

Chronic urticaria due to autoreactivity to progesterone

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doi:10.1111/ced.12632

Summary

A 23-year-old, regularly menstruating woman presented with recurrent urticarial eruptions, which occurred premenstrually. A skin prick test was positive for progesterone, but the urticaria was unresponsive to standard treatments. The patient was treated with goserelin (Zoladex), which suppressed her menstrual cycle, leading to the resolution of her symptoms. Subsequent flares were controlled by further goserelin injections, and the urticaria is currently in remission. However, the risks of inducing menopause artificially are significant, and alternative long-term solutions may need to be considered in the event of a relapse.

Autoreactivity to progesterone (ARP) is a rare condition, with a cyclical presentation. It can present with urticaria, erythema multiforme, eczema, angio-oedema, or even progesterone-triggered anaphylaxis.¹ Symptoms usually occur between 3 and 10 days prior to menses, coinciding with the luteal phase of the cycle, and resolve with the beginning of menstruation.²

The cause of ARP is unknown. It occurs most often in women who have been exposed to exogenous sources of progesterone, either from an intrauterine system, or the oral contraceptive pill. More rarely, ARP is associated with endogenous progesterone during menarche or pregnancy.³

There are around 50 published cases of this condition, with the first case being described in 1921.¹ Some cases have been associated with spontaneous resolution, or resolution via menopause; others have progressed to anaphylactic shock.¹ We report a young woman with ARP treated with goserelin.

Report

A 23-year-old woman presented in July 2013 with a provisional diagnosis of 'chronic idiopathic urticaria'.

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Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 5 October 2014

She experienced eruptions of chronic spontaneous urticaria and angio-oedema over her trunk and limbs, which had a negative impact upon her sleep and self-esteem, and resulted in extended periods of absence from work. The urticaria did not respond to anti-histamines at off-label doses (fexofenadine 360 mg twice daily), and the patient was unresponsive and intolerant to ketotifen (1 mg twice daily) and doxepin (20 mg at night). She also experienced insomnia, fatigue and malaise when taking corticosteroids. She had a history of adverse reactions to aspirin and ibuprofen, both of which exacerbated her urticaria, as well as to tetracycline.

The patient was regularly menstruating 3–5 days every 28 days, and was not using hormonal contraception. It was noted that there was a marked premenstrual exacerbation of the urticaria roughly 7 days before onset of menses. The patient had been prescribed Yasmin (Bayer, Newbury, Berkshire, UK), an oral contraceptive containing ethinylloestradiol and drospirenone, from 2007 to 2010, and had first noticed symptoms during this period when 'doubling up' (taking two doses simultaneously) on the pill.

Clinical examination revealed unremarkable urticarial wheals (Fig. 1), each of which had been present for < 24 h. There were no clinical signs suggestive of urticarial vasculitis. Physical examination was otherwise normal.

The patient's full blood count, differential white cell count, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, serum C3 and C4, thyroid



Figure 1 Example of urticaria (patient's own photo).

function, and thyroid autoimmune screen yielded negative or normal results. Her serum IgE was slightly raised at 400 kIU/L (normal < 100 kIU/L). Serum basophil histamine release (HR) test (REFLAB, Copenhagen, Denmark) was performed to exclude autoimmune reactivity against the high-affinity IgE receptor or to IgE,⁴ and was negative (< 16.5%).

A skin biopsy taken from an urticarial weal showed histological appearances consistent with urticaria, and there was no evidence of vasculitis.

A skin prick test for progesterone (Gestone, 50 mg/mL in aqueous alcohol; Nordic Pharma, Reading, Berkshire, UK) produced an immediate hypersensitivity reaction, with a weal and surrounding flare of 6 mm after 15 min, whereas the saline control was negative. Intradermal injection of 0.05 mL Gestone caused a weal 5 mm in diameter, with a large flare and itching at 15 min, whereas the saline control was negative.

The patient was referred to the gynaecology department on 1 August 2013 for an opinion on hormonal treatment, and was trialled with an injection of goserelin (Zoladex; AstraZeneca, Cambridge, UK) 3.6 mg. Following the first injection, she had a flare of urticaria from 10 to 14 August, and menstruated from 20 to 26 August. From 26 August onwards, her urticaria was almost completely resolved. The patient had a second goserelin injection on 27 August, and a third on 24 September 2013. She remained well on goserelin, with occasional mild episodes of urticaria, which were thought to be associated with alcohol consumption. However, she was apprehensive about the possibility of relapse if the goserelin injections were stopped, and was therefore referred to a psychotherapist. She experienced a severe flare of urticaria on

21–22 November 2013, which was followed by menstruation on 1 December 2013. The patient requested a further injection of goserelin, which was administered on 10 December 2013. She had a final goserelin injection on 16 January 2014. She is currently in a period of remission, with a regular menstrual cycle.

ARP is an unusual presentation, occurring in fertile women.³ Onset can occur at any time between menarche and menopause.⁵

When confirming the clinical diagnosis for our case, the serum basophil HR test was used, incubating normal donor basophils with the patient's serum, and the negative result excluded autoimmune chronic urticaria due to anti-FcεR1 or anti-IgE autoantibodies. A direct challenge of autologous basophils with progesterone could also have been of interest, but was not performed. A negative result would have been difficult to interpret, but a positive result, with suitable controls, would have supported the diagnosis of progesterone-induced urticaria.

Goserelin, a gonadotropin hormone receptor agonist, relieves symptoms effectively, but patients are unable to conceive for the duration of their treatment. Although menses would be expected to start again after stopping goserelin, its prolonged use could lead to hypo-oestrogenic problems, including osteoporosis. Alternative hormonal treatments, including tamoxifen or stanozolol, have a poor track record of efficacy and tolerability, and third-line treatments such as ciclosporin, methotrexate or omalizumab may have to be considered in the event of a further relapse of our patient's urticaria.

The psychological element of this case was particularly important. The patient found the initial diagnosis of 'chronic idiopathic urticaria' distressing, and had sought help from alternative practitioners before her presentation to the dermatology department. Once a diagnosis was established, she was able to self-manage her condition more effectively. She also experienced bouts of anxiety in relation to the possible recurrence of the urticaria, which in itself could be responsible for a flare of her condition.⁶ Once her anxiety was managed, her symptoms improved significantly.

This case demonstrates how an unusual presentation of urticaria may cause significant distress and discomfort to a nulliparous woman. Successful management required input from both dermatologists and gynaecologists, with psychological support to manage associated anxiety. Although suppression of ovulation provided short-term, symptomatic relief, long-term strategies are required to ensure that the patient's oestrogen levels remain adequately high. The patient may thus be considered for third-line treatment in the event of a future recurrence.

Learning points

- ARP, although rare, can produce urticaria in menstruating women of any age.
- The presentation is usually cyclical, with a marked premenstrual exacerbation.
- Treatment options are affected by the patient's age and the importance of retaining fertility.
- Although ovarian suppression was effective in the short term in our patient, long-term suppression could result in significant hypo-oestrogenic morbidity.
- It was necessary to recognize and manage the patient's anxiety, as this directly affected her symptoms.
- Multidisciplinary management of this complex case was necessary to produce the best outcome for the patient.

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