Progesterone-responsive urticaria and eosinophilia

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A 30-year-old black albino woman was first observed with a 4-year history of monthly urticarial episodes associated with hypereosinophilia. Hives consistently began at the end of menses and lasted for 1 to 2 weeks. A comprehensive evaluation excluded underlying malignancy and infection. There was no evidence of extracutaneous visceral involvement consistent with the primary hypereosinophilic syndrome. A 6-month prospective evaluation was performed, during which daily hive symptoms were recorded and weekly determinations of eosinophils, serum total IgE, progesterone, estradiol, and 24-hour urine histamine were obtained. Eosinophil counts (range, 4002 to 37,350 cells per cubic millimeter) increased in association with the onset of hives and decreased to baseline levels after their resolution. The 24-hour urine histamine peaked at the onset of each urticarial episode. When serum progesterone levels increased, the hives were quiescent and peripheral eosinophils decreased to baseline levels. Progesterone caused in vitro dose-related inhibition of antihuman IgE-induced histamine release from peripheral basophils of this patient. Treatment with oral medroxyprogesterone resulted in remission of urticaria and a decrease in eosinophil counts. This patient represents a unique case of chronic cyclic urticaria and hypereosinophilia that appears to be modulated by the effects of progesterone. (J ALLERGY CLIN IMMUNOL 1989:84:304-10.)

Chronic urticaria and angioedema in association with hypereosinophilia is a rare clinical entity. In 1976, Cooper and Patterson reported a female patient who developed premenstrual fatigue, edema, hypereosinophilia, and an elevated IgM. In 1984, Gleich et al. reported four patients who experienced recurrent attacks of angioedema, urticaria, weight gain, and fever in association with hypereosinophilia. In some of these cases, cutaneous biopsy specimens revealed infiltration of the urticarial lesions with eosinophils. Subsequently, Katzen described a child who was first observed with cyclical episodes of pruritic papules, angioedema, fever, and absolute eosinophil counts as high as 32,000/mm³. Because extracutaneous visceral manifestations were not observed in any of these previous studies, these urticarial syndromes believed to be distinct clinical entities not related to the primary hypereosinophilic syndrome.

Abbreviations used
- RIA: Radioimmunoassay
- LH: Luteinizing hormone
- FSH: Follicle-stimulated hormone

Chronic urticaria has been recognized to occur in female subjects who experience cyclical hives in relationship to their menstrual cycles. In some of these studies, it has been hypothesized that urticaria may occur either as a result of sensitization or as an autoimmune response to endogenous progesterone. In some of these patients, intracutaneous reactivity to progesterone has been demonstrated. Meggs et al. first documented clinical hypersensitivity to progesterone in a female patient as a direct cause of recurrent urticaria and anaphylaxis. Subsequently, Slater et al. were able to demonstrate in two women an etiologic relationship between endogenous progesterone and recurrent anaphylaxis. In this article, we describe a patient with chronic cyclical urticaria and hypereosinophilia occurring in direct association with the menses. The clinical expression of urticaria and eosinophilia in this unique patient appeared to be modulated by endogenous secretion of progesterone.
Case report

In October 1986, a 29-year-old black albino female subject was first observed with a 4-year history of recurrent attacks of angioedema and hives associated with peripheral eosinophilia. The patient did not have any apparent congenital or developmental disorders associated with her albinism. She reported the appearance of pruritic urticarial lesions on the back, neck, axillae, and genital areas since June 1982. The hives consistently began several days after the onset of her menses, lasted for approximately 10 days, and recurred monthly on a cyclical basis. The patient complained of mood swings and reported "hot flashes" during these episodes. There were no concurrent symptoms of fever, change in body weight, chills, night sweats, palpitations, or abdominal symptoms. The onset of the hives was not precipitated by identifiable physical stimuli, foods, or medications. There was no familial history of urticaria or angioedema. Diphenhydramine was effective for controlling the associated pruritus but did not cause resolution of the urticarial lesions. The patient was nulliparous, sexually inactive, and denied prior administration of oral contraceptives or parenteral hormones. She had regular menses until the age of 20 years, at which time she developed oligomenorrhea of unknown etiology for 5 years. The urticarial episodes appeared soon after the return of normal menses. There was no significant atopic history.

