

CASE REPORT

Progestogen hypersensitivity: case report

Hipersensibilidade ao progestogênio: relato de caso

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ABSTRACT

Progestogen hypersensitivity is characterized by heterogeneous skin eruptions that cyclically aggravate during the luteal phase of the menstrual cycle, corresponding to a rise in progesterone levels. The clinical presentation is highly variable, with urticarial, angioedema, and eczematous lesions being prominent. Both endogenous progesterone and exogenous progestogens may represent an initial trigger. We report the case of a 42-year old woman who was unresponsive to all treatments, including progestin desensitization, that ultimately required bilateral oophorectomy to control her symptoms.

Keywords: progestins, hypersensitivity, progesterone, hypersensitivity, pruritus.

RESUMO

A hipersensibilidade ao progestogênio é caracterizada por erupções cutâneas heterogêneas, que se agravam ciclicamente, durante a fase lútea do ciclo menstrual, correspondendo ao aumento dos níveis de progesterona. A apresentação clínica é variada, com lesões urticariformes, angioedema e eczema predominando. Ambos os progestogênios endógenos e exógenos podem atuar como os fatores desencadeantes iniciais. Nós relatamos o caso de uma mulher de 42 anos de idade que não respondeu a todos os tratamentos instituídos, incluindo a dessensibilização à progestina, culminando na ooforectomia bilateral para controle dos seus sintomas..

Palavras-chave: progestinas, hipersensibilidade, progesterona, hipersensibilidade, prurido.

INTRODUCTION

Progestogen hypersensitivity (PH) is a rare entity and a challenge for allergologists and gynecologists. This rare case of PH required oophorectomy as the patient was unresponsive to medical management/progesterone desensitization.

CASE DESCRIPTION

A 42-year-old, Caucasian woman, mother of one child, G1P1Ab0, with asthma/allergic rhinitis/atopic dermatitis history, already treated and investigated by her allergist, presented to her allergist's private office in January 2019 with recurrent maculopapular pruritic rash¹ involving the face, chest, and abdomen (Figure 1), which had been ongoing for two years. She sought medical help several times and

took oral H1-antihistamines/glucocorticoids, with temporary relief. Previous oral and vaginal contraceptives, each one used for six months, caused dyspnea or pruritus. She received a Levonorgestrel intrauterine implant in May 2017, developing, after three months, pruritus of increasing intensity over two months. Due to concerns that the implant could contribute to itching, it was removed, resulting in the complete temporary resolution of symptoms.

In June 2020, the patient returned with the same complaints and dyspnea. The three months before, she was diagnosed with depression and took antidepressant drugs without any results. One allergist diagnosed the condition as severe atopic dermatitis and prescribed Cyclosporine, which offered some relief but increased the blood pressure and was discontinued. Gradually, the patient observed her

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symptoms were cyclical, beginning with the luteal phase and improving after menstruation.

A progesterone skin prick test was negative and a progesterone-specific serum IgE assay (P-s-IgE) could not be performed, as this was not available in Rio de Janeiro. Although she intended to travel to the USA to be tested, the COVID-19 pandemic restricted flights from Brazil to the USA. Furthermore, serum shipment was delayed by local authorities, which would compromise the sample.

Based on the cyclical nature of the patient's clinical symptoms, a diagnosis of progestogen hypersensitivity was made. In January 2021, the patient started gonadotropin-releasing hormone (GnRH) inhibitor, resulting in complete improvement of the symptoms mid-cycle, but she continued with pruritus and skin lesions before and after menses. After three months on GnRH, she underwent a 10-day progesterone desensitization protocol². On the first day of desensitization, she developed pruritus and, by the third day, angioedema/cutaneous lesions arose, requiring discontinuation. An attempt with Tamoxifen alleviated some of the pruritus. While on GnRH and Tamoxifen treatments, the patient developed arterial hypertension and pain in the lower extremity, discontinuing these drugs.

Another attempt with Omalizumab was recommended, but, due to its off-label use, insurance would not approve it. Danazol was proposed but the patient decided she no longer wanted to suffer and opted for a therapeutic bilateral oophorectomy in May 2021, being symptom-free ever since.

