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Case Report

Autoimmune progesterone dermatitis presented as acute generalized exanthematous pustulosis

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Abstract Autoimmune progesterone dermatitis (AIPD) is a rare autoimmune response to endogenous progesterone, characterized by cyclic cutaneous and mucosal lesions at the end of the luteal phase with varied type of skin lesions include urticaria, angioedema, erythema multiforme, eczema, folliculitis, papulovesicular eruptions, fixed drug eruption, purpura, or vulvovaginal pruritus and anaphylaxis. We report a case of AIPD presenting as acute generalized exanthematous pustulosis (AGEP). She had papulovesicular lesions with sheet of pustules that appeared in relation with menstrual cycle. Progesterone intradermal test was positive. She was treated successfully with combination oral pills.

Key words
Autoimmune progesterone dermatitis, cyclical, acute generalized exanthematous pustulosis.

Introduction

The menstrual cycle is a cyclical change in the female genital tract caused by estradiol and progesterone. Many women notice changes in their skin and hair during the course of monthly cycle i.e. increase in acne in premenstrual phase or skin becomes greasier. Pre-existing skin disorders, other than acne, may also undergo pre-menstrual exacerbation; examples are psoriasis, rosacea, atopic dermatitis, lupus erythematosus, anogenital pruritus, recurrent aphthae and herpes simplex. There are patients in whom the regular appearance of skin changes in premenstrual period is associated with evidence of hypersensitivity to progesterone.[1]

Autoimmune progesterone dermatitis (AIPD) is a rare autoimmune response to endogenous progesterone, characterized by cyclic cutaneous and mucosal lesions at the end of the luteal phase when progesterone levels are elevated. Symptoms occur 3 to 10 days before menses, with the postovulation rise in progesterone. These lesions usually disappear 1-2 days after menstruation ceases.[2] Skin lesions include urticaria, angioedema, erythema multiforme, eczema, folliculitis, papulovesicular eruptions, fixed drug eruption, purpura, or vulvovaginal pruritus. Anaphylaxis is also reported.[3]

Acute generalized exanthematous pustulosis (AGEP) is an uncommon skin eruption characterized by superficial nonfollicular aseptic pustules. AGEP is usually classified as a severe cutaneous adverse reaction to a prescribed drug. Typically the AGEP rash starts on the face or in the armpits and groin, and then becomes more widespread with appearance of areas of red skin studded with small sterile pustules Facial swelling often arises and may be associated with fever and malaise. The rash may last for one to two weeks and then the skin peels off as it resolves. Leukocytosis may occur.[4]

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We report a case of autoimmune progesterone dermatitis presented as acute generalized exanthematous pustulosis.

Case Report

A 38-year-old female presented with systemic features like fever and skin rash with sheet of pustules, vesicles and generalized exfoliation on face, trunk (both back an chest), upper and lower extremities on an erythematous background for 3-4 days duration (**Figure 1a**, **b**, **c**). Lesions began as erythema and pruritic papules appeared on face, followed by folds of all joints and upper back and rapidly progressed peripherally extending to large areas of body. Papules turned to sheet of pustular lesions shortly, that dried and began to exfoliate in next 3-4 days. There was no history of drug intake and the patient was menstruating (3^{rd} day) at the time of presentation. Patient was treated with oral glucocorticoids and antihistaminic and the lesions subsided shortly. Full blood count and liver function and renal function tests were normal. She was discharged with in few days with a diagnosis of acute generalized exanthematous pustulosis.

