AUTOIMMUNE PROGESTERONE DERMATITIS IN A PATIENT WITH NO MEDICAL HISTORY OF HORMONAL CONTRACEPTION OR PREGNANCY

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Abstract

Context. Autoimmune progesterone dermatitis (AIPD) is a rare, cyclical dermatosis, with variable clinical presentation, occurring exclusively or being aggravated during the luteal phase of the menstrual cycle, when levels of progesterone rise. Its pathogenesis is still unclear. AIPD is thought to occur as an autoimmune reaction to endogenous possibly modified progesterone, but it could also be triggered by exogenous progesterone exposure. AIPD is a diagnosis of exclusion. Usually there is no or limited response to oral H1 antihistamines and a partial response to steroids. Ovulation inhibitors represent the specific treatment.

Case report. We report a case of AIPD in an 18-year-old nulliparous patient with no medical history of allergic diseases and no exposure to oral contraceptive pills. AIPD was suspected based on the clinical picture (recurrent cyclical eczematous eruption on the face and abdominal area) and confirmed by positive intradermal test and positive progesterone challenge. This diagnosis was supported by the result of the skin biopsy, which also helped to exclude other dermatoses with premenstrual aggravation. The rash responded satisfactorily to treatment with a combination of oral contraceptives, levonorgestrel and estrione, which is currently considered first line therapy.

Conclusions. This case is of particular interest due to the lack of previous pregnancy or exposure to progesterone therapy. Recurrent, cyclical eruptions in fertile women should raise the suspicion of AIPD. If early recognized, the patient may benefit from non-invasive treatment that improves significantly the quality of life.

Key words: progesterone dermatitis, immunological reaction, progesterone challenge.

INTRODUCTION

Autoimmune progesterone-induced dermatitis (AIPD) is a rare, cyclic dermatosis with variable clinical presentation, occurring exclusively or being aggravated during the luteal phase of the menstrual cycle, when levels of progesterone rise. Its exact pathogenesis is unclear. An autoimmune reaction to endogenous, possibly modified progesterone is suspected (1-3), but it could also be triggered by exogenous progesterone exposure. It has been hypothesized that antigen presenting cells could take over, process and present progesterone to T helper (Th) 2 cells, generating type I and IVb, apparently dose-dependent, hypersensitivity reactions (4). Progesterone was shown to upregulate membrane progesterone receptor-a (mPRα) on CD8+ cells and to alter Th1/Th2 balance in favour of the Th2 profile, suggesting that progesterone possesses immunomodulatory properties (5). Moreover, progesterone can modulate an inhibitory G-coupled protein on / inside T cells (6).

Some authors suggest that an altered form of endogenous progesterone may appear, leading to anti progesterone - antibody production and a type III hypersensitivity reaction (7). Previous sensitization to exogenous progesterone could determine cross-reactivity with other substances (e.g. steroid groups) (8-13). Exacerbation of type I and IV hypersensitivity reactions by elevated progesterone levels, through a metabolic effect, has also been described (14, 15).

The clinical presentation of AIPD is highly variable and laboratory and skin biopsy findings are often nonspecific. The diagnosis is confirmed by specific tests and positive progesterone challenge test. Usually there is no or is a limited response to H1 antihistamines and a partial response to steroids administered in medium to high doses. Ovulation inhibitors represent the specific treatment (3, 16).

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Acta Endocrinologica (Buc), vol. XI, no. 1, p. 99-102, 2015
We report a case of AIPD in a nulliparous patient with no previous exposure to oral contraceptives.

CASE REPORT

An 18-year-old Caucasian female patient was referred to our clinic for an erythematous-papulo-vesicular eruption that occurred monthly perimenstrually on her face and abdominal area since the age of 14. Pruritic erythematous papules developed cyclically on her face and abdominal area 4 days before the onset of menses and resolved 3 days into menses, affecting the quality of the patient’s life. The initial diagnosis was allergic contact dermatitis and medium potency dermatocorticoids were recommended, with unsatisfactory results. The patient presented to our clinic, 2 days before the onset of menses, for a second opinion.

She had no history of allergic disease, exposure to oral contraceptive pills or pregnancy. Age of menarche was 12 and menses were regular.

Physical examination revealed erythematous papules, vesicles and several residual hyperpigmented macules on her face and abdominal area (Fig. 1). The patient gave her written informed consent for the photographs to be used in medical publications.

Full blood count, routine biochemical work-up, complement serum levels, antinuclear antibodies (ANA) serum levels, and the erythrocyte sedimentation rate (ESR) were normal. Thyroid function tests and serum total immunoglobulin (Ig) E level were within normal limits as well. In addition, a skin biopsy was performed. The histopathologic exam revealed the presence of an interface dermatitis, with lymphocyte and eosinophil exocytosis and spongiosis (Fig. 2).

