Catamenial anaphylaxis in three patients

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Catamenial anaphylaxis, also called cyclical anaphylaxis, describes recurrent episodes of multi-system allergic reactions occurring at the time of menstruation. This case reports demonstrates the management of three women with catamenial anaphylaxis. The first patient is a 38 years old woman who presented with symptoms consistent with anaphylaxis in relation to her menstrual cycle. Her symptoms were controlled with cetirizine at a dose of 20 mg daily. The second patient is 33 years old with similar symptoms coinciding with her menses. We were able to control her symptoms with leuprolide (Lupron), a luteinizing hormone releasing hormone (LHRH) agonist. The third was a 29 years old woman with catamenial anaphylaxis who was successfully treated with Depo-Provera (medroxyprogesterone). Catamenial anaphylaxis is a rare yet an important presentation to the Allergist/Clinical immunologist. The management of the patients we present here represents a spectrum of the different therapies tried in the medical literature. Here, we report the first successful use of medroxyprogesterone for such rare, yet critical medical condition.

Key words: Anaphylaxis, Menstrual period, Allergic reactions.

Introduction

Acute allergic reactions or exacerbations of pre-existing chronic allergies in association with the female menstrual cycle are well documented, especially the premenstrual exacerbation of urticaria (1) and bronchial asthma (2). Several reports have described the uncommon occurrence of peri-menstrual anaphylaxis. Anaphylaxis around the time of the menstrual period may be related to certain drugs used for menstrual cramps or to specific foods ingested around that time. However, in some instances, no obvious etiology is seen in spite of exhaustive investigations. Catamenial anaphylaxis, also called cyclical anaphylaxis, describes recurrent episodes of multi-system allergic reactions occurring at the time of menstruation. The present paper reports 3 patients with recurring life-threatening peri-menstrual allergic reactions.

Case reports

Case one

A 38-year-old woman was first seen in the clinic with a two-year history of episodic re-

actions that occurred temporally in relation to her menstrual period. At the time of consultation, she had had a total of twenty-four reactions, with twelve to fifteen associated with loss of consciousness. Manifestations included a 'draining sensation' in the chest, followed by itching of the palms and palpitations. These were followed by crampy abdominal pain leading to diarrhea, lightheadedness and loss of consciousness. On some occasions, there was associated flushing, urticaria, and chest tightness. Systolic blood pressure was documented to be as low as 70 to 80 by paramedics on several occasions.

All of these episodes were peri-menstrual, starting either the day prior to, the day of, or the day after the onset of menses. Episodes were not related to food, exercise, alcohol, or to use of any medications. Past medical history was only significant for hypothyroidism for which she was controlled on replacement therapy. Investigations done on this patient are shown in Table 1. She was started on cetirizine 10 mg, an antihistamine, daily and prednisone 60 mg daily for 1 week, followed by prednisone 60 mg on alternating days without improvement. Later, prednisone was discontinued and cetirizine was increased to 20 mg daily with near-total suppression in the frequency of such reactions. Follow-up for a period of one year on cetirizine 20 mg daily showed the occurrence of only one mild reaction.

Case two

A 33-year-old woman was first seen in the clinic with an 18-month history of recurrent anaphylactic reactions. Her first reaction consists of generalized flushing, itching with facial swelling, itching of the oropharynx and uterine cramps. There was associated nausea, vomiting, crampy abdominal pain, diarrhea and a sensation of lightheadedness and presyncope. The second reaction happened several months later, but it was more severe, involving respiratory symptoms, syncope, and hypotension documented by paramedics. By the time she was seen in consultation, she had experienced a total of twelve such reactions with ten of them coinciding with her menstrual period. The other two were mid-cycle. She was not on any medications at the time of the reactions, and the reactions were not associated with any specific food, or with alcohol intake or exercise.

