

Catamenial Dermatoses: Rarity Revisited

Mohammad Abid Keen, Swati Watwani

Consulting Dermatologist, Jammu and Kashmir Health Services, Maharashtra, India

INTRODUCTION

Cyclic premenstrual physiological changes in healthy skin and various dermatoses represent common ailments reflecting the direct or indirect response of skin to fluctuations in circulating sex steroid hormones. A subset of chronic dermatoses are not specifically induced but are merely exacerbated at the end of the ovarian cycle, while as catamenial eruptions are specifically restricted to only the menstruation periods. Thus, catamenial dermatoses may be defined as cyclical skin reactions to hormones produced during the menstrual cycle.(1,2) The most common of these reactions is autoimmune progesterone dermatitis (APD), caused by an autoimmune response to endogenous progesterone in women of reproductive age.(3) It has an onset anytime between menarche and menopause and is clinically characterized by a myriad of presentations including urticaria, eczema, papulovesicles, angioedema, anaphylaxis, pruritus and erythema multiforme.

Ovarian Cycle, sex hormones, and the skin: the interplay

Skin contains receptors to estrogens, progesterone, and androgens, thus making it prone to the effects of these sex steroids. There is an obvious modulation of the sebaceous gland activity by these endocrine fluctuations. Estrogens possibly increase the density in intracellular dermal versican and in extracellular hyaluronic acid, resulting in an increased hydration which in turn leads to tissue water retention and turgescence. In women there are also differences in cutaneous blood flow at different stages of their menstrual cycles, with a possible contribution of sex hormones to these differences.(4) Peripheral skin circulation has been seen to vary significantly within one menstrual cycle.(4) Estrogens may also stimulate the intraepidermal melanogenesis, accounting for a possible transient patchy hyperpigmentation around the eyelids and nipples during the premenstrual phase. The effects of progesterone on skin have not been firmly established.

Premenstrual Syndrome

Premenstrual Syndrome is a common condition described as a constellation of physical and mental symptoms tied to a woman's menstrual cycle. Although dermatoses may also occur, they are infrequently mentioned, probably due to their rarity or failure of association with the predominant mental and behavioural symptoms. Various signs and symptoms developing during the premenstrual phase are tabulated in [Table 1].

Table 1: Salient features of premenstrual syndrome.

Pain/swelling of breasts
Frequency of micturition, constipation
Nausea, vomiting, abdominal bloating
Headache, malaise, backache, leg cramps
Anxiety, irritability, restlessness, insomnia,
Fluid retention, edema, weight gain
Seborrhea, acne

In addition, it has also been noted that certain other disorders are prone to exacerbations during the premenstrual phase of cycle.(5) Thus, migraine and epilepsy have been described as more difficult to control during this period.(5) It is well known that almost 75% of female patients with acne vulgaris complain of a premenstrual flare, while many other dermatoses, such as atopic dermatitis, chronic urticaria, and interdigital dermatitis, exhibit similar exacerbations in some persons.(5)

Catamenial exacerbation of preexisting dermatoses

Increased cutaneous blood flow and dermal edema, as well as increased premenstrual activity

may aggravate pruritic conditions such as eczema and pruritus vulvae. It has also been seen that acne vulgaris, rosacea, and cutaneous lupus erythematosus commonly deteriorate.

Correspondence to: Mohammad Abid Keen, Consulting Dermatologist, Jammu and Kashmir Health Services, Maharashtra, India, Tel: 9419963692; E-mail: keenabid31@gmail.com

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Premenstrual flare-up has been recognized in a variety of dermatoses including psoriasis, atopic dermatitis, perioral dermatitis, lichen planus, dermatitis herpetiformis, erythema multiforme, pompholyx, and urticaria.(6,7)

Autoimmune Progesterone Dermatitis (AIPD)

Autoimmune Progesterone Dermatitis was first described by Geber in 1921.(8) In the year 1995, Herzberg et al.(9) reviewed the existing English and German literature and discovered 42 documented cases. Nine years later in 2004, Baptist and Baldwin(10) stated that since Gerber’s description, there have been approximately 50 cases of APD in the medical literature. AIPD is a broad term encompassing a variety of skin disorders characterized by cyclic recurrent premenstrual exacerbations related to fluctuations in serum progesterone levels. Although this condition has been exclusively reported only in ovulating women, two third of the cases have been exposed to progesterone ingestion under oral contraception prior to the eruption.

Pathogenesis

There have been several theories proposed for the pathogenesis behind autoimmune progesterone dermatitis. The exact pathophysiology of the disease is unknown, only some commonalities in the few cases ever reported may give clues into this potentially life-threatening disease. Although the exact pathogenesis has not been fully elucidated, it is considered as an autoimmune reaction to both endogenous and exogenous progesterone, because the skin eruptions are observed during the luteal phase of the menstrual cycle and resolve a few days after menses. The evidence for autoimmunity include a positive intradermal test with progesterone, preferably in an aqueous or aqueous alcohol solution, and/or existence of circulating antibody to progesterone, and by suppression of symptoms with agents that inhibit ovulation and result in decreased serum progesterone. (9,11) Two patients with recurrent premenstrual erythema multiforme and autoreactivity to 17 α -hydroxyprogesterone have been described (12,13); in one case, the eruption spread in pregnancy, cleared after abortion and was associated with a high-affinity binding factor to 17 α -hydroxyprogesterone in the serum.(13)

