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Clinical characteristics of exogenous progestogen hypersensitivity

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Background: Autoimmune progesterone dermatitis is a rare disease characterized by eruption recurrence in the luteal phase of each menstrual cycle. As synthetic progesterones are increasingly used for assisted reproductive techniques (ARTs) for infertility or prevention of abortion, cases of dermatitis caused by exogenous progesterone have been reported.

Objective: To investigate the clinical characteristics of exogenous progestogen hypersensitivity (PH).

Methods: We retrospectively reviewed data from patients presenting with dermatitis induced by exogenous progesterone between 2011 and 2016.

Results: Nine patients had exogenous PH. Six patients were treated with progesterone for threatened abortion, and three for ARTs. Their mean age was 33.6 years, and their mean body mass index was 26.3 kg/m^2. They had never experienced an adverse drug reaction. The mean latency to symptom onset was 5.8 days (range 1 h to 11 days). The patients complained of hives, erythema and itching, and one developed anaphylaxis. All patients were treated with antihistamines, and six patients were treated with systemic corticosteroids. Epinephrine was administered to one patient with hypotension. The symptom duration was 1-14 days. Skin tests were performed in four patients; all were positive. Two patients were treated successfully by progesterone desensitization.

Conclusions: The clinical features of exogenous PH were similar to those of type I hypersensitivity reactions, but tended to develop later and did not respond to antihistamines or steroids. As use of progesterone increases, an understanding of the clinical features of exogenous PH becomes ever-more important.

Key words: Dermatitis, desensitization, exogenous, hypersensitivity, progesterone

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Introduction

Progestogen hypersensitivity (PH) is a rare hypersensitivity reaction to endogenous or exogenous progesterone. Endogenous PH previously known as autoimmune progesterone dermatitis (APD) is characterized by periodic skin rashes during the menstrual luteal phase. APD was first described by Shelley *et al.* in 1964; they used the term "autoimmune" to describe PH because the patient reacted to endogenous progesterone.[1] However, there is little evidence to support an autoimmune reaction, and APD does not accurately represent the clinical features. Therefore, Foer *et al.* proposed the name PH, classified as endogenous or exogenous depending on the route of progesterone exposure.[2] PH has various cutaneous manifestations, *e.g.*, hives, eczematous eruptions, vesiculopustular eruptions, fixed drug eruptions, erythema multiforme, and anaphylaxis.[3-7] Endogenous PH is frequently associated with prior exposure to exogenous progesterone.[3-5] Exogenous progesterones are increasingly used for assisted reproductive techniques (ARTs) for infertility or prevention of abortion, and cases of dermatitis due to progesterone have been reported. However, most studies have focused on endogenous, rather than exogenous PH. Moreover, not all patients with PH have periodic skin lesions. Therefore, we investigated the clinical manifestations of patients with exogenous PH.

Methods

Study subjects

We reviewed data of patients with cutaneous adverse drug reactions to progesterone reported in the spontaneous adverse drug reaction reporting system from January 2011 to July 2016.

This study was approved by the Institutional Review Board of Pusan National University Hospital (H-1709-001-058), and all participants gave their informed consent.

Progesterone skin test

Skin prick tests and intradermal tests were performed with 50 mg/ml progesterone, as has been typical in previous studies.[3,8,9] A skin prick test result was considered to be positive when the progesterone wheal to histamine wheal diameter ratio was ≥ 1. An intradermal test result was considered to be positive when the initial wheal diameter increased by ≥ 3 mm after 15-20 min.

Progesterone desensitization

We designed a seven-step desensitization protocol using intramuscular progesterone (**Table 1**). Premedication with antihistamines and corticosteroids was not performed. The target dose of progesterone was 50 mg twice daily, and the initial dose was 1/10,000 of the therapeutic dose. Dose escalation occurred every 20 min. After successful desensitization, subsequent 50-mg doses were administered simultaneously.