Physical examination revealed a black albino woman with coalescent urticarial lesions noted on the posterior neck, trunk, axillae, and pubic areas. The lungs were clear to auscultation. The cardiovascular examination revealed no murmurs, gallop, or friction rub. There was no evidence of hepatosplenomegaly or abdominal masses. A complete pelvic examination performed by a gynecologist was normal. A complete blood count revealed a hemoglobin of 13.1 g/dl, hematocrit, 38.8; mean corpuscular volume, 89.3; mean corpuscular hemoglobin, 30.2; and mean corpuscular hemoglobin concentration, 33.8. The white blood count was 20,100/mm³, the peripheral absolute eosinophil count was elevated at 12,944/mm³ (normal range, 0 to 450/mm³), and the platelet count was 203,000. The serum total IgE was 500 IU/ml (normal range, 10 to 150 IU/ml). Results of an electrocardiogram and chest x-ray film were normal.

Subsequently, a comprehensive evaluation was undertaken to identify a possible underlying etiology for the eosinophilia. Stools for ova and parasites were negative on three occasions. A Westergren sedimentation rate was 24 mm/hr. The C3 was 138 mg/dl (83 to 177 mg/dl), C4 was 46 mg/dl (15 to 50 mg/dl), and the CH₅₀ was 105 mg/dl (>50 mg/dl). The antinuclear antibodies and anticientromere antibodies were negative. Quantitation of serum immunoglobulins revealed an IgG of 1200 mg/dl (530 to 1420 mg/dl), an IgA of 220 mg/dl (70 to 290 mg/dl), and an IgM of 121 mg/dl (50 to 375 mg/dl). An M-mode echocardiogram demonstrated no evidence of increased left ventricular wall thickness or pericardial effusion. A skin biopsy specimen demonstrated moderately dense perivascul ar and interstitial mixed cell infiltrates consisting predominantly of eosinophils with lesser numbers of identifiable neutrophils, lymphocytes, and histiocytes. A bone marrow biopsy specimen demonstrated a mildly hypercellular marrow with normal amounts of megakaryocytes. The myeloid to erythroid ratio was moderately increased, predominantly because of an increase in eosinophils and eosinophilic myeloid precursor cells. Special stains for fungal and acid-fast organisms were negative.

METHODS

Clinical studies

The patient was evaluated prospectively for 6 months. During that time, she maintained a daily record of hive symptoms and requirements for supplementary diphenhydramine. Weekly measurements of the absolute eosinophil count, serum total IgE, and Westergren sedimentation rate (erythrocyte sedimentation rate) were obtained. Serum levels of progesterone and estradiol were also determined weekly to note possible relationships between endogenous hormones and the urticarial episodes. Assays for 24-hour urine histamine were also obtained on a weekly basis for 6 months.

After a 3-month baseline evaluation, a 28-day trial of medroxyprogesterone acetate (20 mg by mouth, every 8 hours) treatment was begun to evaluate the possible modulatory effects of progesterone on the urticaria. During this period, weekly determinations of serum progesterone, estradiol, erythrocyte sedimentation rate, total IgE, absolute eosinophil counts, and urine histamine were determined.

Laboratory methods

The serum total IgE was determined by Tandem-E (Hybritech Inc., San Diego, Calif.), which is a solid-phase, two-site immunoenzymetric assay. The results were obtained by measuring optical density at 405 nm in a spectrophotometer (Hybritech Inc.), and the coefficient of variation for this assay ranged between 5% and 6%. Serum progesterone was evaluated by direct RIA, as described by Garza et al. Serial LH and FSH determinations were also performed with previously described RIAs. Skin prick tests were performed with progesterone, 1 mg/ml, diluted in peanut oil (Eli Lilly & Co., Indianapolis, Ind.), and estradiol cypionate at 1 mg/ml in cottonseed oil (Steris Laboratories, Phoenix, Ariz.). Peanut oil, cottonseed oil, histamine phosphate (1 mg/ml), and phosphate-buffered saline served as control reagents. All reagents were sterilized with a Millipore filter (Millipore Corp., New Bedford, Mass.) before use for skin testing.

