [74], which may exacerbate the disease as observed in one patient [31].

Conjugated equine estrogen and ethinyl estradiol therapy resulted in eight patients achieving partial remission and one patient attaining complete remission at the time of reporting. The pharmacological effects of estrogen therapy are mediated by interactions between the subtypes of estrogen receptors [75]. The doses of estrogen therapy in these patients were often high. This may pose a long-term risk for endometrial cancer [76] and possibly reduce the cardioprotective effects of estrogen therapy [75].

GnRH had helped patients achieve partial remission on therapy [17,31,64]. The use of GnRH therapy was limited to six months because of the side effects from estrogen suppression [31]. Some of the reported side effects included vaginal dryness, hot flashes and decreased bone density [73,77]. Hence GnRH may be most beneficial to patients who are in the perimenopausal period.

Tamoxifen is a selective estrogen receptor modulator and may cause symptoms of estrogen withdrawal similar to GnRH [78]. Long-term use of tamoxifen may increase the patient's risk for thromboembolism and uterine cancer [78]. Tamoxifen acts as a partial agonist to the estrogen receptor in the endometrium and its use has been linked to endometrial cancer in some women [79]. Reports on the use of the alkylated steroid danazol were also limited [52]. The side effects of abnormal hair growth and hepatic dysfunction may have limited its use

Table 4
Reported treatments of patients with APD in the literature.

Therapies	Clinical outcomes							
	Recurred		Disease control		Partial remission		Complete remission	
	Patients	Reference	Patients	Reference	Patients	Reference	Patients	Reference
None			1	[48]			4	[18,32], [37] (2)
Antihistamine with or without topical CS	5	[9,32,43,59,60]	4	[30,37,45,47]	2	[56,67]		
Systemic CS	2	[21,29]			2	[24,51]		
OCP			2	[37,41]	7	[2] (2), [6,10,11,50] (2)		
CE/EE	1	[28]	8	[2,8,21–23,25,44,59]	8	[7,10,12,14], [21] (4)	1	[55]
Tamoxifen					5	[20,27,35,39,62]		
GnRH	2	[13] (2)	3	[13] (2), [26]	3	[17,31,64]	4	[50,58,63,65]
Danazol			2	[52] (2)				
Progesterone desensitization	1	[2]	1	[54]			4	[1], [2] (2), [19]
TAH-BSO							14	[3,15,16,33,34,36,38,40,42,46,49,53,61,66]
Total # of patients	11		21		27		27	

APD – Autoimmune Progesterone Dermatitis; CS – corticosteroids; CE/EE – conjugated estrogen, ethinyl estradiol; GnRH – gonadotropin releasing hormone; OCP – oral contraceptive; TAH-BSO – total abdominal hysterectomy bilateral salpingo-oophorectomy.

[52,73]. The intermittent use of either tamoxifen or danazol during the perimenstrual period may decrease the risk of aforementioned side effects [5,73].

In patients who desired definitive therapy, hysterectomy and bilateral salpingo-oophorectomy may be an option. All patients who elected for this surgery had complete resolution of symptoms within a month. Since APD most commonly occurs in women during the fertile, childbearing years, surgery should be reserved for severe cases of APD, or for patients who do not desire having children or have already completed their families. The risk and benefits of hormone replacement therapy (HRT) in women with surgical menopause have been discussed [80].

Desensitization with progesterone has been reported to be effective in patients undergoing IVF [2]. The protocol involved increasing doses of vaginal progesterone suppositories that eventually resulted in successful pregnancies [2]. Some authors have also proposed a different protocol for desensitization [5]. Patients would receive increasing doses of progesterone injections at monthly intervals until a negative skin test is obtained [5]. Preliminary reports suggest a favorable outcome but development of latent autoimmunity in genetically susceptible individuals may be of concern [5].