In the next week patient again came with complain of appearance of pruritic papules on her arm upto elbow **(Figure 1d)**, back of legs and thigh. A detail history revealed that, she used to develop that kind of rash in each month, began 3-4 days before starting of menstruation and subsided spontaneously or with antihistaminic within 4-5 days after stoppage of menstruation. She had also history of taking progesterone containing combination oral pill for few years and stopped 1 year back. A skin biopsy was taken, showed dermal perivascular lymphohistiocytic inflammation **(Figure 2a)**, Progesterone intradermal skin test was done in dermatology operation theater keeping all emergency management kit ready in hand. It showed positive progesterone skin test with >15 mm erythema and wheal on the site of (progesterone 50mg/ml at a dilution of 1:1 aqueous solution) and more than 10mm erythema and wheal at (1:10 dilution) site, taking normal saline as negative control **(Figure 2b)**. Skin test lesions were persisting till 7 days after the test **(Figure 2c)**. Serum progesterone level was estimated in the luteal phase, it was high (35ng/ml; normal 0.37- 18.4 ng/ml).

Based on this result, the patient was diagnosed with APD. She was treated with antihistaminics and combination oral pill containing with 30µg of ethinyl estradiol and 0.1mg of levonorgestrel and during last two months she didn't develop any such skin reaction.

Discussion

Autoimmune progesterone dermatitis patients may present with varied type of skin lesions. It may be urticarial lesions, eczema and erythema multiforme-like eruptions (with or without mucosal or perineal involvement), purpura and recurrent anaphylaxis.[5-9] The skin lesions develop 3-10 days before menstruation and persist up to 1-2 days after the end of the menstrual cycle, with recurrent cyclic aggravation, closely related to the serum progesterone concentration.[5] Our patient also had the same cyclical pattern of skin lesions that appeared 3-4 days before menstrual cycle, presented with sheet of papulovesicles and pustules involving face, body folds and extremities associated with fever. The age of onset is variable, with the earliest age reported at menarche.[10] Some studies have noted that a majority of patients had taken an oral contraceptive (OCP) prior to the onset of APD, but multiple cases exist in which women have

Figure 1a Erythema, edema and exfoliation on face and upper trunk

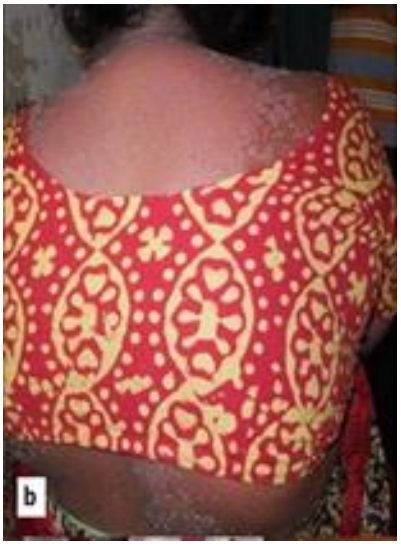

Figure 1b Erythema and exfoliation on back

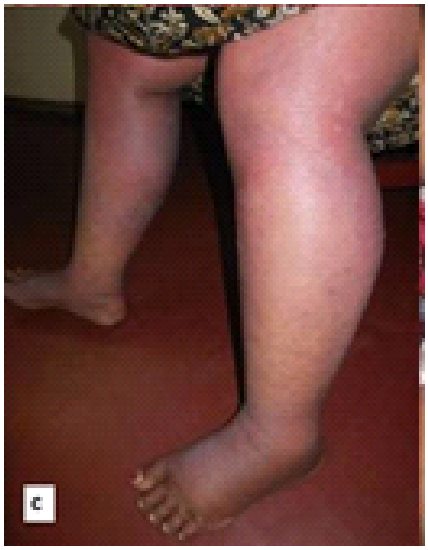

Figure 1c Vesicopustules, erythema and edema on both lower limbs

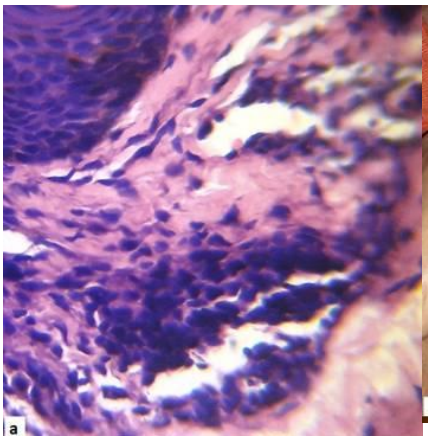

Figure 2a Dermal perivascular lymphohistiocytic inflammation. (hematoxylin-eosin; original magnification X10).