Clinical examination, normal levels of complement, ANA, ESR, and serum total Ig E levels and the interface dermatitis aspect on lesional skin biopsy led to the exclusion of other dermatoses that can flare-up perimenstrually such as acne vulgaris, systemic lupus erythematosus, atopic dermatitis, rosacea. An autoimmune progesterone dermatitis was suspected.

Progesterone level measured from fasting blood samples on day 21 of the patient’s menstrual cycle was 9.7 ng/ml (normal range 1.7-27.0 ng/ml, using chemiluminescence immunoassays), documenting ovulation.

Progesterone prick and intradermal tests were performed during the first week of the menstrual cycle, when levels of progesterone are the lowest. Progesterone in aqueous solution, 100 mg/ml, diluted in saline at concentrations of 0.01%, 0.1% and 1% was used. Emergency medication and equipment were

Figure 1. Papulovesicular eruption located on the abdominal area.

Figure 2. Hematoxylin-eosin staining of the skin specimen showing minimal hyperortho/parakeratosis, moderate acanthosis, marked spongiosis with lymphocyte exocytosis, perivascular eosinophilic infiltrate, dermal eosinophils (A: x100 magnification, B: x400 magnification).
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readily available during the testing period and for the following 8 hours. No immediate reaction was observed. Nevertheless, 26 hours after the intradermal test, 5 mm red papules appeared for progesterone at 0.1 % and 1% concentration and we witnessed an exacerbation of the preexisting skin lesions.

Six days following the intradermal test we undertook 100 mg progesterone pessary challenge. The patient was kept under observation for 8 hours after the insertion of the pessary, in order to monitor potential development of systemic reactions. A typical eruption occurred on her face and abdominal area 24 hours later, confirming the diagnosis of AIPD.

We decided to initiate treatment with a combination of oral contraceptives that inhibit ovulation (levonorgestrel and estrione), associated with oral H1 antihistamines. The skin lesions resolved completely and did not recur during the 12 months follow-up period, demonstrating a good response to the inhibition of the post-ovulatory peak in endogenous progesterone release.

DISCUSSION

AIPD is a rare dermatological disorder characterized by a cyclic rash. Urticarial, papular, papulovesicular eruptions and erythema multiforme lesions are the most frequently encountered clinical pictures (17-19). Ulcerative or erosive stomatitis has also been reported (20).

The exact pathogenic mechanisms of AIPD are still unknown. As discussed above, type I, III and IV hypersensitivity reactions to progesterone seem to be implicated in AIPD pathogenesis (Fig. 3).

In our case, AIPD was suspected based on the clinical appearance (eczematous rash) and confirmed by epicutaneous tests followed by a positive progesterone challenge (progesterone pessary). The histopathologic findings (interface dermatitis, lymphocyte and eosinophil exocytosis, spongiosis) support the diagnosis and suggest a type IV hypersensitivity reaction.

In the absence of a typical clinical picture, AIPD is a diagnosis of exclusion. Whenever confronted with a recurrent, perimenstrual eruption in a woman during her fertile period, AIPD should be considered. The following three main criteria are currently considered necessary for the diagnosis of this disease: (1) a cyclic dermatosis in the luteal phase of the menstrual cycle, (2) a positive progesterone intradermic test or a positive challenge test and (3) prevention of a progesterone - induced skin rash with specific treatment (3, 17-19). Our patient met all these criteria.

Treatment options include oral H1 antihistamines, corticosteroids with limited benefit and medication that inhibit ovulation. In the presented case a combination of oral contraceptives (levonorgestrel and estrione) and oral H1 antihistamines led to complete clinical remission.

Figure 3. Postulated Type IVb and IVc hypersensitivity reaction induced by progesterone: Progesterone is internalized and processed by the antigen presenting cells (APC) and presented to Th0 cells, activating them and driving their differentiation towards CD4+ Th2 or CD8+ cytotoxic lymphocytes (CTLs) subtype. Direct linkage to Th cells is possible. Th2 cells produce interleukin (IL) 4, IL5, IL13 that lead to eosinophilic inflammation.
In conclusion, we report a well documented case of AIPD in an 18-year-old nulliparous patient. This case is of particular interest due to the lack of previous exposure to progesteron therapy. It is our belief that many AIPD cases remain undiagnosed due to the variability of the clinical picture. Recurrent, cyclical eruptions in fertile women should raise the suspicion of AIPD. If early diagnosed, patients may benefit from non-invasive, clinically efficient treatment that can improve the quality of life significantly.

Conflict of interest
We declare that there is no conflict of interest.

References