Autoimmune Progesterone Anaphylaxis in a 24 Year Old Woman

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Progesterone hypersensitivity, also known as autoimmune progesterone dermatitis, is a rare clinical condition in which patients display hypersensitivity to endogenous or exogenous progesterone. It is characterized by the appearance of variable cutaneous manifestations in a cyclic manner; such manifestations appear at the end of the luteal phase of the menstrual cycle 3–10 days before menstruation when the progesterone levels are high, and resolve partially or completely a few days after menses.

APID occurs as the result of an autoimmune response to endogenous progesterone production but can also be caused by exogenous intake of a synthetic progestin. The disorder is not limited to ovulating females and has also been reported to occur during pregnancy, in the postpartum period, in post-menopausal women taking hormone replacement therapy, and even in men taking exogenous synthetic progesterone [1,2]. The age of AIPD onset is variable, with the earliest age reported at menarche.

The clinical symptoms of AIPD are variable and may include urticaria, eczematous eruptions, vesicles, pustules, erythema multiform, vulvovaginal pruritus and stomatitis, but rarely does the disorder present as an anaphylactic reaction [3,4]. In such cases the disorder is called autoimmune progesterone anaphylaxis. The diagnosis is clinically suspected and confirmed by progesterone-positive skin tests or intramuscular progesterone challenge test, or both. The definitive etiologic treatment consists of ovulation inhibition by pharmaceutical agents or by oophorectomy [1]. We report here a case of AIPA diagnosed in a 24 year old woman who had been suffering from recurrent anaphylactic attacks in the past but had never been properly diagnosed.

AIPD = autoimmune progesterone dermatitis

AIPA = autoimmune progesterone anaphylaxis

PATIENT DESCRIPTION

A 24 year old Caucasian woman, an immigrant from the Ukraine, was referred to our allergy clinic due to five episodes of anaphylactic attacks during the previous 2 years with no identifiable source. She had a lifelong history of non-seasonal allergic rhinitis and asthma that was treated with fluticasone propionate, budesonide/formoterol fumarate dihydrate and montelukast. At age 21, she was diagnosed as having chronic idiopathic urticaria and treatment with fexofenadine 180 mg once a day was started, without significant clinical effect. Since age 22 she had five episodes of anaphylactic attacks in the Ukraine and required emergency treatment for hypotension, giant urticaria, laryngeal edema, and asthma. Upon further questioning in our clinic, it was discovered that all urticaria/angioedema episodes began approximately 3–4 days prior to the onset of menses and lasted about 4 days into menses. All the anaphylactic attacks occurred 3–4 days prior to the onset of menstruation as well. The addition of hydroxyzine (Otarex®, Teva, Israel) 25 mg twice a day and ranitidine (Zantac®, GlaxoSmithKline, Israel) 150 mg twice a day did not prevent the attacks of anaphylaxis or reduce the severity of urticaria. The gynecologic history of the patient included intermittent use of oral contraceptives and one pregnancy with a miscarriage during the first trimester at age 21.

The physical examination was unremarkable except for mild urticarial rash. The complete blood cell count, erythrocyte sedimentation rate, immunoglobulins, antinuclear antibodies, anti-double-stranded DNA antibodies, chemistry panel, liver tests, thyroid-stimulating hormone, thyroxine, thyroid antibodies, CH50, C3, C4, C1 esterase inhibitor activity, 24 hour excretion of urinary 5-hydroxyindoleacetic acid and vanilmandelic acid were all normal.

Skin prick tests for aeroallergens were positive for dust mites, local tree pollen, grass and ragweed pollens. Skin prick tests revealed no sensitization to food allergens.

Since the flaring of urticaria/angioedema as well as the anaphylactic episodes were associated with the menstrual cycle, we performed an intradermal skin test using progesterone 50 mg/ml at dilutions of 1:10 and 1:1 in normal saline. Histamine was used as a positive control and normal saline as a negative control.

The immediate reaction was measured 15 minutes after intradermal injection of the test solutions, and the late reaction was measured at 48 hours. The results revealed a 25 mm wheal with 45 mm erythema response to progesterone. The histamine control showed an 8 mm wheal with 20 mm erythema and the negative control showed 2 mm wheal and 5 mm erythema. No late response was noted. The patient was diagnosed as having autoimmune progesterone anaphylaxis.

Treatment with conjugated estrogen 0.625 mg (Premarin®, Pfizer, Israel) once a day was started. The patient was also given one dose of gonadotropin-releasing hormone agonist triptorelin embonate S.R. 11.25 mg (Diphereline®, Ipsen, France). Within one month, there was a dramatic amelioration of her urticaria and angioedema, and the respiratory symptoms and these manifestations have not returned since initiation of the treatment.

COMMENT

Since Géber first described AIPD in 1921, approximately 50 cases have been published in the medical literature [5]. AIPA, on the other hand, is extremely rare with only nine cases having been reported to date. APID/AIPA is difficult to recognize because of its diverse clinical presentation. Women can suffer for many years before a diagnosis is made.

Due to the rarity of the disorder, AIPD should be considered a diagnosis of exclusion, and it is wise to first exclude more common skin disorders. According to Warin [5], there are three main criteria for diagnosing progesterone-induced dermatitis: a) skin lesions related to the menstrual cycle, b) positive response to intradermal testing with progesterone, and c) symptomatic improvement after inhibiting progesterone secretion by suppressing ovulation.

The pathogenesis of autoimmune progesterone dermatitis remains poorly understood and highly speculative. One theory is that antibodies that are formed in response to food, medication or viral antigens may cross-react with progesterone. Because both the skin and oral mucosa contain specific progesterone receptor sites, antigen will be preferentially deposited in these sites, leading to cutaneous inflammation.

A previous exposure to a synthetic progestin may stimulate the immune system to produce antibodies that cross-react with endogenous progesterone. Most patients, like the patient described here, have prior exposure to exogenous progestins; however, previous hormone use is not an absolute feature in this condition [1,5].

AIPD and AIPA are not responsive to antihistamines and steroids. The mainstay of treatment for AIPD/AIPA is to inhibit endogenous progesterone secretion by suppressing ovulation, as progesterone is only produced in ovulatory cycles. In our case, the GnRH3 analogue (Diphereline S.R. 11.25 mg) showed efficacy but other agents such as estrogens, tamoxifen, GnRH, luteinizing hormone-releasing hormone, dapsone or thalidomide can be used. If this disorder is caused by an exogenous administration of progestin, the medication should be discontinued. The skin eruptions will resolve once the offending agent is removed.

While in some patients the disorder completely resolves spontaneously, in others it requires chronic pharmacological treatment. The definitive treatment modality that can be offered to patients who no longer desire fertility or who are refractory to all the methods mentioned above is bilateral oophorectomy. Patients who have undergone this procedure have had complete resolution of AIPD outbreaks.

In conclusion, we report a case of autoimmune progesterone dermatitis that was misdiagnosed for a long time and treated without symptomatic improvement. AIPA was diagnosed following a comprehensive anamnesis that revealed the relationship between the appearance of symptoms and the timing of the menstrual cycle, and a positive response to an intradermal test with progesterone. The patient was successfully treated with GnRH analogues. AIPD should be included in the differential diagnosis of a female with recurrent eczema refractory to the conventional treatments.

GnRH = gonadotropin-releasing hormone

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It usually takes more than three weeks to prepare a good impromptu speech

Mark Twain (1835-1910), American author and humorist, most noted for his novels, *The Adventures of Tom Sawyer* and its sequel, *Adventures of Huckleberry Finn*