Investigations done on this patient are shown in Table 1. Initially, she was treated with a suppressive regimen for idiopathic anaphylaxis using prednisone at a daily dose of 50 mg PO. This failed to suppress her reactions. Prophylactic treatment with cetirizine 10 mg twice daily in combination with ketotifen 4 mg twice daily failed to control her symptoms. Celecoxib, a cyclooxygenase 2 (cox-2) inhibitor was tried, but this caused episodes of angioedema. Finally, leuprolide (Lupron), a luteinizing hormone releasing hormone (LHRH) agonist, was started, with no recurrence of her symptoms during a one-year follow-up period.

Case three

A 29-year-old woman was initially seen in the clinic with a two year history of recurrent episodes of chest pain, generalized urticaria, swelling of her face, lips and neck, cough, vomiting, crampy abdominal pain, dizziness and lightheadedness. These reactions typically started one week prior to the beginning of her menstrual cycle with worsening over the course of the week and peak symptoms on the first day of her menstrual cycle. At the time of her initial evaluation, she had had a total of twelve such reactions, none of which was associated with food, alcohol or exercise. At the time of her first visit she was on rofecoxib with no change in the frequency or severity of her attacks. Past medical history was significant for fibromyalgia for which she was on daily Tylenol number 3 (acetaminophen with codeine). Results of investigations done on this pa-

tient are shown in Table 1. Initially, she was treated with cetirizine 10 mg twice daily and prednisone 40 mg daily from three days premenstrually until two days after the onset of her menstrual cycle. This failed to suppress her reactions. Later, she was started on Depo-Provera (medroxyprogesterone) and over the ensuing three years she had total suppression of her multi-system reactions. Later, she decided to become pregnant. Depo-Provera was stopped, and three months later she had a recurrence of her anaphylactic symptoms. Those were initially mild, but worsened over the course of several months with generalized urticaria associated with nausea, abdominal cramps, and crampy uterine pain. Even more worrisome, were associated symptoms of lip swelling, throat constriction, dysphonia, dysphagia, chest tightness, wheezing, and presyncope. Due to those life-threatening manifestations, Depo-Provera was restarted again with no further recurrence over a follow-up period of two years.

Discussion

Catamenial anaphylaxis is an uncommon clinical entity. It is a diagnosis of exclusion that represents considerable challenge from the standpoint of management. We conducted a literature search through the pubMED database by typing the phrases cyclical AND anaphylaxis, catamenial AND anaphylaxis, and hormonal AND anaphylaxis, and found very few reports describing such reactions (3-7).

Anaphylactic reactions around the time of the menstrual period may be either allergic or pseudo-allergic. Conditions mimicking anaphylaxis include carcinoid syndrome, pheochromocytoma and systemic mastocytosis (8). Allergic reactions may often be due to medications, especially aspirin, non-steroidal anti-inflammatory drugs (9), or foods, amongst other causes. Such etiologies need to be kept in mind while working up a patient presenting with cyclical anaphylactic reactions, and should be ruled out first. Upon excluding extrinsic triggers of anaphylaxis as well as conditions that mimic multisystem allergic reactions, the diagnosis of catamenial anaphylaxis should be considered. The mechanism involved in catamenial anaphylaxis is not clearly understood. Some authors have suggested hypersensitivity to progesterone as an underlying cause (3). This theory was supported in some patients by a positive cutaneous and systemic reaction to intradermal challenge with medroxyprogesterone (3). However, in a report

Table 1 Investigations done for the three patients

Investigations	Case 1	Case 2	Case 3
Skin test to common foods	Negative	Negative	Negative
Skin test to inhalants	Negative	Negative	Negative
Skin test to medroxyprogesterone[1]	Negative	Negative	Negative
Total serum IgE[2]	31.0	19.2	27.0
Serum tryptase[3]	Normal	46.9[A]	Normal
24-hour urine for 5-HIAA	Negative	Negative	Negative
24-hour urine for VMA	Negative	Negative	Negative
24-hour urine for Catecholamine	Negative	Negative	Negative