DISCUSSION

Progestogen hypersensitivity, also referred to as autoimmune progesterone dermatitis, is a rare endogenous progesterone/synthetic progestins hypersensitivity reaction. "Progestogen" hypersensitivity is used rather than "progesterone" as it encompasses natural progesterone and synthetic progestins². PH can start at any time from menarche to menopause³.

Women typically report histories of current/prior exogenous progesterone exposure as risk factors; some experience symptoms without prior exogenous exposure. The symptoms correlate with endogenous exposure during menses or pregnancy². Oral contraceptive pills (OCP) are usually the primary exposure source. In 24 PH case reports, 58% had symptoms after previous exogenous exposure and 25% specifically OCP-related⁴. Rash and skin test positivity to *megestrol acetate* were reported in a male receiving progestins as an appetite stimulant³.

Exogenous progestins may induce P-s-IgE in susceptible patients. When patients are subsequently exposed to exogenous/endogenous progestogens, they react, due to cross-linking of these antibodies on mast cells³. Although the pathogenesis of PH is unclear, evidence favors the role of immediate/Type I hypersensitivity based on positive skin testing and/or a functional role of P-s-IgE, confirmed by basophil activation. Reports of delayed reactions to progesterone skin prick

or intracutaneous testing support a Type IV, cell-mediated mechanism. This later mechanism is further supported by a case report of a PH-Stevens-Johnson-like syndrome. Another report of progesterone-specific immunoglobulin G (IgG) antibodies was made, leading to immune complex deposition, consistent with a Type III reaction. Another report describes two patients: one with IgG containing a 17-hydroxyprogesterone binding component and the other with immune complexes, following challenge with medroxyprogesterone³.

Non-specific clinical presentations including urticaria, dermatitis, vesiculobullous eruptions, ulcerative stomatitis, erythema multiforme, purpura/petechiae, fixed drug eruption, pregnancy loss, dyspnea, and anaphylaxis were described^{5,6}, all presenting the pathognomonic feature of a cyclical rise in serum progesterone levels.

Diagnosing PH may be challenging. While positive testing may help support a diagnosis of PH, the positive and negative predictive value of progesterone skin testing is unknown and currently not considered useful. The diagnosis is largely based on the unique association of clinical presentation recurring with each menstrual period and can be confirmed by an intracutaneous progesterone challenge, an allergic test performed with injection of small and progressive amounts of progesterone to observe local/systemic allergic reactions.

Other diagnostic tests include a recently validated *in vitro* enzyme-linked immunosorbent assay to assess for P-s-IgE⁷, a leukocyte histamine release assay to assess basophil histamine release, and an interferon-gamma release assay to assess T cell-mediated activity related to progesterone. This later *in vitro* study demonstrates a TH1-type cytokine release pattern but remains experimental². A tissue biopsy is rarely indicated as it is usually non-diagnostic⁵.

Treatment options are determined based on the severity of the symptoms. Shared decision-making should be used when recommending treatment options and should take into consideration the patient's short and long-term goals and the impact of the disease on the quality of life. Symptomatic management using topical/systemic corticosteroids, antihistamines, and leukotriene modifying agents are seldom effective but should be considered and followed by omalizumab and/or the suppression of ovulation using selective estrogen receptors modulators, such as Tamoxifen or GnRH agonists, the latter confirming the diagnosis. Progesterone desensitization protocol reports are successful, but requires the patient to take a daily dose continually. The last treatment option, a surgical bilateral oophorectomy, should only be indicated in severe refractory cases, as the case reported herein⁵.

CONCLUSION

This case report describes a tumultuous journey of a PH patient who had her diagnosis delayed due to unrecognized symptoms of a cyclical nature and unavailability of confirmatory diagnostic testing.



Figure 1. Maculopapular rash over chest and abdomen (A) with and (B, C and D) after removal of the intrauterine implant; (C and D) eczematous lesions involving the face and periorbital region.

Bilateral oophorectomy was required as a wide range of other treatments had been poorly tolerated.

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DECLARATION OF PATIENT CONSENT

The authors certify they have obtained appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported. The patient understands her name will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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