

## Patient report

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# A patient developing anaphylaxis and sensitivity to two different GnRH analogues and a review of literature

**Abstract:** Gonadotropin-releasing hormone analogues are used in the treatment of prostate cancer, breast cancer, endometriosis, and uterine leiomyomas in adults and often in the treatment of precocious puberty in children. Many adverse effects have been reported for gonadotropin-releasing hormone analogues, but anaphylaxis is rarely reported as an adverse effect. Frequent cross-reactions, particularly during childhood, and diversity of the time of onset of anaphylactic manifestations complicate the diagnosis. A patient who exhibited anaphylactic allergic reactions to two different agents used in the treatment of central precocious puberty presented here because the case has an atypical course and is the first in the literature.

**Keywords:** anaphylaxis; GnRH analogues; precocious puberty.

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## Introduction

Gonadotropin-releasing hormone (GnRH) analogues are used in the treatment of prostate cancer, breast cancer, endometriosis, and uterine leiomyomas and commonly in the treatment of central precocious puberty (CPP) in

childhood. Local effects of GnRH analogues including induration and aseptic abscess are generally well known. Rare adverse effects of the agents on the nervous system, skin, gastrointestinal tract, and cardiovascular system have also been reported (1–7).

Anaphylaxis is an acute type 1 hypersensitivity reaction against an allergen, which is accompanied by severe life-threatening systemic complications (8). Allergic reactions are not limited to active substances but may also develop against the adjuvants or preservatives contained in the medicinal product. Drug lymphocyte stimulation test (DLST), radioallergosorbent test, and skin tests are used to determine the causative allergen (1, 9).

Although GnRH analogues are widely used in childhood precocious puberty, anaphylactic reaction has been reported only in one child so far. A patient who had an anaphylactic reaction to the GnRH analogue leuprolide acetate (LA) given for CPP and then developed allergic sensitivity associated with triptorelin acetate (TA) is presented in this study as this was a rare occurrence.

## Case

A 75-year-old female patient presented with premature thelarche which started 2 months ago. In her physical examination, height was 129.5 cm (75–90p) and weight was 28 kg (75–90p). Her pubertal examination revealed pubic and axillary hair growth at stage 1 and breast development at stage 2 according to the Tanner scale. Other systemic examinations yielded normal results. Her bone age was 10 years. Pelvic ultrasonography showed long axis of the uterus was 40 mm, right ovary was 2.1 mL and left ovary was 2.4 mL. Luteinizing hormone releasing hormone (LHRH) test was performed and the peak of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) was 6.1 and 8.6 mIU/mL, respectively. Magnetic resonance image of the pituitary gland was normal. Thus,

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signs of idiopathic central precocious puberty (ICPP) was considered and monthly LA (3.75 mg) treatment was started. Three hours after the third dose of the treatment, the patient developed dizziness, syncope, palpitations, sweating, cramp-like abdominal pain and therefore was presented to a health care facility where hypotension (70/40 mm Hg) was detected. She was prescribed steroid and antihistaminic treatment by that health care center and was referred to our clinic with the initial diagnosis of anaphylaxis. When questioned again, the patient had no regular concomitant medications, and no history of drug reaction, atopy, or asthma. Drug provocation tests at the stage of intradermal test with LA yielded positivity in 1/100. Thus, treatment with another preparation, TA, as an alternative treatment with a provocation test was considered beforehand. The result was 1/100 positive in prick test as in LA. Therefore, treatment with medroxyprogesterone as an alternative treatment was started to prevent pubertal progression only and the patient did not develop any reactions. The patient is still on this treatment with no complications.

## Discussion

The side effects of the drugs may be mistaken for anaphylactic symptoms, for example, drug-induced vasovagal syncope or respiration suppressive effects of the sedatives. In such cases, there is no hypersensitivity to the drug and allergy tests give negative results. On the contrary, urticaria, angioedema, and anaphylaxis developing due to sensitivity to the drug are allergic reactions, that is, type 1 hypersensitivity reactions (10). Antigen-antibody binding on the cellular surface results in enzymatic reaction induction and several mediators emerge. In anaphylaxis, the findings occur early, while the occurrence of the manifestations may be delayed in depot-form drugs (11, 12). In anaphylactic shock, hypotension, general vasodilatation leading to collapse, laryngeal and glottal edema, and bronchospasm occur few minutes after the release of large amounts of histamine. When the antigens are carried in blood, skin manifestations such as urticaria and subcutaneous angioedema occur (11).

