Original Article

Progestogen Hypersensitivity in 24 Cases: Diagnosis, Management, and Proposed Renaming and Classification

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What is already known about this topic? Progestogen hypersensitivity causes heterogeneous symptoms including dermatitis, urticaria, asthma, and anaphylaxis.

What does this article add to our knowledge? It adds in-depth knowledge about progestogen hypersensitivity presentation, diagnostic testing, and management including progestogen desensitization.

How does this study impact current management guidelines? The authors propose a new naming and classification system to facilitate diagnosis and management for future study as well as a treatment algorithm for patients presenting with progestogen hypersensitivity.

BACKGROUND: Autoimmune progesterone dermatitis is a poorly recognized syndrome associated with a hypersensitivity to progestogens. Symptoms present heterogeneously, which may complicate diagnosis. Management has generally centered on symptomatic control with medication. Recently, an increasing number of cases have been reported with *in vitro* fertilization (IVF). Desensitization to progestogens is suggested as an approach to tolerate fertility treatments and provide symptom control.

OBJECTIVES: To describe the diagnosis and management of progestogen hypersensitivity (PH) and to detail the use of desensitization. We also propose a new terminology of progestogen hypersensitivity instead of autoimmune progesterone dermatitis, and a classification system based on exogenous and endogenous progestogen triggers to facilitate diagnosis and management.

METHODS: Twenty-four cases of PH were evaluated retrospectively. Symptom presentation, diagnostic modalities, desensitization protocols, and outcomes were analyzed.

RESULTS: Symptom onset was classified as a reaction to either endogenous progesterone (42%) or exogenous progestogens (58%). Symptoms were heterogeneous and included cyclical dermatitis, urticaria, angioedema, asthma, and anaphylaxis. Triggers were also heterogenous and included progesterone as well as progestins. Eleven patients underwent intramuscular (27%) or oral (73%) desensitization. Desensitization resulted in symptom control in 8 patients, IVF medication tolerance in 3 patients, and 2 pregnancies.

CONCLUSIONS: This is the largest case series of patients with PH with successful treatment outcomes. The new terminology progestogen hypersensitivity more accurately represents the diversity of presentations to endogenous or exogenous progestogens. We demonstrate that progestogen desensitization is successful in multiple patients and can result in symptom control and fertility. Women with cyclical allergic symptoms, including those undergoing IVF, should be evaluated for PH. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: *Progesterone; Progestogen; Infertility; Progestin; Desensitization; Autoimmune progesterone dermatitis; Catamenial anaphylaxis*

Autoimmune progesterone dermatitis (APD) is a poorly recognized, complex syndrome occurring in women of childbearing age. First described in the medical literature in 1964 by Shelley et al[1] as a dermatitis flare related to premenstrual

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Conflicts of interest: A. R. Gargiulo has received consultancy fees from Medicaroid and OmniGuide. M. Castells is on the boards for the American Academy of Allergy, Asthma & Immunology (AAAAI), Board of Directors, and Association of American Medical Colleges; has received consultancy fees from Merck, Sanofi, Allergy Therapeutics, and Neurophage; is employed by Brigham & Women's Hospital; has received research support from Ovations for the Cure; and has received travel support from American College of Allergy, Asthma, and Immunology, European Competence Network on Mastocytosis, AAAAI, Federation of American Societies for Experimental Biology, and Texas Allergy, Asthma, and Immunology Society. P. G. Wickner has received consultancy fees from AMAG Pharmaceuticals; has received research support from Brigham and Women's Physician Organization Grants; and has received travel support from World Allergy Organization as a speaker. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used
APD- autoimmune progesterone dermatitis
BWH- Brigham and Women's Hospital
IM- intramuscular
IVF- in vitro *fertilization*
OCP- oral contraceptive pill
PH- progestogen hypersensitivity

progesterone exposure, subsequent case series have reported hypersensitivity reactions to exogenous sources of progestogens[2] as well as endogenous progesterone[3,4] related to menses or pregnancy.

Symptoms of APD present heterogeneously, and can range from dermatitis[1,5,6] to dyspnea, cough, and anaphylaxis[7,8] though patients often report multiple manifestations.[2,3,9-14] This heterogeneity may delay diagnosis by years.[6] Despite the identification of APD in the literature more than 40 years ago,[1,15] the definitive underlying pathogenesis remains unknown. Broadly, symptoms may be considered a type I or type IV hypersensitivity mediated by a T_H2 rather than T_H1 response,[16] which is supported by positive skin test results.[17,18] An autoimmune explanation for APD has also been proposed.[12,19]

The heterogeneity in presentation is paralleled by the variety of approaches to management. These include topical or systemic corticosteroids and antihistamines[7,17] for symptomatic relief. Endogenous progesterone suppression via anovulatory therapies has been pursued with hormone antagonists[20,21] and agonists.[14,22] To date, bilateral oophorectomy[1,23-25] continues to be used when alternative therapies fail to achieve symptom control.

