

## CASE REPORT

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# Autoimmune Progesterone Anaphylaxis

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## ABSTRACT

Progesterone induced dermatitis is a rare disorder. It typically occurs in females due to an autoimmune phenomenon to endogenous progesterone production, but can also be caused by exogenous intake of a synthetic progestin. Here in, we present a case of autoimmune progesterone anaphylaxis (AIPA) observed in an adolescent female.

The patient is an 18-year-old Caucasian female with no significant past medical history and no prior exogenous hormone use, who presented to her primary care physician complaining of cyclic skin eruptions with dyspnea, cough and respiratory distress. She noted that her symptoms occurred monthly, just prior to her menses. An intradermal skin test using 0.1 cml of progesterone was performed. The patient developed a 15mm wheal after 15 minutes, confirming the diagnosis of AIPA. The patient was started on a continuous regimen of an oral conjugated estrogen (0.625mg). The skin eruptions and respiratory symptoms have not returned since the initiation of this therapy.

Autoimmune progesterone dermatitis manifests via the occurrence of cyclic skin eruptions. Women with the disorder commonly present with dermatologic lesions in the luteal phase of the menstrual cycle, if there are any other organ involvement in addition to skin (e.g. lung, GI) the reaction should be called as autoimmune progesterone anaphylaxis. Diagnosis of AIPA is confirmed by performing a skin allergen test using progesterone.

**Key words:** Anaphylaxis; Autoimmune; Progesterone

## INTRODUCTION

While many women complain of worsening acne and water retention during their menstrual cycle, there are a small number in whom the menstrual cycle is

associated with a variety of other skin manifestations such as urticaria, eczema and angioedema and rarely symptoms of asthma or anaphylaxis. This condition is known as autoimmune progesterone dermatitis (APD) due to the fact that progesterone is most frequently identified as the etiologic agent.<sup>1,2</sup> The clinical symptoms of APD (eczema, urticaria, angioedema, etc.) usually begin 3–10 days prior to the onset of menstrual flow and end 1–2 days into menses. Severity

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of symptoms can vary from nearly undetectable to anaphylactic in nature and symptoms can be progressive.<sup>3,4</sup> The age of onset is variable, with the earliest age reported at menarche.<sup>5</sup> The symptoms of APD correlate with progesterone levels during the luteal phase of the menstrual cycle.<sup>6</sup> Skin test results with progesterone have shown immediate reactions (within 30 minutes), delayed reactions (24–48 hours later), reactions with features of both immediate and delayed reactions.<sup>7</sup> The diagnosis of APD requires an appropriate clinical history accompanied by an intradermal injection test with progesterone.<sup>8</sup> Some authors have recommended further tests to evaluate the immunologic evidence in APD. These include circulating antibodies to progesterone, basophil granulation tests, direct and indirect immunofluorescence to luteinizing cells of the corpus luteum, in vitro interferon- $\gamma$  release and circulating antibodies to 17- $\alpha$ -hydroxyprogesterone.<sup>9</sup> However, most case reports in the medical literature do not routinely check for serologic evidence of APD and when checked these markers have not always been found to be reliable. Autoimmune progesterone dermatitis is usually resistant to conventional therapy such as antihistamines. The use of systemic glucocorticoids, usually in high doses, has been reported to control the cutaneous lesions of APD in some studies, but not in others.<sup>10</sup> Current therapeutic modalities often attempt to inhibit the secretion of endogenous progesterone by the suppression of ovulation.<sup>11</sup>

### CASE REPORT

An 18 year old girl was referred due to cyclic skin eruptions with dyspnea, cough and respiratory distress. The patient noted that the urticaria began at the age of 13, and did not seem to have any obvious trigger. Each individual lesion would last from 12–24 hours, and the entire episode would last 3–4 days. Lesions would usually start on the face and then spread over the entire body (Figure 1), and with each episode she had dyspnea, noisy breathing and cough.

She had been visited by different physicians, including pulmonologist and dermatologists, and had been treated with a variety of medications including antihistamines, salbutamol (Inhaler), beclomethasone (Inhaler) with temporary relief in respiratory symptoms but no improvement in skin manifestations. In addition, she complained of occasional angioedema, usually at

the same time as the hives present.

There was family history of allergic rhinitis in her sister. Multiple laboratory tests had been unremarkable. These included CBC, ESR, immunoglobulins, CH100, C2, C3, C4, ANA, anti double-stranded DNA, chemistry panel, liver tests, TSH, T4, thyroid antibodies, rheumatoid factor. Upon further questioning, it was found out that the hives and/or angioedema would begin approximately 2-3 days prior to the onset of menses, and would last about 2 days into menses. The symptoms would occur with each episode of menses.

Physical examination showed diffuse wide spread figurate urticaria and mild respiratory distress with expiratory and inspiratory wheezing in chest examination. Allergy skin testing was performed with progesterone 50 mg/mL in normal saline. The prick test was normal, but a full strength intradermal test (0.01 ml full strength progesterone) revealed a 15 mm wheal with erythema. The histamine control showed a 9 mm wheal with 25 mm erythema, and saline control was 3mm and 5mm for wheal and erythema (Figure 2). the patient was diagnosed with autoimmune progesterone anaphylaxis, and conjugated estrogen (0.625mg) was started once a day as the treatment. Within one month, she had dramatic improvement in her urticaria and angioedema and respiratory symptoms.



**Figure 1. Skin manifestation in patient with autoimmune anaphylaxis**

### DISCUSSION

The first documented case of APD was reported in 1930. It was observed that a patient's premenstrual serum caused acute urticarial lesions.



**Figure 2. Intradermal skin test in patient with autoimmune anaphylaxis**

In addition, it was shown that the patient's premenstrual serum could be used to desensitize and improve the symptoms<sup>12</sup> Since 1921, approximately 50 cases of APD have been published in the medical literature, but reported case of autoimmune progesterone anaphylaxis is extremely rare. Our patient had respiratory syndrome in addition to skin eruption, thus regarding the World Allergy Organization definition it should be designated as anaphylaxis. The exact pathogenesis of it is unknown, and is thought to be related to hypersensitivity reaction to progesterone. The diagnosis of autoimmune progesterone anaphylaxis is made by an appropriate clinical history accompanied by an intradermal injection test with progesterone.<sup>13</sup> Current treatment modalities often attempt to inhibit the secretion of endogenous progesterone, but this may be unsuccessful. In cases believed to be due to an endogenous production of progesterone, several methods of therapy have been attempted. The ultimate goal of therapy is the suppression of ovulation, which will prevent endogenous hormone production as progesterone is only produced in ovulatory cycles. Currently, the first-line choice of therapy is a combination of oral contraceptive. If this treatment is ineffective, patients will be treated with danazol, gonadotropin releasing hormone analogs, tamoxifen, and oophorectomy with varying successes. In the presented case we were successful to manage the patient with only oral conjugated estrogen (0.625mg), once a day

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