

REFERENCES

1. Yunginger JW, Jones RT, Fransway AF, Kelso JM, Warner MA, Hunt LW. Extractable latex allergens and proteins in disposable medical gloves and other rubber products. *J Allergy Clin Immunol* 1994;93:836-42.
2. Hamilton RG, Adkinson NF Jr. Natural rubber latex skin testing reagents: safety and diagnostic accuracy of nonammoniated latex, ammoniated latex, and latex rubber glove extracts. *J Allergy Clin Immunol* 1996;98:872-83.
3. Primeau M-N, Adkinson F Jr, Hamilton RG. Natural rubber pharmaceutical vial closures release latex allergens that produce skin reactions. *J Allergy Clin Immunol* 2001;107:958-62.

doi:10.1016/j.jaci.2004.05.058

Chronic idiopathic urticaria exacerbated with progesterone therapy treated with a novel desensitization protocol

To the Editor:

Chronic idiopathic urticaria and angioedema (CIU) is a more common skin disorder that is usually responsive to inhibitors of mast cell mediators, such as histamine type I (H1) antagonists alone or in combination with H2 antagonists, leukotriene inhibitors, and corticosteroids. This disorder has an autoimmune component, with approximately 45% of patients demonstrating evidence of circulating IgG autoantibodies directed against the α subunit of the high-affinity IgE receptor or antibodies to the α subunit of IgE.^{1,2} CIU has also been observed with other autoimmune diseases, such as Hashimoto and Graves thyroid disease.^{1,3}

In comparison, progesterone-induced urticaria and angioedema is a rare disorder characterized by cyclic skin eruptions 10 to 14 days before the onset of menses. This disorder is related to a spectrum of diseases termed *autoimmune progesterone dermatitis* that is characterized by erythema multiforme, papulovesicular eruptions, eczematous lesions, urticaria, and angioedema. Whereas history is usually sufficient for diagnosis, confirmation by means of positive intradermal skin test results to progesterone or a provocative progesterone challenge can be performed. Treatment is aimed at reducing levels of serum progesterone or suppressing ovulation. In the 1950s, desensitization with corpus luteum extracts by means of serial injections was used.⁴ Today, treatment options have included cyclic norethisterone and ethinyl estradiol, conjugated estrogens, 17- α -alkylated steroids, gonadotropin releasing hormones, and bilateral oophorectomy.⁵

We report a patient with CIU exacerbated by progesterone with laboratory evidence of autoantibodies to the high-affinity IgE receptor who clinically responded to a novel progesterone desensitization protocol. The patient is a 28-year-old woman with a history of chronic urticaria and angioedema since puberty at age 13 years. Symptoms initially occurred monthly approximately 10 to 14 days before menses, with complete resolution of hives at the onset of menses. Episodes were under good control with antihistamines. During the pregnancy of her only child in 1997, she had complete resolution of urticaria and angioedema. She underwent bilateral oophorectomy in

April 2001 for serous ovarian carcinoma detected during exploratory laparoscopy for chronic abdominal pain. Surgical margins were free, and there has been no recurrence of carcinoma detected to date through appropriate screening measures.

Immediately after oophorectomy, she had symptoms of menopause, including hot flashes, vaginal dryness, and irritability, which were alleviated by estrogen replacement therapy. However, supplementation with progesterone caused severe life-threatening recurrence of urticaria and angioedema, including throat swelling, wheezing, and shortness of breath. She required multiple emergency department visits for rescue treatment with subcutaneous epinephrine, steroids, and antihistamines. Frequent prednisone burst tapers were also prescribed. Multiple agents tried for hormone replacement therapy included Orthonovum, Premarin plus Provera, Yasmin, and micronized progesterone. A low-dose challenge with micronized progesterone at 25 mg caused immediate urticaria, followed by angioedema, necessitating rescue treatment at a local emergency department. The patient strongly desired *in vitro* fertilization, and therefore she refused a hysterectomy. Her obstetrician-gynecologist referred her to our center for possible desensitization to progesterone because progesterone replacement therapy was necessary for future *in vitro* fertilization plans.

Otherwise, her medical history was unremarkable and without evidence of allergic rhinitis, asthma, or food allergy. There was no family history of eczema, atopy, asthma, autoimmune disorders, chronic urticaria-angioedema, or immunodeficiencies. Her initial physical examination revealed urticarial lesions on the left forearm and antecubital fossa.

Laboratory data showed a normal complete metabolic panel and complete blood count. Both the erythrocyte sedimentation rate and C-reactive protein levels were increased at 30 mm/h and 2.8 mg/dL, respectively. The results of complement studies were normal, as follows: C4, 29.5 mg/dL; C5a, 9.2 ng/mL; and CH50, 358 U/mL. Results of thyroid function studies, including antithyroid antibodies (antithyroglobulin and antimicrosomal), were normal. There was no evidence of cryoglobulinemia. Serum IgE levels were increased at 405 kU/L. Basophil histamine release assay for indirect determination of detecting antibodies to the high-affinity IgE receptor were positive (Allen Kaplan, MD, Laboratory testing, Charleston, SC).