To evaluate in vitro effects of progesterone and estrogen, direct leukocyte histamine release in response to progesterone and estradiol was studied. Leukocyte histamine release was performed according to the method of May et al. One milliliter of leukocytes at a concentration of 6 x 10⁶ in buffer was aliquoted into reaction tubes. Direct histamine release was measured in response to progesterone (Sigma Chemical Co., St. Louis, Mo.) at concentrations of 5 x 10⁻¹, 5 x 10⁻², 5 x 10⁻³, and 5 x 10⁻⁴ pg/ml, and to β-estradiol (Sigma Chemical Co.) at concentrations of 5 x 10⁻¹, 5 x 10⁻², 5 x 10⁻³, and 5 x 10⁻⁴ µg/ml.
FIG. 1. Six-month prospective evaluation of hive symptoms, menses, eosinophil counts, serum progesterone, serum total IgE, and 24-hour urine histamine levels.

2 × 10^5, 2 × 10^6, and 2 × 10^7 pg/ml. In separate experiments, progesterone inhibition of rabbit anti-IgE (Meloy Laboratories, Springfield, Va.)-induced histamine release was evaluated by preincubation of leukocytes with varying concentrations of progesterone before stimulation with rabbit anti-IgE. The rabbit antihuman IgE preparation had been previously demonstrated to precipitate between 320,000 and 400,000 IU of human IgE myeloma protein per milliliter of reagent. The 1:10,000 concentration of rabbit antihuman IgE was selected because optimal histamine releasability had previously been demonstrated at that dilution. Progesterone was dissolved in 95% ethanol and diluted in phosphate-buffered saline to a final ethanol concentration of 0.001%. Separated leukocytes were preincubated at 37°C for 1 hour with dissolved progesterone at concentrations ranging from 5 × 10^-7 to 5 × 10^7 pg/ml. After two washes and resuspension, the cells were incubated for 1 hour at 37°C with anti-IgE. Histamine was extracted with butanol/NaCl/3 N NaOH, and then with N-heptane/0.12 N HCl. After the extractions, samples in 0.12 N HCl were reacted with 1% o-phthalaldehyde in methanol and 0.1 N NaOH. After a fluorescent development time of 40 minutes at room temperature, the reaction was stopped by the addition of 2 mol/L of phosphoric acid. Fluorescence was measured on a spectrophotofluorometer (Aminco Bowman, Silver Springs, Md.). Results were expressed as percent of histamine release compared to the amount of histamine released from perchloric acid-treated leukocytes.

Twenty-four hour samples for urine histamine were collected and stored at −20°C until assay. Determination of urine histamine was done according to the single isotopic method of Taylor and Snyder. Final results were determined by measurement of [3H]-methylhistamine. The results were expressed as micrograms of histamine excreted per 24 hours.

RESULTS

A consistent cyclical pattern of urticaria occurred in close association with the menses. Serum levels of...
TABLE I. Summary of direct leukocyte histamine release in response to progesterone and β-estradiol

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Concentration (pg/ml)</th>
<th>mol/L</th>
<th>Patients*</th>
<th>Control*</th>
</tr>
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<tbody>
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<td>5 × 10^-1</td>
<td>10^-7</td>
<td>5</td>
<td>4</td>
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<tr>
<td></td>
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<td>7</td>
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<td>10^-9</td>
<td>0</td>
<td>8</td>
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<td>5 × 10^-4</td>
<td>10^-10</td>
<td>1</td>
<td>0</td>
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<tr>
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<td>10^-7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
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<td>2 × 10^-6</td>
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<td>1.5</td>
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</table>

*Data represent mean of two experiments.

