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A case of catamenial erythema multiforme major successfully treated with goserelin

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Summary

We report a case of catamenial erythema multiforme major in a 46-year-old female. She was treated successfully with goserelin, a GnRH agonist, until the expected age of menopause; however, its therapeutic effects persisted for longer than expected, possibly due to accumulation in adipose tissue.

Learning points

- A group of menstrual cycle-related dermatoses and hypersensitivity syndromes exist but are rarely reported in the literature.
- A history of recurrent cutaneous eruptions in premenopausal females should be considered in the context of the menstrual cycle.
- The diagnosis of menstrual cycle-related dermatoses is largely clinical, although provocation testing can assist.
- Treatment options are broad and are aimed at reducing the immune response and/or suppressing ovulation.
- Goserelin may accumulate and have a gonadotrophin-suppressing effect for longer than expected.

Background

There is a diverse group of recurrent menstrual cycle-related dermatoses and hypersensitivity syndromes affecting women of childbearing age (1). These syndromes are rarely reported in the literature and mechanisms are poorly understood (1, 2). We describe the first reported case of catamenial erythema multiforme major, a rare cutaneous manifestation generally triggered by herpes simplex virus (HSV) (3), occurring in the catamenial phase of the menstrual cycle, and report its successful treatment with goserelin.

Case presentation

A 46-year-old female patient was referred to endocrinology clinic for a 1-year history of recurrent erythema multiforme major (EMM), which appeared to coincide with her menstrual cycle. Her medical history was otherwise significant for type 2 diabetes, obesity (weight: 178 kg and BMI: 56 kg/m^2), hypertension and hypercholesterolaemia. She had been reviewed in immunology, dermatology and infectious diseases clinics for EMM. Her clinical features were typical of erythema multiforme major and the clinical diagnosis was agreed upon by all three teams. She had been commenced on valaciclovir for potential HSV reactivation which was ineffective. She had longstanding oligomenorrhoea, and the onset of EMM coincided with the resumption of regular menses following intentional weight loss of 35 kg. She described onset of lip tingling, eruption of painful targetoid lesions over her arms, hands and feet, mouth ulcers and conjunctival erythema coinciding with menstruation. New lesions would occur daily from day one of her menstrual cycle with the final lesions appearing on the last day of menses. These would heal

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over several days with no lesions occurring during the remainder of her 28–30 day menstrual cycle. However, by the time she was seen in the endocrinology clinic, her periods had again become irregular which made the eruptions difficult to predict with significant impact on her quality of life and ability to work. A clinical diagnosis of catamenial EMM was made, where the term catamenial denotes symptoms during the menstrual period as opposed to other phases of the menstrual cycle.

Investigation

Viral serology revealed HSV1 IgG positivity indicating previous infection, and a herpetic viral PCR panel from a lip lesion swab was negative. Reproductive hormone measurement was consistent with the luteal phase of an ovulatory menstrual cycle with oestradiol: 300 pmol/L, progesterone: 33 nmol/L (reference range (RR): >30), LH: 1.9 U/L and FSH: 2 U/L.

Treatment

Given the lack of response to antiviral therapy, the patient was offered two options by way of therapeutic trial: first, a trial of gonadotropin releasing-hormone agonist (GnRHa) therapy to suppress ovulation and her menstrual cycle, and secondly transdermal oestrogen therapy just prior to and during menstruation in order to mitigate the physiological fall in circulating oestradiol which occurs in the late luteal phase. Possible benefits and risks of each approach were discussed. In particular, the hypo-oestrogenic effects and potential for precipitation of symptoms during the downregulation phase with GnRHa was discussed. Transdermal oestrogen therapy was thought difficult to time correctly as her menstrual cycles had become irregular. She opted for a trial of GnRHa treatment and was commenced on goserelin 3.6 mg monthly for 3 months. This was well-tolerated and resulted in amenorrhoea, without precipitation of EMM with the downregulation phase of treatment. She was subsequently changed to a depot goserelin preparation (10.8 mg 3 monthly) and continued this until age 50, as the expected age of menopause.