Significantly, an increasing number of APD cases have been reported with the advent and increasing use of *in vitro* fertilization (IVF), during which women are exposed to supraphysiologic levels of progesterone.[1] In this setting, previously used approaches for symptom control and surgical interventions are no longer sufficient given the need for high-dose progesterone to support pregnancy with the ultimate goal of fertility. Desensitization represents an option for women with progestogen hypersensitivity (PH) seeking pregnancy. Intravaginal, intramuscular (IM), and oral desensitization protocols to progestogens have been described in single or small case series.[26,27] Here, we present the largest case series of patients with PH that highlights progestogen desensitization protocols resulting in symptom resolution and successful pregnancy. We also propose a new name instead of APD, progestogen hypersensitivity, to reflect the heterogeneity of presentation as described above. We also suggest a classification for PH to facilitate diagnosis and management.

METHODS

Twenty-four cases of patients with APD followed at the Brigham and Women's Hospital (BWH) (Boston, Mass) Allergy and Immunology clinic were retrospectively reviewed. The diagnosis of APD was made on the basis of clinical history of urticaria, angioedema, dermatitis, airway obstruction, or anaphylaxis after exposure to either endogenous or exogenous progestogen (Table I). All patients underwent skin prick and intradermal skin testing to progesterone, with the concentration of progesterone for skin prick testing being 50 mg/mL and for intradermal skin testing being 0.005, 0.05, and 0.5 mg/mL with either benzyl alcohol or olive oil as a diluent. Eleven patients underwent progestogen desensitization (Tables II and III). Slow oral progestogen desensitization was initiated in the clinic and completed on outpatient basis for patients not undergoing fertility treatments. Rapid IM progesterone desensitization was completed in the BWH outpatient infusion center for patients needing precise timing of desensitization for fertility treatments or for patients with more severe reactions such as anaphylaxis.

TABLE I. Characteristics of patients with PH (N = 24)

	Value
Medical history	
Age of onset (y), mean (range)	29.7 (13-48)
Endogenous progesterone trigger, %	42
Exogenous progestogen trigger, %	58
	25 OCP
	25 IVF
	4 Emergency contraception
	4 IUD
Relation to menses, %	75% within week before menses
Atopy*	46%
Symptoms, %	
Dermatologic†	54 Dermatitis‡
	54 Urticaria/angioedema
Asthma	13
Anaphylaxis	8
Positive skin testing, %	50

Diagnostic modality	Concentration progesterone (mg/mL)§
Skin test	50
Intradermal	0.005
	0.05
	0.5

IUD, Intrauterine device.
*Defined as history of asthma, eczema, food or environmental allergies.
†Includes patients with multiple dermatologic manifestations.
‡As documented by clinicians at patient visit.
§Diluent was either benzyl alcohol or olive oil.

Progesterone used for IM desensitization was prepared by the BWH pharmacy as 50 mg/mL suspended in sesame oil. Given the oil base, the doses could not be diluted with a water-soluble solution. Therefore, incremental concentrations were achieved by varying the volume only. For example, to prepare a dose of 0.5 mg, a volume of 0.01 mL of progesterone is drawn (calculation, 0.5 mg = 0.01 mL of 50 mg/mL solution). Because of the very small volumes involved in IM desensitization, a 1-mL TB syringe was used, and contained overfill for needle priming.

Oral capsules used in oral desensitization protocols were prepared by the BWH pharmacy by geometric dilution using microcrystalline cellulose as the diluent. Capsules were prepared in standardized incremental concentrations based on the target progestogen desensitization dose. For example, capsules for the slow oral desensitization protocol described in Table II were prepared in 1.25, 12.5, 50, and 125 μg progestin concentrations.

Patients were maintained on a total daily dose of 90 to 180 mg progesterone after IM desensitization as needed for fertility treatment depending on the specific IVF protocol as determined by the reproductive endocrinologist. For oral protocols, patients were continuously cycled on oral contraceptive pills (OCPs) at typical doses to suppress ovulation. Follow-up was conducted with patients