Table 1. Progesterone desensitization protocol.

Step	Dose (mg)	Time interval (min)
1	0.05	20
2	0.1	20
3	0.5	20
4	1	20
5	5	20
6	10	20
7	50	20

Statistical analysis

All statistical analyses were performed using SPSS software (ver. 18.0 for Windows; SPSS, Inc., Chicago, IL, USA). Data are presented as mean values and ranges.

Results

The clinical characteristics of the nine patients with exogenous PH are shown in **Table 2**. The patients had no history of allergy or cyclic skin eruptions. Six patients were treated with progesterone for threatened abortion, and three patients were prescribed progesterone as part of ARTs. Their mean age was 33.6 years, and their mean body mass index was 26.3 kg/m^2. They had never experienced an adverse drug reaction. The mean latency to symptom onset was 5.8 days (range, 1 h to 11 days). They complained of urticaria, erythema and itching; patient 7 also complained of neck tightness, shortness of breath,

Table 2. Clinical characteristics of progestogen hypersensitivity

Patient	1	2	3	4	5	6	7	8	9
Age	31	34	29	38	35	38	33	33	31
BMI	24.4	32.5	30.1	25.3	24.7	22.0	22.9	22.0	33.0
Allergy history	None	None	None	None	None	None	None	None	None
Diagnosis	Threatened abortion	Threatened abortion	Threatened abortion	Threatened abortion	Threatened abortion	Threatened abortion	Infertility	Infertility	Infertility
Route of administration	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intravaginal	Intravaginal	Intramuscular
Symptoms	Urticaria	Urticaria, itching	Erythema, itching	Erythema, itching	Urticaria	Urticaria, itching	Urticaria, itching, dyspnea, hypotension	Erythema, itching	Erythema, urticaria, itching, fever
Onset from administration of progesterone	1 day	2 days	10 days	10 days	6 days	8 days	9 days	1 hour	6 days
Duration of symptoms	5 days	7 days	9 days	1 day	3 days	7days	11 days	7days	14 days

Table 2. (Continued)

Patient	1	2	3	4	5	6	7	8	9
Prior exposure to progesterone	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Eosinophil count	Not done	95	Not done	Not done	Not done	81	16	63	20
Tryptase (μg/l)	Not done	Not done	Not done	Not done	Not done	Not done	30	Not done	Not done
Treatment	Antihistamine, steroid	Antihistamine	Antihistamine, steroid	Antihistamine	Antihistamine, steroid	Antihistamine, steroid	Antihistamine, steroid, epinephrine	Antihistamine	Antihistamine, steroid
Skin test	Not done	Not done	Not done	Not done	Not done	Positive IDT	Positive IDT	Positive SPT and IDT	Positive IDT
Desensitization	Not done	Not done	Not done	Not done	Not done	Done	Not done	Done	Not done
Prognosis	-	-	-	-	-	Chronic urticaria	-	-	Chronic urticaria

Abbreviations: BMI, body mass index; SPT, skin prick test; IDT, intradermal test

and hypotension. All patients were treated with antihistamines, and six patients were treated with systemic corticosteroids. The severe symptoms of patient 7 occurred on day 9 of progesterone administration. She was treated with epinephrine because of a decrease in blood pressure. Furthermore, patient 7 had an elevated serum tryptase level. Progesterone skin tests were performed in patients 6, 7, 8, and 9; all were positive. Two patients (patients 6 and 8) were treated successfully by progesterone desensitization. Patient 6 suffered an adverse reaction after administration of progesterone for a threatened abortion, and subsequently underwent desensitization therapy because administration of progesterone was required as a sterilization procedure. Two patients tolerated the desensitization procedure with no hypersensitivity reaction. No patient has experienced cyclic skin eruptions following exogenous progesterone–induced dermatitis, but two have developed chronic urticaria.

