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Two Cases of Autoimmune Progesterone Dermatitis. Immunohistochemical and Serological Studies

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Two cases of autoimmune progesterone dermatitis are reported. The patients developed recurrent pruritic erythematous and edematous eruptions on the extremities, trunk or face, with occasional vesicles on the palms and soles. The eruptions appeared 7 to 10 days prior to their menstruation and persisted for several days. They showed immediately positive skin tests with 0.1 mg/ml and 0.2 mg/ml of aqueous progesterone suspension, respectively. The patients had IgG serum factor which bound rat corpus luteum. Positive indirect basophil degranulation tests against progesterone were demonstrated in both patients. Circulating autoantibodies to patients' own progesterone may cause or modulate the intermittent eruptions of the disease. ***Key words: Menstruation; Skin test; Autoantibody.***

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Autoimmune progesterone dermatitis (APD) is an uncommon skin disease. APD is clinically characterized by the occurrence of cyclical eruptions in each menstrual period. It has been suggested that the disease is related to autoimmunity to endogenous or exogenous progesterone by antibody- or cell-mediated reactions. These reactions may result in basophil and/or mast cell degranulation, causing the development of the eruptions (1). Here, we report the clinical features of APD, a positive basophil degranulation test against progesterone and the positive immunofluorescent reaction of "autoantibody" to endogeneous progesterone.

CASE REPORTS

Case 1. A 21-year-old female visited our department on June 15, 1985, with recurrent pruritic erythematous and edematous eruptions on the extremities and trunk. The eruptions began at the age of 20 and continued to recur prior to each menstrual period. The rash appeared 7 to 10 days prior to menstruation and persisted until one or two days after the flow. The eruptions were ill-defined edematous erythema (Fig. 1), and erythema with vesicles on the palms and soles. Swelling and hotness were noted on the hands and lower legs. The cycle of her menstruation was regular. She had not taken oral contraceptives. She had a history of atopic dermatitis and allergic rhinitis. Abnormal laboratory data were eosinophilia (814–2 618/mm^3) and high serum IgE (4 000<) in routine tests. Hormonal analysis revealed normal levels of serum progesterone and estrogen. Administration of 1.25 mg of conjugated estrogens daily for a month moderately controlled the development of the lesions. After stopping the administration of estrogens to permit menstruation, the eruptions reappeared. Thereafter, she was controlled by topical steroids and antihistamines, and a moderating effect resulted.

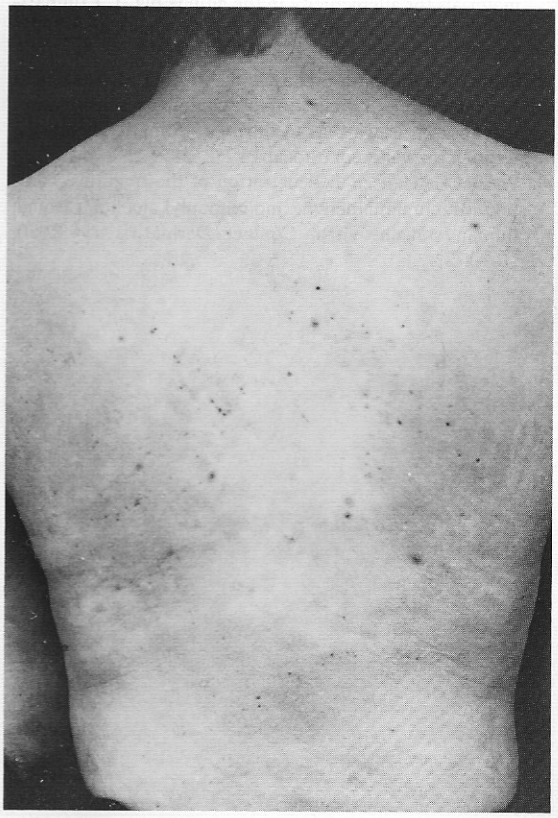

Fig. 1. Edematous erythema on the back of case 1.

