

Autoimmune Dermatitis associated with Endogenous Progesterone Hypersensitivity: a case report

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Abstract

Progesterone hypersensitivity (HP), also known as autoimmune progesterone dermatitis, is a rare condition with dermatological or systemic manifestations associated with progesterone, whether endogenous or synthetic. Its symptoms appear in the luteal phase and precede the menstrual flow a few days and may extend after the end of menstruation. The pathophysiology is still uncertain, and some hypotheses have been published in an attempt to explain the cases associated with both endogenous and synthetic progesterone. The diagnosis is clinical, but some tests are described in an attempt to help confirm the diagnosis. Hormonal contraceptives, antihistamines, corticosteroids and even bilateral oophorectomy are therapeutic options described. This paper describes the case report of a 28-year-old woman, nulliparous, with symptoms of macules and papules that started three days before the menstrual flow, without external triggering factor. After using a combined oral contraceptive and antihistamine, she progressed with significant clinical improvement. In view of these points and due to the scarcity of evidence on hypersensitivity to progesterone, it is essential to produce more studies on the clinical presentation, triggering factors and therapeutic possibilities for a better diagnostic elucidation and treatments of these patients.

Keywords: Hypersensitivity; Autoimmune Diseases; Progesterone; Dermatitis; Menstrual Cycle.

Introduction

Hypersensitivity to progesterone (HP), also known as autoimmune der-

matitis to progesterone, is a rare syndrome with dermatological and/or systemic manifestations associated with

progestogen, whether endogenous or synthetic [1]. The first case was published in 1964, when was described the appearance of heterogeneous vesiculobullous eruptions in a young patient, which clinically resembled dermatitis herpetiformis and was associated with the menstrual cycle, beginning in the premenstrual period. Since then, in the last 57 years, less than 200 cases of hypersensitivity to progesterone have been published, denoting its rare and not very enlightening [2,3].

The syndrome occurs predominantly in women of reproductive age, between 13 and 55 years, being more frequent after menarche and around 20 years of age [4,5]. The clinical presentation of this dermatitis is heterogeneous, with description of maculopapular rash, eczema, pustules, stomatitis, petechiae, purpura and may include systemic manifestations, which are rarer, such as anaphylaxis and bronchospasm [1,6].

Regarding its pathophysiology, the mechanism is still unclear. However, it is known that the etiology is closely related to progesterone in two ways: endogenous or exogenous. The first occurs without an external triggering factor and the second route occurs after the use of synthetic progestogen or after high doses of progestogen for assisted reproduction procedures [7,8].

Given the shortage of evidence regarding this rare syndrome and the need for further work on the clinical presentation, triggering factors and therapeutic possibilities, the following case of hypersensitivity to endogenous progesterone in a young patient is presented.

Case report

We report the case of a 28-year-old woman, single, referred from the dermatology service because of papules associated with menstrual flow and treated a Brazilian public gynecology service. The patient reported the appearance of pruritic and non-scaly macules and papules since menarche, which begin in the breasts and extend to the back, abdomen, buttocks, thighs and appear 3 days before menstruation and persist for 2 to 3 days after. menstrual flow.

The patient reported the appearance of pruritic and non-scaly macules and papules since menarche, which begin in the breasts and extend to the back, abdomen, buttocks, thighs and appear 3 days before menstruation and persist for 2 to 3 days after. menstrual flow. She reported that symptoms and signs partially improved after the use of antiallergic (dexchlorpheniramine), but with spontaneous return after the drug had been in action. Associated with the condition, before the menstrual flow, it

courses with swollen breasts, mild dysmenorrhea, increased intestinal rhythm and headache. She reports a history of allergic rhinitis and denies drug allergies and dermatitis.

She reports menarche at age 11. Regular cycles, lasting 28 days, moderate flow with exit of clots lasting 04 days and appearance of macules and papules. She reports sexarche at 16 years of age and inactive sexual life for 2 years. She was using a combined oral hormonal contraceptive (3mg drospirenone + 0.03mg ethinylestradiol) but stopped using it on her own 03 years ago. History of Sexually Transmitted Infection by HPV, diagnosed in 2020, where she performed electrocautery of the cervix. Nulliparous.

On physical examination, she was eupneic, comfortable on room air, and flushed. There were no elementary lesions on skin examination. During the medical appointment, the patient presented photographs recorded in October 2021 (see figures 1 and 2).

Initially, she was advised that the signs and symptoms suggested hypersensitivity to progesterone. Therapeutic possibilities were discussed and combined oral contraceptives (COC) were introduced, consisting of 75 mcg of gestodene + 20 mcg of ethinylestradiol continuously and the use of loratadine, if any lesions appear. The patient returned to the outpatient

clinic after 42 days for reassessment, informing that he made continuous use of ACHO and presented breakthrough bleeding lasting 01 day and mild hyperemia in the chest with smaller and slightly pruritic papules for 03 days. She used loratadine, as instructed, with improvement of symptoms.