Outcome and follow-up

The patient remained amenorrhoeic with complete resolution of EMM. She reported mild vasomotor symptoms, which were not affecting her quality of life and declined add-back menopausal hormone therapy. Following cessation of goserelin at age 50, she remained amenorrhoeic. Interestingly, 11 months following her last dose of goserelin, female reproductive hormones demonstrated a picture of hypogonadotropic hypogonadism rather than menopause (oestradiol <40 pmol/L (RR: 40–130), LH: 0.3 U/L, FSH: 2 U/L (RR: >18)). It was thought that this might be explained by goserelin accumulation in adipose tissue, acting as an ongoing depot. The onset of pituitary dysfunction was considered less likely, and other anterior pituitary biochemistry was unremarkable. At the most recent review, 24 months after goserelin cessation, her gonadotropins had begun to rise (LH: 6 U/L and FSH: 11 U/L, oestradiol: <40 pmol/L, progesterone: <1 nmol/L), which we believe represents goserelin wearing off. She remained symptom free of EMM and amenorrhoeic.

Discussion

Reproductive hormones regulate skin homeostasis and influence the cutaneous immune environment, which may play an important role in menstrual cycle-related dermatoses (1). There are widespread oestrogen receptors, and to a lesser extent progesterone and androgen receptors in the epidermis and dermis (2), and many cutaneous immune cells express sex hormone receptors (2). Altered immune and barrier functions as a result of cyclical changes in oestrogen and/or progesterone are thought to contribute to menstrual cycle-related dermatoses (1).

Catamenial dermatoses occur with the onset of menses, following the steep decline of circulating oestradiol and progesterone (4, 5). These syndromes are thought to be triggered by oestradiol withdrawal or hypersensitivity to uterine prostaglandins (6, 7). Anaphylaxis, anaphylactoid reactions and Stevens–Johnson syndrome have been described (4, 5), but there has been no previously published report of EMM. Some reported cases of catamenial cutaneous manifestations have recorded therapeutic response to non-steroidal anti-inflammatory treatment or to oestrogen or progestogen treatment (4, 5, 6, 8). It was felt that in this patient, the most likely aetiology of catamenial EMM was the steep decline of oestradiol levels prior to menses, although the decline in progesterone levels and hypersensitivity to uterine prostaglandins are also plausible mechanisms. It is important to note that the term catamenial has been used variably by some authors to describe any part of the menstrual cycle including luteal

phase reactions (4, 5). However, in this article we define catamenial as relating to menses.

Progesterone hypersensitivity is the more frequently described of the three subtypes of menstrual cycle-related dermatoses (4, 5, 9). Its manifestations coincide with the progesterone peak in the luteal phase of the menstrual cycle (10). Less commonly, oestrogen hypersensitivity occurs with the oestradiol peaks in the late follicular and luteal phases. There have been 19 reports of EMM due to progesterone hypersensitivity in the literature (2).

The clinical manifestations of menstrual cycle-related dermatoses are broad and are shared across all phases of the menstrual cycle. Diagnosis is made primarily on history, with careful interpretation of the onset of symptoms in relation to the patient's menstrual cycle (2). Provocation testing, particularly with progestogen challenges, has been utilised in some cases. In all cases, treatments are aimed at symptomatic control. Various treatments are described including those aimed at reducing the immune response (antihistamines, systemic and topical glucocorticoids), suppression of ovulation via pharmacological agents and rarely, oophorectomy (1, 2). Suppression of ovulation with GnRHa depot therapy is associated with hypo-oestrogenic effects including reduction in bone density, which should be carefully considered, particularly in younger patients. Specific treatments used in catamenial syndromes include transdermal oestrogen (6) and prostaglandin antagonists, and in progesterone hypersensitivity, desensitisation has been used.

We believe this to be the first reported case of catamenial EMM, which has been successfully managed with goserelin. This case also highlights that the gonadotrophin-suppressing effects of GnRHa depot therapy can persist long after the last depot injection.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the case study reported.

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Patient consent
Written informed consent for the publication of their clinical details was obtained from the patient.

Author contribution statement
JPW, BGAS and LTT were involved in the patient's clinical care for this condition. LTT prepared the manuscript and JPW and BGAS reviewed and edited it.

Patient's perspective
I'm well and have not had an attack or a menstrual period since I first started the Zoladex injections. I only wish the doctors had listened to me from the start and then it might have been sorted a lot quicker.

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