Discussion

In the present study, we examined the clinical manifestations of exogenous PH. Few cases of exogenous PH have been reported; they include erythema multiforme due to progesterone in a low-dose oral contraceptive pill;[10] generalized, pruritic, intensely erythematous, morbilliform, scaling dermatitis in reaction to oral megestrol acetate;[11] and urticaria due to synthetic intramuscular progesterone administered in association with *in vitro* fertilization (IVF).[9] Foer *et al*. reported 24 cases of endogenous and exogenous PH, in which the most common symptoms were dermatitis, urticaria, and angioedema, followed by asthma and anaphylaxis.[2] We analyzed the clinical features of patients diagnosed with exogenous PH over a 6-year period. The most common symptoms were urticaria and erythema, and one patient experienced anaphylaxis; their clinical features and skin test results suggested type I hypersensitivity. However, symptom onset was several days after progesterone administration. The patient's symptoms improved following administration of antihistamines and steroids for several days. PH has been the subject of several studies, its pathogenesis is unclear. Several theories have been proposed, and an immunoglobulin E (IgE)-mediated response to progesterone is the most accepted,[12] being supported by progesterone skin test positivity observed in our study and previous studies.[8,9,13,14] However, how patients become sensitive to progesterones is not clear. Endogenous PH is frequently associated with prior exposure to exogenous progesterone.[5] Exogenous progesterone exposure leads to sensitization through generation of progesterone-specific IgE antibodies, which cross-react with the increasing endogenous progesterone level in the luteal phase of the menstrual cycle.[8,13-15] However, Endogenous PH can develop without previous progesterone exposure, which suggests steroid cross-sensitivity as an alternative sensitization mechanism.[7,16] Alternatively, antibodies formed in response to food, medication, or viral infection may cross-react with progesterone, the binding of which to progesterone receptors in the skin and oral mucosa results in cutaneous inflammation.[6] Not all PH patients in previous reports had clinical features of IgE-mediated reactions; some cases showed delayed hypersensitivity responses.[17-20] This may be explained by Th2 modulation by progesterone

via G-protein receptors, or by activation of a progesterone membrane receptor α on CD8+ cells.[21,22] An immune complex -mediated mechanism has also been proposed; a 17-hydroxyprogesterone-binding IgG was identified in the serum of the patient with cyclical perineal rashes;[23] and immune complexes were detected in the serum after challenge with medroxyprogesterone in a patient with recurrent erythema multiforme during the luteal phase of the menstrual cycle.[5] Our cases of exogenous PH likely had a similar mechanism, i.e., a type I hypersensitivity reaction, according to the positive skin test results associated their clinical features. However, symptoms developed 1-11 days after exposure to progesterone. One patient showed clinical features of anaphylaxis, and a positive skin test result and elevated tryptase level suggested an IgE -mediated response. However, symptom onset occurred 9 days after progesterone administration. The delayed symptom onset may be due to latency between exposure to progesterone and the production of specific IgE. In addition, it is possible that low progesterone tolerance and the development of an inflammatory reaction in response to increased hormone levels may be the reason for late manifestations of exogenous PH, considering that endogenous PH is associated with the peak progesterone levels of the luteal phase.[17]

Diagnostic modalities of PH in clinical practice include progesterone skin testing and provocation tests. *In vitro* assays have also been used to investigate PH: a leukocyte histamine relasese (LHR) functional assay on basophils; specific IgE antibody assays, such as enzyme-linked immunosorbent assays (ELISAs); and an interferon-γ assay to assess drug-related T-cell activity.[24] We used 50 mg/ml progesterone for skin testing.[3,8,9] Stranahan *et al.*,[8] who also used 50 mg/ml progesterone, reported a possible irritant reaction due to the inclusion of sesame oil in the progesterone solution. In a recent study of 24 patients with PH, false-positive reactions caused by benzyl alcohol or oil-based diluents were described, and only 50% of patients were reported to be positive by progestogen skin testing.[2] All four patients in our study who underwent skin testing showed positive results. It is possible that these may have represented irritant or false-positive reactions. However, the authors of previous studies diagnosed PH based on clinical manifestations, and we also consider that progesterone may have been responsible for the hypersensitivity reactions of our patients. Although our cases were not confirmed by provocation tests or *in vitro* assays, we diagnosed PH based on the clinical features and positive skin test results.