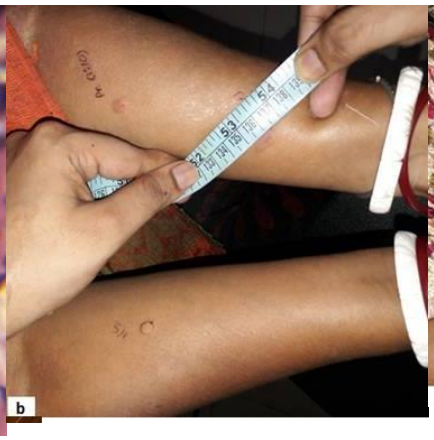

Figure 2b Intradermal test with progesterone (1:10, 1:1), positive after 15 min. erythema and induration more than 15 mm at 1:1 dilution site

Figure 2c Healing vesicle persisting after 7 days of test.

never been exposed to exogenous progesterone.[11]

The pathogenesis of autoimmune progesterone dermatitis remains unclear.[5] It is proposed that after exposure to exogenous progesterones, especially oral contraceptives or intrauterine devices, sensitized presenting cells and T helper-2 lymphocytes generate specific IgE antibodies, which then cause skin lesions via type 1 hypersensitivity reaction as progesterone levels rise.[6,12] Expression of membrane progesterone receptors (mPRs) in peripheral blood lymphocytes (PBLs) and T lymphocytes of nonpregnant women have been described. It has also shown that progesterone results in Gi-protein activation in immortalized T cell line. So, progestin, both innate and external can produce this undesirable effects.[13]

Intradermal tests with progesterone shows both immediate reactions (within 30 minutes) and delayed reactions (24-48 hours later) and may indicate both types I and IV hypersensitivity

reactions.[10] Skin test results in our patient with progesterone had shown immediate reactions (within 30 minutes), delayed reactions (24-48 hours later), and reactions with features of both immediate and delayed features. A small ulcerated papule was present even after 7 days, in the site where (1:1) dilution progesterone was given. We could not perform a progesterone patch test to evaluate a type IV reaction. The presence of anti-progesterone antibodies suggests other pathogenic mechanisms, including type III hypersensitivity reaction to antigen-antibody complexes that are deposited in the skin, which could induce dermatitis, as progesterone secretion increases before and after menstruation. Since this antibody is not detected in all patients, this hypothesis only partially explains the pathogenesis.[2] We could not test anti-progesterone antibodies in our case.

The diagnostic criteria for autoimmune progesterone dermatitis proposed by Warin[14] are as follows: (1) premenstrual flare (2) reproducibility of rash with intramuscular progesterone; and (3) symptomatic improvement after inhibiting progesterone secretion by suppressing ovulation.[14] In the intradermal test, immediate and late reactions may occur, so the reactions should be monitored for up to 24-48 hours after allergen injection.[15]

Autoimmune progesterone dermatitis is not very responsive to conventional antihistamines and steroids. Therefore, current treatment modalities are inhibiting progesterone secretion by suppressing ovulation. Conjugated estrogens, GnRH analogues, tamoxifen can use successfully but has profound side effects.[5] Bilateral oophorectomy can be considered in patients refractory to medical treatment.[15]

Oral contraceptive pills containing ethinyl estradiol and levonorgestrel produce a very good result, even a short course of OCP can produce a long lasting suppression. Our patients also responded very well with combination OCP. This effect may be due to suppression of ovulation and desensitization to progesterone.[16]

It is difficult to diagnose AIPD at the first time due to its varied presentation. Whenever the dermatological manifestations are in a cyclical fashion around an woman's' menstrual cycle possibility of AIPD should be suspected. Till now AIPD is not reported to present as AGEP.

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