estradiol, progesterone, LH, and FSH followed normal physiologic patterns during the menstrual cycle. Results of serial laboratory studies performed in this patient during a period of 6 months are illustrated in Fig. 1. The peripheral absolute eosinophil counts ranged between 4002 to 37,350 cells per cubic millimeter. Each month the eosinophil count rose in association with the onset of urticaria and, after these lesions subsided, fell close to baseline values. Interestingly, serum progesterone levels fell to their nadirs during the periods when the hives were most active and at the same time that elevations in the eosinophil counts were most prominent. There was no discernible relationship between LH, FSH, or estradiol to the occurrence of urticarial lesions. Rises and falls in serum total IgE were observed to range between 250 and 490 IU/ml. The serum total IgE levels appeared to increase in association with both the onset of urticaria and the rises in the eosinophil counts and then appeared to decrease after the hives remitted. Changes in the sedimentation rate did not correlate with the eosinophil counts or the urticarial episodes. Increases in 24-hour urine histamine values coincided with the monthly onset of hives and subsequently decreased to normal ranges until the next urticarial episode.

During the 3-month baseline evaluation, the patient required an average monthly diphenhydramine dose of 266.7 mg. During a 28-day course of oral medroxyprogesterone acetate, at a dose of 20 mg every 8 hours, urticaria and pruritus remitted, and supplemental antihistamines were not required. As illustrated in Fig. 1, during medroxyprogesterone treatment, the eosinophil count diminished from 21,600 cells per cubic millimeter to levels ranging between 1704 and 2597 cells per cubic millimeter. However, an increase in IgE was noted during the month of progesterone therapy, despite the absence of hives and lower eosinophil counts during this period of time. After 10 days of medroxyprogesterone therapy, the serum progesterone decreased from 3580 to 220 pg/ml. The latter decrement was attributed to suppression of endogenous progesterone by large doses of exogenous medroxyprogesterone acetate. Menstruation was also suppressed during medroxyprogesterone treatment. One day after medroxyprogesterone was stopped, her menses returned. Hives reappeared 4 days later, at which time the absolute eosinophil count rose from 2597 to 8178 cells per cubic millimeter.

Skin prick tests to progesterone and estradiol were negative. Results of LHR studies are presented in Table I. Histamine release was not demonstrated in response to progesterone or estradiol at the various concentrations tested. Similar findings were noted in a control, nonatopic female subject without a history of urticaria, hypereosinophilia, or hormone therapy. Results of LHR-inhibition studies are illustrated in Fig. 2. The patient’s leukocytes demonstrated 32%, 51%, and 31% direct histamine release in response to rabbit antihuman IgE at concentrations of 1 × 10^-3, 1 × 10^-4, and 1 × 10^-5, respectively. When the patient’s leukocytes were preincubated with progesterone for 1 hour before anti-IgE challenge (1 × 10^-4), there was a dose-related inhibition of anti-IgE-induced histamine release. As illustrated in Fig. 2, progesterone concentrations more than 1 × 10^-4 pg/ml caused >50% inhibition of anti-IgE-induced histamine release. Inhibition of leukocyte histamine release was not observed in control cells from the patient after preincubation with 0.001% ethanol, the original solvent of progesterone. Five control patients did not exhibit significant inhibition of anti-IgE-induced histamine release after preincubation with equivalent physiologic concentrations of progesterone (illustrated in Fig. 2).
DISCUSSION

This patient presented with cyclic urticaria that varied in relationship to her menstrual cycle and was associated with hypereosinophilia. The unusual finding of moderately dense eosinophilic infiltration on skin biopsy specimen and the monthly occurrence of hives in association with marked elevations in peripheral eosinophil counts suggests that the urticarial lesions were elicited by cutaneous infiltration with eosinophils. In this case, release of eosinophil granular contents containing major basic protein or other cytoplasmic constituents that are capable of activating release of mast cell mediators could provide the stimulus for the urticarial response. This patient's clinical and laboratory evaluation excluded other possible causes of eosinophilia. Furthermore, her benign clinical course was not consistent with the primary hypereosinophilic syndrome, inasmuch as patients with this disorder exhibit various forms of visceral infiltrative disease that may include cardiac lesions.

The clinical findings in this patient represent a unique case of medroxyprogesterone-responsive urticaria and eosinophilia. A similar but distinct syndrome has been reported by Gleich et al., characterized by hives, angioedema, weight gain, leukocytosis, and eosinophilia. Some patients in that study were noted to have hypocomplementemia and elevated IgE and IgM. Despite eosinophil counts as high as 95,000 mm³, the clinical syndrome in our patient was benign, and there was no evidence of weight gain, hypocomplementemia, and hyperimmunoglobulinemia M.