Relief of our patients' symptoms required the administration of antihistamines and corticosteroids for 1-14 days. Treatment of endogenous PH usually focuses on controlling symptoms or inducing anovulation. Although antihistamines or topical and oral corticosteroids have been trialed to control symptoms, PH is less responsive to antihistamines, and oral corticosteroids are not a viable option due to adverse side effects.[24] Endogenous PH could be treated with estrogen-containing oral contraceptives to suppress the progesterone surge of the luteal phase of the menstrual cycle, estrogen receptor modulators to suppress ovulation and the postovulatory rise in progesterone, and gonadotropin-releasing hormone (GnRH) agonists to inhibit ovulation.[3,5,25] In addition, the 17-α-alkylated steroids stanozolol and danazol have been used in combination with glucocorticoids.[26,27] Oophorectomy may offer permanent relief.[7] Our patients had no history of cyclic skin eruptions after their episodes of exogenous PH; thus, we considered that our patients likely had isolated hypersensitivity to exogenous progesterone, or secondary PH according to the classification of Foer *et al.*[2] Therefore, we suggested that our patients undergo drug withdrawal followed by desensitization therapy when progesterone therapy was necessary. Desensitization therapy can be applied in cases with severe symptoms that are not controlled by conventional therapy, or where there is a need for high -dose progesterone for medical treatment, such as with IVF.

Maguire explained that risk factors for autoimmune progesterone dermatitis, as an autoimmune reaction to endogenous progesterone, include fertile age, exogenous progesterone, and pregnancy.[17] However, since these conditions are manifested in various clinical features, and since there is a lack of evidence for an autoimmune mechanism, this response is thought to be due to hypersensitivity to progesterone, correlated with endogenous or exogenous exposure. Therefore, the age of patients with PH may vary depending on the route of progesterone exposure. Most of the endogenously triggered cases reported by Foer *et al.* were young, and most patients with exogenous PH had symptoms during their 30s.[2] The mean age of our cases was 33.6. Previous studies showed that most women with endogenous PH had a previous exposure to exogenous progesterone. Fourteen of twenty-four patients discussed Foer *et al.* were exogenous PH patients, and 57% of them had symptoms related to menses.[2] Although many case of PH can occur after previous experience of exogenous PH, our findings show that not all patients with exogenous PH develop perimenstrual symptoms.

We report herein the clinical manifestations of exogenous PH. The symptoms experienced by our patients were suggestive of type I hypersensitivity reactions, but their symptoms tended to be delayed, and did not respond well to antihistamines and corticosteroid therapy. Furthermore, in our patients with exogenous PH, perimenstrual symptoms did not occur, which suggests that there are more undiagnosed hypersensitivity reactions to exogenous progesterone than indicated in previous reports. Therefore, patients who require progesterone therapy need to be aware of this adverse reaction. Although a larger number of cases should be analyzed to verify our findings, this study is important because it provides a description of the clinical manifestations of exogenous PH; most previous studies focused on endogenous PH.

Conclusion

Exogenous progesterones are increasingly used to prevent threatened abortion or to treat infertility. Therefore, clinicians should be aware of PH, its clinical manifestations, and available treatments.

Author Contributions

Eun-Jung Jo: conception and design of the study, data generation and interpretation of the data, and preparation of the manuscript

Seung-Eun Lee: data generation and interpretation of the data

Hye-Kyung Park: conception and design of the study, interpretation of the data, and critical revision of the manuscript

Conflicts of interest

There are no potential conflicts of interest related to this article or the research described.

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