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Case Report

A Case of Progestogen Hypersensitivity

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ABSTRACT

Progestogen hypersensitivity (PH) is a cyclical dermatosis that occurs in fertile women during the luteal phase of the menstrual cycle. The clinical presentation is variable and non-specific. We report the case of a 42-year-old woman with a 10-year history of itchy skin lesions that recurred monthly. Determined with her basal body temperature chart, her skin symptoms were related to progesterone surges. Skin examinations revealed multiple and extensive monomorphic red papules, mainly on her arms and legs, as well as on her chest and back. She had no history of associated fever or dyspnea. Her hair, nails and mucous membranes were normal. A blood test at the time of the worst skin eruption revealed mild elevation of serum thymus and activation-regulated chemokines and eosinophilia. Her total serum IgE level was normal. She showed a delayed skin reaction to progesterone. Ultra-low-dose combined oral contraceptives (COCs) improved her symptoms by suppressing ovulation. Accordingly, a diagnosis of progestogen hypersensitivity was made. A T-helper (Th)2 response rather than a Th1 response was suggested to be involved in this case. Atopic dermatitis (AD) can be classified into the major extrinsic type with high serum IgE levels and the minor intrinsic type with normal IgE levels. PH and AD share similarities in that they present with eczema, IgE-mediated sensitization and delayed hypersensitivity responses, and their pathophysiology remains to be fully elucidated because of their heterogeneous aspects. The symptoms of this case were in line with IgE-low AD rather than IgE-high AD, which implicates endogenous progesterone as a trigger.

Keywords
Progestogen hypersensitivity; Woman's issues; Dermatitis; Diagnosis.

INTRODUCTION

Progestogen hypersensitivity (PH) is a condition that typically occurs in women in childbearing years with a spectrum of symptoms, which includes urticaria with or without angioedema, dermatitis, and systemic anaphylaxis.[1] PH, also known as autoimmune progesterone dermatitis, was first described by Shelly et al[2] in 1964. In 2016, Foer et al[3] proposed the name PH because it is more likely a hypersensitivity reaction than an autoantibody reaction. The term, "progestogen," encompasses both natural progesterones and synthetic progestins, which can be triggers of the disease.[3] Because the pathogenesis of this disorder is unclear, there is no established method for the diagnosis of PH. A history of cutaneous eruptions beginning 3-10-days before the menstrual cycle that persists for several days into menses suggests a diagnosis of PH. The diagnosis is confirmed by the demonstration of progesterone sensitization. A therapeutic response with combined oral contraceptive (COC)) provides confirmation of the diagnosis of PH.[1,3]

CASE REPORT

The patient was a 42-year-old Japanese woman (gravidity, 0; parity, 0) with no remarkable medical history who presented with systemic red papules, which had recurred monthly for 10-years (Figure 1). The systemic skin eruption appeared approximately 7-days before menses, was worst on the first day of the period, and resolved spontaneously following menstruation without leaving post-inflammatory hyper/hypopigmentation. Previously unsuccessful medical managements included topical and oral steroids and antihistamines. A skin examination revealed multiple and extensive monomorphic red papules that were mainly located on her arms and legs, as well as on her chest and back . The lesions were pruritic and were not associated with fever or dyspnea. Her hair, nails and mucous membranes were normal. A blood test on the first-day of the period revealed mild elevation of serum thymus and activation-regulated chemokine (TARC) 1766 pg/mL; normal <450 pg/mL) and eosinophilia (eosinophil 560 /μL; normal 70-440 /μL). Her

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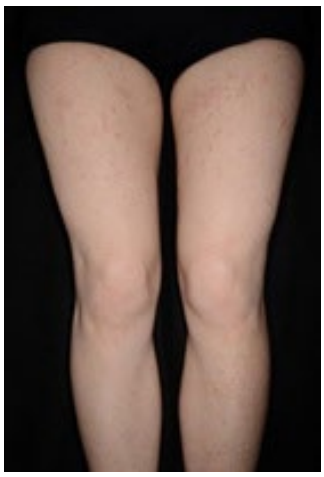
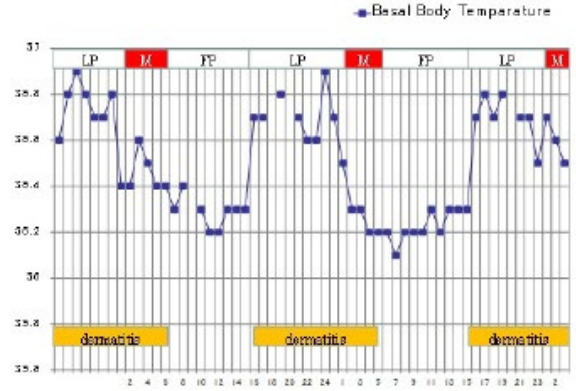
total serum IgE level was within the normal limits. A biopsy specimen from the right femur revealed spongiosis with perivascular inflammation. The results of intradermal testing (125 mg/mL of progesterone and 5 mg/mL of estrogen at dilutions of 1:1,000, 1:100, and 1:10 respectively, with saline solution as a control) were all negative until 48-hours later. At five-days after the test, at the same time as the cyclical eruption started to occur, strong erythema appeared in the skin challenge area. Since she had complained of not only eruptions but also premenstrual syndrome, she was prescribed ultra-low-dose COCs containing drospirenone and ethinyl estradiol. After the initiation of this treatment both her cutaneous and emotional symptoms showed improvement. In the present case, the patient's symptoms were related to progesterone surges (Figure 2). She had progesterone sensitization with a delayed skin reaction at the intradermal testing site. The ultra-low-dose COCs improved her symptoms by suppressing ovulation. Based on these clinical findings, a diagnosis of progestogen hypersensitivity was made.

Figure 1. *A Clinical Picture*



The Eruption on the Lower Limbs on the First Day of the Menstrual Period

Figure 2. *The Relationship between the Menstrual Cycle and Dermatitis*



The skin eruption appeared approximately 7-days before menses (at the beginning of the luteal phase), was worst on the first day of the period, and spontaneously resolved following menstruation without leaving post-inflammatory hyper/hypopigmentation.

DISCUSSION AND CONCLUSION

The pathogenesis of PH remains unclear but likely involves multiple mechanisms. Specific IgE to progesterone was measured in some cases, while delayed hypersensitivity was shown in others.[1] The increased serum TARC, eosinophilia and the normal level of serum IgE at the time of the worst skin eruption and the delayed skin reaction suggest that T-helper (Th)2 response rather than a Th1 response was involved in this case.

Atopic dermatitis (AD) can be classified into the major extrinsic type with high serum IgE levels and the minor intrinsic type with normal IgE levels. AD is well known to be a Th2-polarized disease; however, the intrinsic type shows less Th2-skewing or relative overproduction of Th1 cytokine IFN-γ.[4] In a Japanese study, patients with IgE-low AD differed from those with IgE-high AD by their increased frequency of Th1-cells and lower TARC levels (mean±SD: IgE-high AD, 2430±2820 pg/mL; IgE-low AD, 851±771 pg/mL).[5]

Progestogen hypersensitivity and AD share similarities in that they present with eczema, IgE-mediated sensitization and delayed hypersensitivity responses, and the fact that their pathophysiology has not been fully elucidated because of their heterogeneous aspects.[1,5] The symptoms of case suggest IgE-low AD rather than IgE-high AD, which implicates endogenous progesterone as a trigger.

CONSENT

The authors have received written informed consent from the patient.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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