The patient returned after 05 months to the clinic reporting that since the beginning of COC, she had 04 episodes of allergic manifestation. Such allergy is described with erythematous plaques on the chest, upper limbs and buttocks, associated with itching and local heat sensation. She shows improvement in these symptoms after single dose use of loratadine 10 mg. There are no reports of bronchospasm, anaphylaxis, going to the emergency room due to dyspnea or exacerbations of dermatitis.

Chosen together with the patient for not performing skin and intradermal tests of progesterone. Thus, follow-up was maintained in a teaching-assistance outpatient clinic and oriented about signs and symptoms of severity and the possibility of worsening of the lesions in case of pregnancy. This work followed the ethical guidelines established by the Declaration of Helsinki and the informed consent was signed in two copies.



Figure 1: Presence of papules and plaques in the anterior chest, without secondary lesions.



Figure 2: Enlarged image of the left breast with plaques and papules, which extend throughout the breast and proximal third of the left axilla, without desquamation or secondary lesions.

Discussion and Conclusion

Progesterone hypersensitivity is the most frequent catamenial dermatosis, despite being an uncommon condition and with less than 200 cases published in the literature. Foer et al. in 2016 they published a series of 24 reported cases of PH in the Allergy and Immunology section of Brigham Women's Hospital in Boston. They found a mean age for the onset of symptoms of 29.7 years (13 - 48 years), which agrees with our work, since the patient is 28 years old and since the age of 13, after menarche, the symptoms started [9].

There are two hypotheses that help to clarify the pathophysiology of the disease, although they are still unclear and uncertain. The first suggests that previous exposure to exogenous progesterone may have sensitized some patients, causing subsequent exposure to formulate immune complex deposition and produce an immune reaction. The second hypothesis, in turn, suggests that cross-sensitivity to different steroids would induce the production of antibodies against progesterone, which would explain dermatitis in patients without previous contact with progestogen [6,10].

Buchheit and Bernstein [6], in 2017, described the heterogeneity of dermatological and systemic lesions associated with HP, such as macules, papules, urticaria, erythema multiforme, vesicopustular lesions, vaginal itching, petechia and purpura, and even

anaphylaxis and angioedema. Our patient had macules and urticaria, with a condition that is in line with what is proposed in the literature. In addition, other relevant differential diagnoses such as atopic and contact dermatitis, chronic idiopathic urticaria and allergy to non-steroidal anti-inflammatory drugs (NSAIDs) and use of synthetic progestagen were ruled out [11].

Intradermal or patch testing was not performed. Foer and Buchheit [1] in a review of PH, warned that although some patients present with immediate Type I hypersensitivity, a positive test does not guarantee the presence of disease, just as a negative test does not rule out the diagnosis and there is no evidence of the predictive and negative values of such tests. In addition, skin test reagent preparations are not standardized. For these reasons, the diagnosis may be clinical based on the natural history of the disease and tests may be waived. Thus, when faced with a patient in the reproductive phase, with the appearance of macules and urticaria in the luteal phase of the menstrual cycle, with regular cycles, whose appearance of the lesions comprises 3 days before the menstrual flow and extends to 2 to 3 days after the end of the menstrual cycle. menstruation, without external triggering factors, its condition is compatible with hypersensitivity to endogenous progesterone.

Regarding treatment, the therapeutic options can be drug and surgical. Symptomatic drugs, which include

antihistamines and corticosteroids, are used to minimize urticaria, but their effect is limited to their duration of action and may have side effects, such as drowsiness [12]. The most used ovulation inhibitors are the COC that aim to avoid the variation of progesterone during the cycle and thus suppress the triggering factor. Still in this class, but used in refractory cases, there are: tamoxifen, analogues and antagonists of gonadotropin-releasing hormone.

These can cause some side effects secondary to hypoestrogenism, such as loss of bone mass and thus, their use within 03 months is prudent [11, 13]. The surgical alternative, such as bilateral salpingo-oophorectomy, is considered for severe cases, associated with angioedema or anaphylaxis and refractory to pharmacological options [13, 15]. Therefore, we started treatment with COC composed of gestodene and ethnilestradiol with the aim of inhibiting ovulation and associated with an antihistamine. As described, the patient showed a satisfactory response to therapy and was well adapted. It was informed that, if you wish to discontinue the use of COC in order to get pregnant, the symptoms may return during the trial period, as well as during pregnancy and postpartum [6, 16].

This work has some limitations. It is a descriptive study, and it is not possible to test hypotheses about the conditions associated with HP. It does, however, have some advantages: it is a guide, as it corroborates other case

reports on HP, and it strengthens the national literature. In addition, it confirms the importance of diagnosis based on clinical and temporal data, and although it does not test hypotheses, it elucidates that the clinical picture based on the natural history of the disease and its response to ovulation inhibition through hormonal treatment can help in the endogenous HP diagnosis.

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