Anaphylaxis involves symptoms of essentially five organ systems. Anaphylaxis is diagnosed in the presence of a detectable allergen accompanied by symptoms of two systems. These symptoms are (i) findings of the general and central nervous system such as panic state and irritability; (ii) skin findings such as urticaria and purpura; (iii) evidence of respiratory tract obstruction

such as stridor, swelling of the tongue or lips; (iv) cardiovascular system findings such as tachycardia and hypotension; and (v) gastrointestinal system findings such as nausea, vomiting, and abdominal pain (8). Our patient had symptoms of the three systems as described above, that is, panic state, tachycardia, hypotension, nausea, and vomiting.

DLST, radioallergosorbent test, and skin provocations test can be used to identify sensitivity to the allergen in question. In the skin tests, unlike other tests, anaphylaxis may occur during the procedure and epinephrine may be required (9). We used provocation with intradermal test against the suspected drug in our patient with the initial diagnosis of anaphylaxis and the test resulted positive.

The most widely used preparations for idiopathic CPP are the GnRH analogues. These agents include LA, TA, and goserelin acetate (GA). The latter agent is not available in our country.

In the literature, anaphylactic reactions to GnRH have been reported in only six cases, one of which was pediatric. Of the anaphylaxis cases reported in the adult patients, four pertained to LA and one pertained to GA, whereas anaphylaxis reported in the pediatric case both pertained to LA and GA (1, 2, 12–15). The manifesting reaction in these cases was in the form of skin reactions only in two patients (1, 13). No skin reactions were reported in other patients, as was the case in our patient.

The only pediatric case with anaphylaxis due to GnRH analogues was a 4.5-year-old child who started receiving LA treatment for ICPP. No reactions were observed for this patient until the 6th dose of treatment but 2 weeks after the 7th dose, the patient developed urticaria, swelling of the extremities, and polyarthralgia, suggesting allergic reaction. However, the patient was tested negative with the skin test to the drug in question and was nevertheless switched to GA treatment due to clinical suspicion. No side effects were observed during follow-up examinations; however, 5 days following implantation in the 3rd year of therapy, the patient developed severe anaphylactic reaction with respiratory distress and the implant was removed after 3 h. However, severe stridor and anaphylaxis persisted up to day 4 and the symptoms did not resolve completely until week 6. This was attributed to the depot form of the drug and infiltration of the drug to circulation via the subcutaneous route. This patient developed anaphylactic reaction to LA after 14 days and to GA after 5 days (12).

Similarly, TA treatment was planned for our patient because she developed anaphylaxis to LA. However, it could not be used because sensitivity was detected to this drug with provocation test performed before TA treatment.

Fujisaki et al. (1) noted local skin reactions in their article in which they reported anaphylaxis due to LA treatment in a 68-year-old patient with prostate cancer. The DLST test performed to identify the cause of anaphylaxis yielded sensitivity to both LA and polylactic and glycolic acid. In our patient, we detected sensitivity to both LA and TA but were unable to identify to which of the medicinal products formulated with these agents the patient was sensitive. We consider that the source was polylactic and glycolic acid, which were contained in both the drugs and were reported as allergens by Fujisaki et al. (1).

According to the literature, onset of systemic findings may vary from 2 min to 14 days (12, 15). Because GnRH analogues used for ICPP are depot drugs, anaphylactic reactions may be delayed as reported earlier and the findings may persist even after the drug is eliminated in depot and implant formulations (12). Therefore, long-term monitoring in suspected cases is essential.

To the best of our knowledge, there have been no reports discussing allergic reactions to both LA and TA, although there are reports of anaphylactic reactions either to LA or GA. It should be borne in mind that in case of anaphylaxis or allergic reaction to either TA or LA, similar reactions may occur to the other product due to the common excipients of the preparations.

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