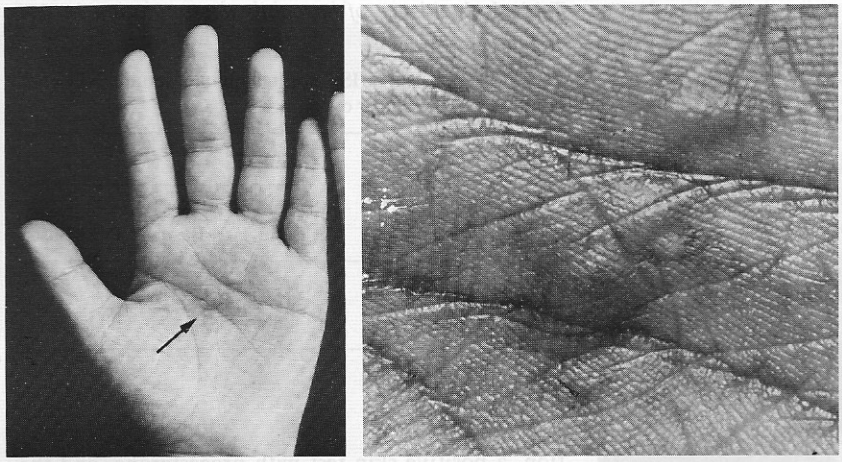

Fig. 2. Erythema with vesicles on the palm of case 2.

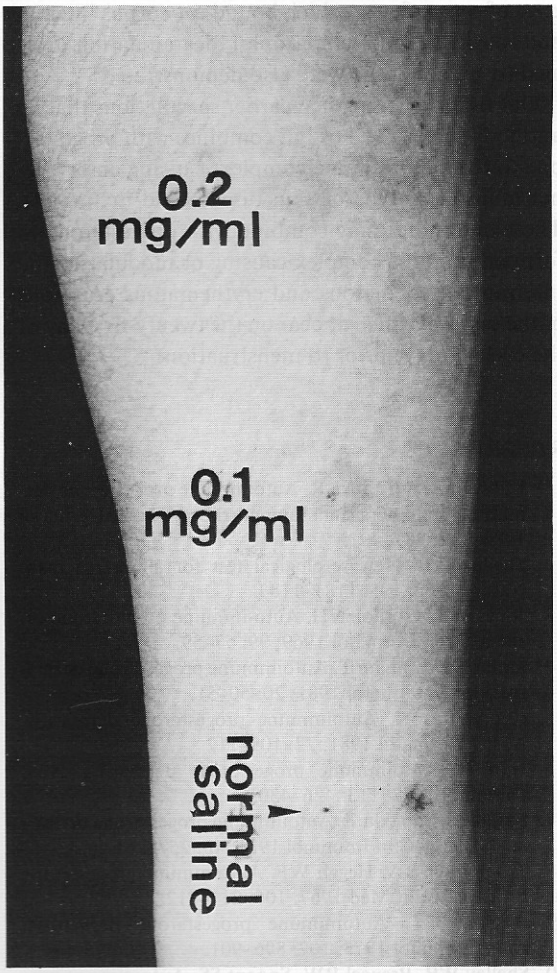

Fig. 3. Positive skin tests with progesterone of case 1.

Case 2. A 31-year-old female who was first seen on July 10, 1985 with a one-year history of intermittent edematous erythema involving her arms, hands, and face, with occasional vesicles on the palms (Fig. 2). These eruptions began 7 to 10 days prior to the menses, with the lesions persisting until 3 or 4 days before the flow. She was otherwise healthy and there was no drug history of contraceptives. Routine laboratory tests were normal except for eosinophilia (624/mm^3). She was treated with topical steroids and antihistamines, relieving most of her symptoms.

Examination and results

Intradermal skin test. Intradermal skin tests were performed by using aqueous progesterone suspensions of 0.1 mg/ml and 0.2 mg/ml. Both patients had positive reactions within 20 minutes, with a wheal formation of about 12×12 mm in case 1 (Fig. 3) and 10×10 mm in case 2, with erythema. The reactions after 48 hours were negative. Two female volunteers, injected intradermally with the same material, displayed no reactions.

Light and electron microscopy. A biopsied specimen was taken from an early edematous erythema on the upper arm of case 1. Mast cells were largely seen in perivascular lymphocytic infiltration and there was mild edema. The degranulation of the mast cell granules was demonstrated in electron microscopy.

