

Clinical Communications

Anaphylaxis due to progesterone hypersensitivity successfully treated with omalizumab

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Clinical Implications

- Anaphylaxis due to progesterone hypersensitivity is a rare and severe allergic disease in women. This is the first reported experience of progesterone-induced anaphylaxis successfully treated with omalizumab, possibly expanding its indication to selected complicated cases of recurrent anaphylaxis.

TO THE EDITOR:

A significant proportion (24%-59%) of anaphylaxis cases, mainly in women, are classified as idiopathic¹ because often it is difficult to identify the causative allergenic source. These reactions can also be associated with enhancing cofactors such as exercise, alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs), or mastocytosis. If idiopathic anaphylaxis recurs for at least 2 episodes in the preceding 2 months or at least 6 episodes in the preceding year, it is defined as frequently recurring idiopathic anaphylaxis.¹

In women, one of the most frequent triggers or enhancing cofactors for allergic manifestations is menses, which can be responsible for recurrent/cyclic anaphylaxis (often classified as “idiopathic”), rarely associated with IgE-mediated allergy to endogenous progesterone² or other hypersensitivity mechanisms. This rare clinical entity has been variably called “catamenial anaphylaxis,”³ “autoimmune progesterone anaphylaxis,”⁴ or “anaphylaxis secondary to progesterone hypersensitivity.”^{2,5} The therapeutic options for this clinical entity, apart from intramuscular epinephrine for the acute treatment of each episode, include high-dose systemic steroids, hormone-targeted therapies (such as gonadotropin-releasing hormone agonists or estrogen-suppressive therapy such as selective estrogen-receptor modulators or aromatase inhibitors), progesterone desensitization, or surgical salpingo-oophorectomy.⁶

A 12-year-old girl (menarche at age 11 years and 3 months) without any history of allergic signs or symptoms presented to our Allergy Outpatient Clinic for a recent (10 days before, 1-3 days before the onset of menses, and a few hours after the intake of paracetamol 1000 mg for menstrual cramps) episode of acute diffuse urticaria associated with labial and eyelid angioedema. At the time of the visit, she was receiving antihistamine (cetirizine 10 mg/d) and systemic corticosteroid (prednisone 12.5 mg/d) treatment, and no symptoms or signs of urticaria or angioedema were present. Having received a diagnosis of acute urticaria (possibly due to paracetamol hypersensitivity with or without menses as an enhancing cofactor), the patient and her parents were advised to gradually reduce and stop the corticosteroid treatment over a 10-day period, and to stop the cetirizine



FIGURE 1. Cutaneous skin tests with progesterone 50 mg/mL: positive intracutaneous 1/100 reaction (wheal 6 mm; histamine wheal 7 mm; negative control 0 mm).

treatment within 20 days. The patient presented again to our clinic 3 months later reporting that during intermenstrual periods she was free of any symptoms, even without taking any antihistamines or corticosteroids, while during both the 2 preceding menses (2 days before the onset of them) she had acute urticaria, labial and eyelid angioedema, dyspnea with chest tightness and wheezing, abdominal pain, nausea, diarrhea, and hypotension (80/50 mm Hg and 90/60 mm Hg, respectively, in the first episode and the second episode). Her baseline blood pressure, measured during the outpatient clinic visit, was 120/80 mm Hg with a pulse of 72 beats per minute without any arrhythmia. She was treated in emergency room with intramuscular epinephrine and systemic corticosteroids and antihistamines. No NSAIDs or other drugs had been taken before the 2 described episodes of anaphylaxis. No consistent history of any other common triggers of anaphylaxis (such as foods or hymenoptera stings) or cofactors (such as NSAIDs or exercise) were identified. Autoinjectable epinephrine was immediately prescribed, and the patient was instructed on its indications and on how to use it in case of a new episode of anaphylaxis. Because the allergological visit was just 3 days before the next expected menses, treatment with prednisone 25 mg/d plus cetirizine 10 mg/d was prescribed until 3 days after the beginning of menses (6 days treatment in total). This approach was only partially able to control the anaphylactic reaction. Indeed, she experienced acute urticaria, labial and eyelid angioedema, mild abdominal pain, and diarrhea even under corticosteroid and antihistamine treatment. Fifteen days after the onset of the subsequent menses, skin prick test results for a panel of common airborne and food allergens were negative. Progesterone 50 mg/mL (Prontogest, in ethyl oleate with benzyl alcohol; IBSA Farmaceutici Italia, Lodi, Italy) was tested as previously described²: intracutaneous injection of 1/100 diluted progesterone (using sesame oil with 10% benzyl alcohol as both diluent and negative control) induced a wheal of 6 mm (Figure 1) (histamine wheal 7 mm; negative control 0 mm). The same skin test protocol was applied to a control group consisting of

