



likely resolve after several weeks, in parallel with the improving renal function.

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Menstrual anaphylactoid reactions and presumed systemic mast cell activation syndrome

Anaphylactoid reactions associated with menstruation are exceedingly rare. The first two patients reported were both treated with hysterectomy and bilateral salpingo-oophorectomy.^{1,2} In 2001, we reported two sisters who both had the syndrome.³ One was resolved with menopause, and the younger sibling had her symptoms controlled with medroxyprogesterone and the selective cyclo-oxygenase (COX-2) inhibitor, celecoxib, on the theoretical basis that prostaglandins, particularly PGF_{2α}, may have been modulating mediator release in mast cells and that as COX-2 is present in the endometrium, selective COX-2 reduction was postulated to be more likely to reduce pro-inflammatory prostaglandins than non-selective COX-2 inhibitors.

In 2009, a further case was reported who proved to have systemic mastocytosis underlying her condition, and it was suggested that the previous cases should be re-evaluated for mast cell disorders.^{4,5} This is a follow-up report on the younger sister (case 1) from our 2001 report.

As has been described in detail, this patient presented at the age of 37 with several episodes of abdominal pain, hypotension, bradycardia, sweating, erythema, pruritus and facial swelling requiring adrenaline and intravenous fluids and, on every occasion, was associated with the onset of menstruation. Medical treatment involving suppression of menstruation with medroxyprogesterone 10 mg twice daily and celecoxib was instituted, and apart from occasional minor attacks of itching and swelling associated with menstrual spotting on about eight occasions, her symptoms were well controlled until 2009. She then began to develop pressure urticaria, particularly over the forearms and related to carrying shopping bags with

handles looped over her arms. In 2012, she developed abdominal symptoms with abdominal cramps and swelling, particularly after eating spicy food or shellfish. Her pressure urticaria became more prominent. She also began to develop flitting musculoskeletal pains in her limbs, with severe pain developing in the muscles and around joints and lasting about 36 h before resolving.

Around this time, her daughter, aged 23, had a mild anaphylactoid reaction associated with a menstrual period. Our patient then consented to have a bone marrow examination, which was entirely normal and showed no evidence of a significant mast cell population. Flow cytometry confirmed there was no significant population of cells expressing the immunophenotype CD2, CD25 and CD117 consistent with mast cells. The c-KIT D816V mutation, which is present in over 90% of cases of adult systemic mastocytosis, was not detected.

Treatment was commenced with inhaled sodium cromoglycate 20 mg four times daily using the Spinhaler™. This immediately abolished all of her abdominal and musculoskeletal symptoms, and she found she could eat spices and prawns without problems. Her pressure urticaria improved considerably but was not abolished. Her symptoms relapsed when sodium cromoglycate became unavailable for a short time.

Attempts to withdraw celecoxib produced a recurrence of skin itching, although without urticaria or rash. The pruritus resolved when celecoxib was re-introduced. Regular measurements of luteinising hormone and follicle stimulating hormone demonstrate that though she is now 55, she is not yet menopausal.

Our original hypothesis that these severe anaphylactoid reactions associated with menstruation could be caused by up-regulation of COX-2 activity in the endometrium related to falling progesterone levels seems to

have had some merit as judged by the success of medical treatment. However, the subsequent development of symptoms consistent with gastrointestinal mast cell activation (though no biopsies were performed to distinguish gastrointestinal mastocytosis from mast cell activation syndrome (MCAS)) and development of pressure urticaria would indicate that our patient does have some underlying mast cell disorder, although systemic mastocytosis seems to have been excluded by the absence of urticaria pigmentosa and by the normal bone marrow examination and lack of relevant c-KIT mutation. The immediate beneficial effect of sodium cromoglycate would also argue in favour of a mast cell disorder.

Sodium cromoglycate has been used orally in the treatment of systemic mastocytosis⁶ but in fact is absorbed very poorly from the gastrointestinal tract, and much higher serum levels are achieved when the drug is given by inhalation.^{7,8} Combined oral and inhaled cromoglycate has been used to treat systemic mastocytosis.^{8,9} In that case, the patient also reported dramatic worsening of symptoms during menstruation and complete abolition of symptoms during pregnancy. Inhaled therapy was chosen in this case as it was felt the higher serum levels attained by inhalation would be more likely to benefit all manifestations of the disorder. In addition, the Pharmaceutical Benefits Scheme refused applications for the increased quantities of drug necessary for oral administration.

In addition to systemic mastocytosis, two further mast cell activation disorders have recently been defined. These are monoclonal mast cell activation syndrome and MCAS.¹⁰ Our patient would not seem to have monoclonal mast cell activation syndrome, although this is not com-

pletely excluded by the examination of a single unfractionated bone marrow sample. The clinical features would best fit MCAS, although it should be noted that she has never had an elevated serum mast cell tryptase; however, samples were never taken in time when she had her most severe reactions as she lives remotely. In addition, her last severe attack was in 1998, before these syndromes were described and laboratory diagnostic criteria proposed. However, many patients with MCAS never have tryptase levels outside the normal range.¹¹

The familial nature of the syndrome is interesting. The patient's daughter has only had a single attack of an anaphylaxis-like reaction associated with menstruation at the age of 23. However, her mother and aunt did not develop symptoms until their mid- to late 30s, and it remains to be seen whether symptoms in the daughter will recur as she ages. Familial occurrence of MCAS has recently been reported.¹²

Although rarely reported, the association of anaphylaxis-like symptoms with menstruation should not only prompt consideration of systemic mastocytosis as Villar *et al.* suggest,⁵ but also consideration of more recently described and perhaps less well-defined mast cell disorders as well as consideration of inhaled cromoglycate as a possible treatment.

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