The explanation for spontaneous remission in four patients is unknown [18,32,37]. One patient reported initial symptoms intrapartum that continued erratically in subsequent pregnancies and occasionally postpartum. She eventually had complete remission without therapy.

5. Conclusion

The spectrum of clinical presentations and varied responses to different therapeutic modalities make it rather challenging to provide a uniform or generalized opinion. Nonetheless, certain features are more common than others. In the majority of patients, the clinical manifestations occur ten days before the commencement of the menstrual cycle. When associated with pregnancy, it continues postpartum. In at least half of the patients, exogenous exposure to progesterone can be documented. The majority of patients complained of pruritus. Half of the patients had urticaria and several had angioedema associated with respiratory distress.

Nearly 50% of patients had generalized distribution of cutaneous disease, suggesting a systemic reaction. Most of the patients had a positive reaction on skin testing with varying doses of progesterone injections. The only therapeutic intervention that produced complete remission is oophorectomy with salpingo-hysterectomy. In some patients, complete clinical remission may be achieved with conjugated estrogen, GnRH and desensitization procedures.

Cumulative evidence from available data included in this report would suggest that APD is not a homogeneous disease. The wide spectrum of clinical presentations, histology, and response to therapy would suggest that there are multiple subsets within this spectrum. The increase in the levels of progesterone may also influence the kind of clinical manifestations it produces. This may account for multiple pathogenetic mechanisms, each defining a different subset. Therefore since what had been described as APD may have been reactions to hormonal fluctuations. The disease entities could be defined by the clinical profile, such as progesterone-associated erythema multiforme and progesterone-associated urticaria.

Itsekson et al have developed a murine model to study exogenous estrogen hypersensitivity in recurrent abortions [81]. This model could be used to study the effects of exogenous and endogenous hormones in recurrent dermatoses. Such studies have the potential to advance our understanding of progesterone hypersensitivity and the resulting clinical subsets.

Most autoimmune diseases are associated with a self-antigen to which an immune response develops. Allergic urticaria is an IgE-mediated reaction that is typically seen in patients with allergy to environmental agents. An example is melittin in bee venom [82,83]. These

patients may present with a spectrum of clinical prototypes ranging from localized to generalized urticaria or anaphylaxis [82]. In Hashimoto's thyroiditis, an autoimmune response is produced to thyroglobulin which is the target antigen and a hormone [84]. In these patients, treatment consists of hormone replacement [84]. Systemic lupus erythematosus (SLE) had been characterized as a heterogeneous disease due to the wide range of clinical manifestations associated with different autoantibodies or clusters of autoantibodies [85]. The types of autoantibodies in a patient with SLE may predict the clinical phenotype and the disease course [85]. In *Toxicodendron* dermatitis, patients may present with erythema, vesicles or large bullae after contact with the plant resin urshiol that is commonly found in poison ivy, poison oak, and poison sumac [86]. In each of these diseases, there is a spectrum of clinical presentation in which there are periods of relapses and remissions.

In the opinion of the authors, in autoimmune progesterone dermatitis, the vast spectrum of clinical presentation may be a consequence of the level of progesterone produced in any patient. These levels may also play a critical role in the nature of the immune response that follows. Different levels may result in different types of immune response and clinical phenotypes. The fluctuations in progesterone levels may also account for its cyclic pattern. The ability to block progesterone often results in a positive clinical outcome. The relative elimination of it by a total hysterectomy may produce a lasting remission. A multicenter study may enhance our understanding of the diverse pathogenic mechanisms and capacity to produce better and specific modalities of treatments to induce lasting, sustained remission.

Take-home messages

- Autoimmune progesterone dermatitis is a rare skin disease that affects women of childbearing age.
- The morphology of the lesions is variable.
- The severity of symptoms and the nature of the immune response may reflect the levels of progesterone during the luteal phase.
- Diagnosis in many patients can be confirmed by intradermal testing with progesterone.
- Treatment consists of blocking the biological activities of progesterone or eliminating its production.

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