Although there have been two previous descriptions of urticaria occurring on a cyclical basis in association with hypereosinophilia, the present case was unique in that the onset of urticaria and eosinophilia consistently occurred after the onset of menses. It was also observed that progesterone levels were uniformly low at the same time the urticaria was most active. Conversely, circulating progesterone was increased during periods when the hives were relatively quiescent and the eosinophil counts had returned to baseline levels. These clinical observations in this patient suggested that endogenous secretion of progesterone modulated both the urticarial episodes as well as the migratory and/or proliferative properties of eosinophils in this patient. This working impression was confirmed by the fact that administration of medroxyprogesterone ameliorated both her hives and high absolute eosinophil counts.

This patient did not exhibit evidence of IgE-mediated cutaneous reactivity to progesterone or estrogen. Moreover, direct in vitro LHR studies in response to physiologic concentrations of progesterone and estrogen did not stimulate histamine release. On the contrary, administration of medroxyprogesterone resulted in resolution rather than exacerbation of the hives and associated eosinophilia. These findings essentially excluded possible autoimmune hypersensitivity or anaphylactic responses to progesterone, as had been previously reported in a few cases. It is unlikely that metabolites of progesterone could have caused a hypersensitivity response in this patient. Me-
tabilities would be expected to be increased concurrently with endogenous progesterone. Thus, if the urticaria and eosinophilia observed in this patient were due to hypersensitivity to progesterone metabolites, it would be expected that her symptoms would be exacerbated rather than reduced when endogenous progesterone was elevated.

The inhibitory effect of progesterone on IgE-induced release of histamine from basophils in this case was an unexpected finding and, to our knowledge, had not been previously reported in humans. Schleimer et al.\textsuperscript{24} reported significant inhibition of anti-IgE-induced histamine release by preincubation of basophils with dexamethasone but not by progesterone in normal subjects. Thus, this in vivo inhibitory effect of progesterone may be unique to our patient. Our findings are consistent with that of Schleimer et al.\textsuperscript{24} in that we did not observe significant inhibition by progesterone of anti-IgE-induced release in five control subjects. In an experimental model, progesterone pretreatment has been demonstrated to inhibit antigen-activated release of histamine from sensitized oviducts and atria in guinea pigs.\textsuperscript{25} In our patient it would appear that the physiologic “protective” effect of progesterone on decreasing urticarial symptoms was no longer effective when plasma progesterone levels decreased to low levels. Subsequent increases in endogenous progesterone or replacement with medroxyprogesterone may have restored the inhibitory effect on cellular release of mediators, thereby resulting in a decrease in urticaria.

The pathogenesis of cyclic fluctuation of total IgE in this case is unexplained. Neither circadian nor supracadidian fluctuations of total IgE have been observed in normal subjects.\textsuperscript{26} However, significant circadian rhythm of a daytime peak and a nocturnal dip has been reported in patients with asthma and with high levels of total IgE.\textsuperscript{27} Postseasonal increases of specific and total IgE may occur in atopic patients stimulated by pollen exposure. Our patient was neither asthmatic nor atopic. In any case, medroxyprogesterone did not appear to affect the IgE variability in this case because IgE levels continued to rise while she was receiving progesterone.

Another interesting observation in this study was the marked decrease of eosinophilia during treatment with medroxyprogesterone. This observation is consistent with known in vitro effects of progesterone as an inhibitor of eosinophil colony formation from bone marrow progenitor cells.\textsuperscript{29} These modulatory effects of progesterone on eosinophil colony formation could also account for monthly decreases of absolute eosinophil counts concurrent with cyclic increase of endogenous progesterone. An inhibitory effect of progesterone on eosinophil chemotaxis could also be considered as a possible mechanism in this case. Further studies will be required to elucidate the exact role of sex steroidal hormones in the pathogenesis of progesterone-responsive urticaria and eosinophilia.

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REFERENCES


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