Recently, it has been suggested that a number of catamenial dermatoses labelled as AIPD are caused instead by PGs, especially when the timing of the rash is not supportive for progesterone or oestrogen as possible triggers.(14) Relative eosinophilia presents in cutaneous symptoms in many patients reported through the years, as well as suggestions that progesterone may induce mast cell degranulation by its nature. (15) Whether the eosinophilia is a random correlation with the disease or a direct cause is unknown.(10)

Clinical features

The cutaneous lesions that have been described in AIPD are very variable, resembling eczema, particularly the pompholyx type, urticaria, erythema multiforme, dermatitis herpetiformis or anaphylaxis.(16,17) [Table 2]. The dermatitis typically flares

during the second half of the ovarian cycle, with a premenstrual peak and rapid resolution within a few days of menstruation. This appearance and resolution has been found to correspond to the rise and fall of progesterone.(18) Rare cases of AIPD have appeared or worsened during pregnancy, with or without postpartum premenstrual cyclic flare up. This condition is tentatively explained by the steady rise in the levels of progesterone and estrogen throughout pregnancy.

Risk factors for the development of AIPD are tabulated in [Table 3].

Table 2: Morphology of skin lesions in AIPD.

Erythema multiforme
Erythema annulare centrifugum
Urticaria
Angioedema
Eczematous and fixed drug eruption-like lesions
Ulcerative stomatitis
Dermatitis herpetiformis
Pompholyx
Papulopustular/papulovesicular lesions,
Vesiculobullous reactions
Steven-Johnson syndrome

Table 3: Risk factors for AIPD.

Fertile women
Previous history of exogenous progesterone intake.
Pregnancy

Diagnosis

To exclude other forms of cyclic catamenial dermatoses and premenstrual flares of existing chronic dermatoses, Warin(19) proffered a diagnostic criteria for APD, which includes:

Association with menstrual cycle.

Positive response to intradermal testing with progesterone [which may be immediate within 30 minutes or delayed after 24-48 hours].

Symptomatic improvement after inhibition of progesterone secretion by suppressing ovulation.

Treatment

A number of treatment modalities have been tried with varying degrees of success [Table 4]. These include topical steroid for

mild cases, oral prednisolone(20) in moderately high dose, conjugated estrogens(21,22) and oral contraceptive pills, (7,10,20,22) antiandrogens like tamoxifen,(23) danazol,(24) and Gonadotropin Releasing Hormone agonist Goserelin.(10,20,21) When the patient is severely affected, surgical oophorectomy has been occasionally recommended for controlling AIPD.(25) Antihistamines are usually ineffective in this rare dermatoses. (10)

Table 4: Treatment options used in APD Treatment.

Treatment modality	Remarks
Antihistamines	Usually ineffective Well tolerated with fewer side effects
Oral contraceptives	Usually tried as initial therapy Act by suppression of ovulation
Glucocorticoids	Act as immunosuppressants Adjuvants to other therapies
Conjugated oestrogens	Avoids progesterone component of OCPs
GnRH agonists	Used in case conventional therapies fail Act by causing pharmacological oophorectomy Risks of premature menopause and relative osteoporosis
Antiandrogens	Act by interfering with gonadal hormone receptors Used in patients unresponsive to conjugated oestrogen
Danazol	By altering immune complex-induced vasculitic reaction
Surgery (Bilateral oophorectomy)	When the patient is severely affected Used in those with cyclic anaphylactic symptoms Also used if conservative medical options have failed Definitive treatment, considered in those not wishing to retain fertility

Catamenial Acne

Catamenial acne consists of a crop of follicular papulopustules supervening in successive perimenstrual periods. It has been seen that the microorganisms involved in the acne process are confined inside the sebaceous hair follicle infundibulum and are

not directly under hormonal influence. Mild facial catamenial acne affects a number of women during the premenstrual period and is often accompanied by increased seborrhea of the scalp. (26,27) There is much variation in the age of onset and the age of resolution of catamenial acne. The severity of catamenial acne seems to peak in the very first days of the ovarian cycle in parallel with variation in the sebum excretion.

Currently, there is a variety of topical and systemic drugs that counteract the main aspects of acne pathology. However, none of them targets specifically catamenial acne with the exception of some oral contraceptives. Treatment options include topical miconazole paste,(28) oral contraceptives,(29) and light/laser therapies.(30) Oral isotretinoin is contraindicated in women with catamenial acne.(28)

Autoimmune progesterone urticaria

Occasionally women notice that their urticaria seems to fluctuate in severity in relation to their menstrual cycle, and there is a rare cyclical form of urticaria, known as autoimmune progesterone urticaria, which occurs 7–10 days premenstrually. (31) Urticaria caused by endogenous progesterone is extremely rare, having been described in the literature in a few case reports.(31,32,33) Progesterone has been incriminated by demonstrating exacerbation of the lesions with progesterone injection, positive skin reactions to progesterone, positive passive transfer with one patient's serum, and immunofluorescence. The exact pathogenesis of autoimmune progesterone urticaria is not known.(31) It might possibly be related to the production of some altered form of the hormone in these individuals. Such an alteration could be of immunologic importance, so that the hormone is no longer recognized as "self" and antibodies form against it.(31) Treatment options include antihistamines, conjugated estrogens, and gonadotrophin-releasing hormone analogue Buserelin.

CONCLUSION

Endocrine fluctuations during the ovarian cycle possibly exert prominent detrimental effects on the skin. Catamenial dermatoses is still a rare distressing disease, and many cases remain undiagnosed due to a lack of awareness of this condition. It is important that further research regarding this disease need to be carried out resulting in a better understanding of the condition, discovery of newer therapeutic agents with less adverse effects and a better quality of life for the persons affected.

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