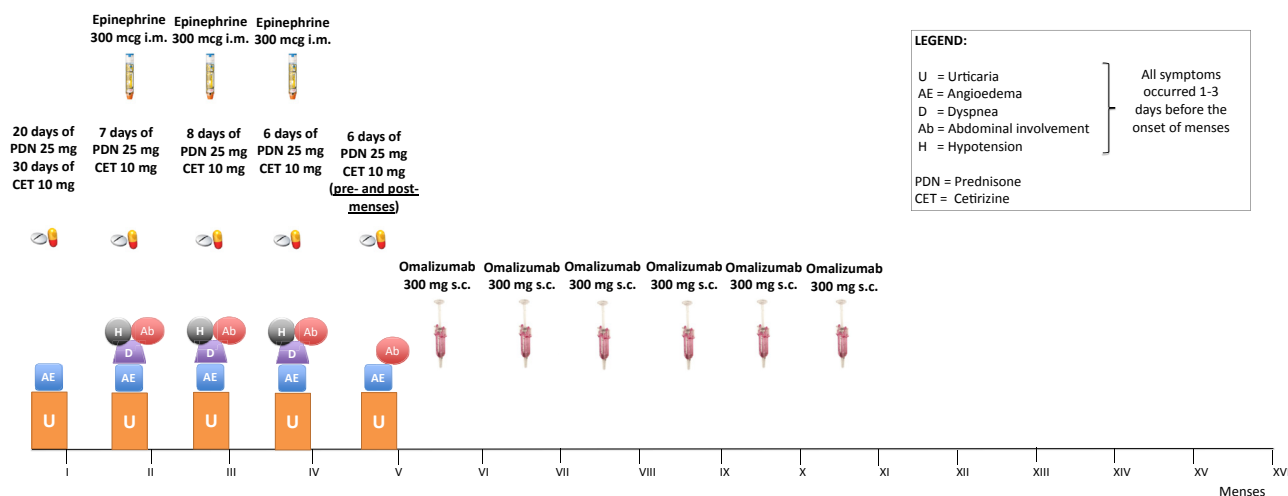


FIGURE 2. Summary of the patient's clinical history with reported use of drugs to treat or prevent anaphylactic episodes. *i.m.*, intramuscular; *s.c.*, subcutaneous.

5 healthy females of reproductive age without any positive results. Masquerading conditions, such as carcinoid syndrome, pheochromocytoma, and systemic mastocytosis, were ruled out. Serum total IgE level was in the normal range (85 kU/L). The patient also reported having again taken paracetamol 1000 mg for an acute fever episode outside of menses without any allergic symptoms.

We therefore made a diagnosis of recurrent/cyclic anaphylaxis due to progesterone hypersensitivity. Considering the very young age of our patient and the possible, potentially severe, endocrinological and gynecological implications of hormone-based treatment or ovarian-suppressive strategies at this age, and the potential risk of severe anaphylaxis during progesterone desensitization, we decided not to opt for these therapeutic options. Instead, we proposed to the patient and her parents to try to prevent the anaphylaxis episodes or at least reduce their severity by using omalizumab, an anti-IgE mAb approved for severe allergic asthma and severe chronic spontaneous urticaria, and proposed as an option for preventing anaphylaxis.⁷ The patient and her parents accepted this therapeutic option, and an informed written consent was signed by both parents. The Institutional Ethics Committee gave us permission to prescribe omalizumab for an off-label indication. The patient was treated with omalizumab 300 mg subcutaneously monthly for a 6-month period as suggested for chronic spontaneous urticaria.⁸ After the first administration she stopped experiencing any allergic symptom before menses, even without taking any other antiallergic drugs. The patient ended the 6-month treatment period 5 months ago as of this report, without relapses of allergic symptoms after the end of the treatment (see Figure 2). After 6 months of treatment with omalizumab, the patient underwent prick and intracutaneous testing with progesterone with negative results.

This is one of the rare cases of anaphylaxis due to progesterone hypersensitivity, and, to our knowledge, the first description of successful treatment with monoclonal anti-IgE therapy. In this particular case, the choice of using omalizumab was dictated by the need to prevent anaphylaxis and to avoid treatment options that may alter the physiological sexual growth and development of a very young patient.

Recurrent anaphylaxis that occurs around menses can be easily confused with recurrent idiopathic anaphylaxis. Therefore, in cases of cyclic idiopathic anaphylaxis occurring in fertile women, investigating the possibility of catamenial or progesterone-hypersensitivity anaphylaxis should be mandatory. Moreover, anaphylaxis due to progesterone hypersensitivity (which classically occurs a few days before the onset of menses, as in the case we described) can be misdiagnosed with catamenial anaphylaxis (generally occurring the day of onset of the menstrual cycle), probably due to the release of endometrial-derived mediators such as prostaglandin F₂-alpha (PGF₂-alpha) or prostacyclin (PGI₂), and not to progesterone allergy.

Omalizumab, apart from the 2 primary and US Food and Drug Administration–approved indications (severe allergic asthma and severe chronic spontaneous urticaria), has been described to be effective in several other allergic conditions, such as in reducing the risk of anaphylaxis due to allergy immunotherapy⁷ and in vernal keratoconjunctivitis.⁹ The precise mechanisms of action of omalizumab, particularly in chronic spontaneous urticaria and in the nonconventional indications, is still not completely clarified. It has been demonstrated that omalizumab exerts its action in at least 3 different ways: binding free circulating IgE and thus significantly reducing the amount of IgE available on the surface of mast cells and basophils to bind antigen; reducing IgE high-affinity receptor (FcεRI) expression on effector cells; and suppressing the basophil response to allergens.⁷ The latter mechanism of action may explain why anaphylaxis can be prevented by omalizumab, independently of the involved allergen (progesterone, in the case of the present case report) and the negativization of the intracutaneous response to progesterone.

In the case we described, omalizumab induced a rapid and sustained regression of cyclic episodes of anaphylaxis induced by progesterone hypersensitivity (similar to what was described for vernal keratoconjunctivitis).⁹ The reason for such a rapid and sustained response is still unclear.

This clinical case report reinforces the concept that omalizumab has a pleiotropic effect on allergic mechanisms, generally

with a good safety profile, and therefore can be considered in selected complicated cases of recurrent anaphylaxis.

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