Immunofluorescent study. Serum from each patient two weeks after the rush, with a dilution of 1/256, was incubated with frozen sections of rat ovarian tissue for 60 min, washed with PBS, and incubated with FITC-labeled rabbit anti-normal human IgG for 60 min. Fluorescent staining was seen in the cytoplasm of the luteinizing cells (Fig. 4). The control serum from normal female was negative. Immunofluorescence was blocked when free progesterone (1×10^{-3} or 1×10^{-4} mM) was added to the patients' sera before incubation with the ovarian tissue. A direct immunofluorescent test showed no deposition of IgG, IgM, IgE, or C3 in the involved skin of case 1.

Indirect basophil degranulation test. Sterile progesterone, 5 mg/ml 40 % ethanol solution diluted 1 : 10 with normal saline,

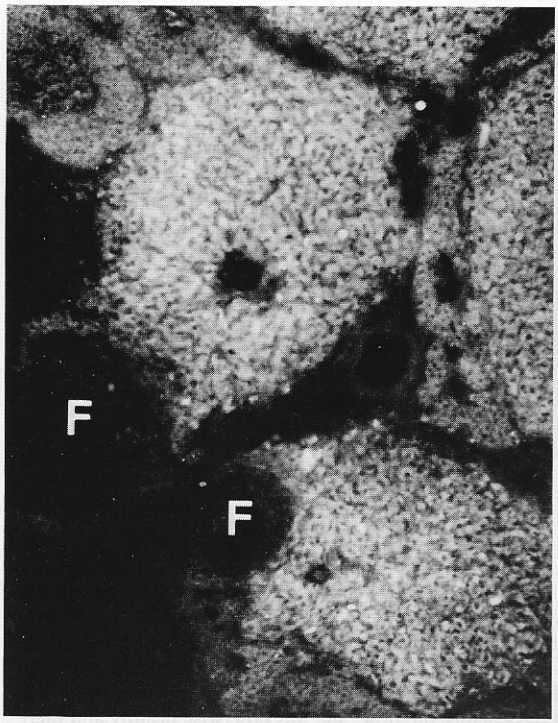

Fig. 4. Note the presence of the immunofluorescent reaction in the cytoplasm of the corpus luteum cells. The ovarian follicles (F) and the interstitial tissue show no reaction (×50).

served as the antigen. This test was performed by the method of Shelley (2), taking one drop of serum, adding one drop of purified test antigen, and mixing with rabbit basophils for 15 min. Cell smears were stained with neutral red. In each patient's serum, the antigen plus rabbit basophils resulted in degranulation of 45% to 64% of the basophils. Three control groups were all negative (Table I).

Table I. *Incidence of basophils degranulation in test sera and controls*

PG=progesterone; NHS=normal human serum; ND=not done. Positive: 30% or over

		Controls		
	Pt. Sera+PG +Baso.	Pt. Sera +Baso.	NHS+PG +Baso.	PG+Baso.
Case 1	47–64%	3–13%	18–23%	5%
Case 2	45–58%	13–23%	ND	ND

DISCUSSION

It has been reported that autoimmune progesterone dermatitis develops cyclic and recurrent eruptions with polymorphic manifestations of eczematous (3) and erythematous patches (1), urticarial- (4–8) and erythema multiforme-like eruptions (4, 6), or vesicular, bullous (6, 9), and papulopustular lesions (10). In these cases, positive skin tests with progesterone have shown immediate reactions (1, 7), delayed hypersensitivities (3, 10), and both the immediate and the delayed types (5, 6). However, there are few reports which demonstrate the presence of "autoantibody" to progesterone by immunohistochemical study (7). The complete criteria for diagnosis of APD should be based on a cyclic skin rash associated with menstruation, a positive skin test with progesterone, and the presence of circulating antibody shown by immunologic or serological tests (1, 3). Our patients showed positive skin tests of the immediate type. The presence of serum factor which bound rat corpus luteum, and positive indirect basophil degranulation tests against progesterone were also demonstrated.

Our findings strengthen earlier speculations that an antibody such as IgG or IgE combines with progesterone to form an immune complex, causing an erythema multiforme-type of skin disease and itching (4). These antibodies may combine with progesterone to form an immune complex causing or modulating the intermittent edematous and erythematous eruptions of the disease, which appear on the twenty-first day of the cycle (7 days prior to menstruation).

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