The patient underwent a 2-day progesterone desensitization protocol, as shown in Table I. Treatment with Benadryl and prednisone was given throughout the desensitization. After desensitization, she was able to tolerate micronized progesterone at 100 mg daily. Her additional daily medications included cetirizine and Estrace. She initially reported significant improvement in symptoms of urticaria. Follow-up has now been extended to 1 year, with occasional flares of urticaria-angioedema noted but overall good tolerance of progesterone.

The patient described in this report had autoimmune CIU exacerbated by progesterone therapy. The role of progesterone in initiating and exacerbating this disorder is unknown. In the clinical disorder progesterone-induced urticaria, a high prevalence of prior use of progesterone supplementation for use as an oral contraceptive has been linked to disease manifestations.⁶ A hypothesis was that antibodies directed to synthetic progesterone might cross-react to endogenous progesterone, eliciting a reaction.⁶ However, the patient described above had reported onset of cyclical symptoms during early puberty before exposure to supplemental progesterone.

Immune mechanisms might also play a role in the pathogenesis of progesterone-induced urticaria. Interestingly, in 1921, Geber⁷ performed an autologous serum-like skin test, whereby a wheal-and-flare reaction was noted in the skin to a patient's own premenstrual serum. Others have demonstrated a positive Prausnitz-Küstner test result or passive transfer test result using serum from patients with progesterone-induced urticaria transferred to healthy control subjects.⁸ In the patient described in this report, her symptoms of urticaria and angioedema were found to be associated with the antibodies to the high-affinity IgE receptor. An autologous serum skin test was not performed. It is interesting that her symptoms followed a cyclical menstrual pattern in early puberty, whereas more recently, her symptoms were severely exacerbated by supplemental progesterone therapy. This could be a case of both CIU and progesterone-induced urticaria-angioedema. A consideration that progesterone might be involved in the clinical manifestations of CIU is speculative, but assessing the role of progesterone in other patients with CIU might be important.

The described patient successfully underwent progesterone desensitization, with a remarkable decrease in her symptoms evident by means of amelioration of her angioedema and discontinuation of prednisone use. Because the exact role of progesterone therapy in provoking the patient's symptoms is unclear, the mechanism by which an increased tolerance to supplemental progesterone was associated with a decrease in her symptoms is unknown. The observed effect could be a result of IgE-dependent mechanisms or nonimmunologic pharmacologic tolerance, such as that seen with aspirin or drug desensitization.⁹ However, this novel approach to the treatment of CIU exacerbated by progesterone is similar in concept to desensitization with corpus luteum extract injections, which was performed in the 1950s.¹ This protocol could be used for other patients with a history of disease refractory to treatment who wish to avoid bilateral oophorectomy.

Jill A. Poole, MD
Lanny J. Rosenwasser, MD
Division of Allergy/Immunology
Department of Medicine
National Jewish Medical and Research Center
1400 Jackson St
Denver, CO 80206

TABLE I. Progesterone desensitization protocol

Time (h)	Dose
00:00 (first day)	0.1 mg
00:45	1 mg
01:30	5 mg
02:15	10 mg
03:00	25 mg
00:00 (next day)	50 mg
00:45	100 mg
01:30	100 mg

REFERENCES

- Kaplan AP. Chronic urticaria and angioedema. *N Engl J Med* 2002;346:175-9.
- Tong LJ, Balakrishnan G, Kochan JP, Kinet JP, Kaplan A. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997;99:461-5.
- Leznoff A, Sussman GI. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity, a study of 9 patients. *J Allergy Clin Immunol* 1989;84:66-71.
- Guy WH, Jacob FM, Guy WB. Sex hormone sensitization (corpus luteum). *Arch Dermatol* 1951;63:377-8.
- Snyder JL, Krishnaswamy G. Autoimmune progesterone dermatitis and its manifestation as anaphylaxis: a case report and literature review. *Ann Allergy Asthma Immunol* 2003;90:469-77.
- Hart R. Autoimmune progesterone dermatitis. *Arch Dermatol* 1977;113:426-30.
- Geber H. Einige daten zur pathologies der urticaria menstruationalis. *Dermat Z* 1921;32:143.
- Farah FS, Shbaklu Z. Autoimmune progesterone urticaria. *J Allergy Clin Immunol* 1971;48:257-61.
- Borish L, Tamir R, Rosenwasser LJ. Intravenous desensitization to beta-lactam antibiotics. *J Allergy Clin Immunol* 1987;80:314-9.
doi:10.1016/j.jaci.2004.05.031

Body burden of mercury is associated with acute atopic eczema and total IgE in children from southern Germany

To the Editor:

Atopic eczema (AE; atopic dermatitis) is the most common inflammatory skin disease among children. Interactions among susceptibility genes, the host's environment, and immunologic factors are involved in its pathogenesis.¹ Most patients show sensitizations against environmental allergens with high serum levels of total and allergen-specific IgE.¹ Increasing prevalence rates of AE during the last decades have been attributed to changes in environmental factors.¹

With industrialization, heavy metals have been increasingly released into the environment, which may be incorporated through food, water, air, tobacco smoke, and medical prostheses.² A variety of these metals, such as arsenic, cadmium, and mercury, are of relevance to human health. They may interact with body stores of iron, vitamin C, and other essential nutrients, induce genomic instability, exert immunomodulatory effects, and cause contact dermatitis in sensitized persons.³ Low doses of mercury salts have been shown to induce an immune response with polyclonal B cell activation, high levels of