[1] Done by intradermal injection of 10 mg, ie 0.03 ml, medroxyprogesterone
[2] Normal range is < 300 IU/ml
[3] Reference range is 3.8 – 11.4 ng/ml. Serum tryptase was done within 2 hrs after acute episodes as well as in between attacks
[A] Done after an episode of a systemic reaction. In the same patient, serum tryptase was normal in between the episodes.

of four patients with similar cyclical anaphylactic reactions, two of four patients failed to show a positive skin test to medroxyprogesterone (5). A similar negative skin test was also seen in one other patient (7). Clearly, this phenomenon cannot account for all cases of cyclical anaphylaxis. Furthermore, the use of depot preparations of progesterone (Depo-Provera) would likely exacerbate the condition in patients allergic to endogenous progesterone, in contrast to Case 3 described above.

Another mechanism proposed to account for catamenial anaphylaxis involves a vasoactive constituent of menstrual fluid, the prostaglandins (4, 6, 7). This was supported by the finding that PGF_2-α plays an important role in modulating mediator release in mast cells (10). Another possibility was involvement of PGI_2 (prostacyclin), which act as a powerful vasodilator leading to such systemic reactions in susceptible persons (4). This theory was supported by a positive intradermal skin test to menstrual fluid in one (4), but not another patient (6).

Extensive investigations for anaphylactic triggers, including foods and medications were negative in all three patients presented in this report. In addition, other conditions masquerading as anaphylaxis such as carcinoid syndrome, pheochromocytoma, and systemic mastocytosis were ruled out by history, by manifestations atypical for these conditions, and by appropriate laboratory tests. Skin tests to progesterone were negative in all of our patients. Interestingly, tryptase remained normal at the time of the acute episodes. This is not surprising, as β-tryptase, a hallmark of mast cell activation, is known to remain normal in some patients with anaphylaxis (11).

The management of all three patients represents a spectrum of therapeutic modalities described in the medical literature. For the first patient, we were unable to control her symptoms with cetirizine 10 mg daily, but increasing the dose of cetirizine to 20 mg per day successfully controlled her reactions. Anaphylactic reactions in the second patient improved remarkably after the start of LHRH-analogue, a finding also seen in two of four patients reported by Slater et al. (5). Of interest is the angioedema observed in the second patient after the start of celecoxib and the lack of suppression of the reactions in the third patient while on rofecoxib. This observation is in contrast with the reports of Simpson et al. (6) and Burnstein et al. (7) in which their patients' symptoms improved after initiation of celecoxib and indomethacin respectively.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are amongst the most common drugs known to precipitate anaphylaxis and other allergic reactions (9). There is also compelling evidence that NSAIDs and aspirin can intensify immediate hypersensitivity reactions in patients with a background of anaphylaxis (12, 13). Also, NSAIDs have been shown in vitro to augment histamine release from human leukocytes (14). The same is true for COX-2 inhibitors, with anaphylactic reactions related to such medications (15, 16).

Of interest is our third patient who had complete suppression of her anaphylactic episodes upon initiating treatment with medroxyprogesterone. Such therapy was tried to our knowledge in only one other patient and failed to control her symptoms (6). In all patients, high dose systemic steroids failed to control the anaphylactic reactions, in spite of the fact that this approach is recommended for the control of idiopathic anaphylaxis (17, 18). Moreover, we found that ketotifen, a mast cell stabilizer with antihistaminic activity, did not help to reduce the frequency or severity of attacks, in spite of its reported efficacy in the treatment of idiopathic anaphylaxis (19).

Conclusion

Whether the mechanism causing cyclical anaphylaxis involves hypersensitivity to progesterone or to prostaglandins, cessation of the menstrual cycle by means of induction of medical or surgical menopause reportedly results in control of such anaphylactic reactions (5, 6, 7). Surgical menopause is generally reserved for patients who fail medical treatment either due to breakthrough reactions or due to intolerable side effects (5). However, the variable response to suppressive medications in the three cases described above suggests that catamenial anaphylaxis is a heterogeneous disorder in which a number of mechanisms and mediators may play a role.

Conflict of interest: The authors declare that they have no conflict of interest. This study was not sponsored by any external organisation.

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