

Case Report**Life-threatening anaphylaxis to leuporelin acetate depot: Case report and review of the literature**Akira Fujisaki,¹ Yoshimasa Kondo,² Kentaro Goto¹ and Tatsuo Morita¹¹Department of Urology, Jichi Medical University, Shimotsuke-city, Tochigi, and ²Department of Urology, Haga Red Cross Hospital, Mooka-city, Tochigi, Japan**Abbreviations & Acronyms**

DLST = drug-lymphocyte stimulation test

DTX = docetaxel

EMP = estramustine phosphate

GA = goserelin acetate

GnRHa = gonadotropin-releasing hormone analog

LA = leuporelin acetate

PLA = polylactic acid

PLGA = polylactic and glycolic acids

PSA = prostate-specific antigen

SI = stimulation index

SpO₂ = pulse oximetry

Abstract: Gonadotropin-releasing hormone analog depots have been widely used for a variety of diseases including prostate cancer, breast cancer, endometriosis, uterine leiomyomas, and central precocious puberty. Most of the side/adverse effects of gonadotropin-releasing hormone analog depots, such as leuporelin acetate depot, are related to hypotestosteronism in males. Anaphylaxis to gonadotropin-releasing hormone analog depot is extremely rare. We present the first case report of a Japanese man who developed anaphylaxis to leuporelin acetate depot during the treatment of metastatic prostate cancer and recovered successfully by conservative treatment. A drug-lymphocyte stimulation test showed that not only leuporelin acetate itself, but also its vehicle polylactic and glycolic acids, might be responsible for the anaphylaxis to leuporelin acetate depot. Because anaphylaxis can be lethal, the present case suggests that one should bear in mind the possibility of anaphylaxis in all patients who receive gonadotropin-releasing hormone analog depot and monitor such patients carefully.

Key words: anaphylaxis, drug-lymphocyte stimulation test, gonadotropin-releasing hormone analog, leuporelin acetate, prostate cancer.

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Introduction

Gonadotropin-releasing hormone analog (GnRHa) depots, such as leuporelin acetate (LA) depot, have been widely used for a variety of diseases including prostate cancer, breast cancer, endometriosis, uterine leiomyomas, and central precocious puberty. Most of the side/adverse effects of GnRHa depots, such as leuporelin acetate (LA) depot, are related to hypotestosteronism in males. Although local reactions to LA depot, such as induration and aseptic abscess at the injection site, have been reported,¹ anaphylaxis to GnRHa depot is extremely rare.²⁻⁶ The examinations, such as skin testing, drug-lymphocyte stimulation test (DLST),⁷ and radioallergosorbent test have been used to determine the causes of anaphylaxis. However, there have been no reports where a drug-lymphocyte stimulation test (DLST) was carried out in patients with anaphylaxis to GnRHa depot. We, herein, present the first case report of a Japanese man with metastatic prostate cancer who developed anaphylaxis to LA depot in whom DLST showed that not only LA itself, but also its vehicle polylactic and glycolic acids (PLGA), might be responsible for the anaphylaxis to LA depot, and review the literature.

Case report

A 68-year-old Japanese man with metastatic prostate cancer received subcutaneous injection of 3.75 mg 1-month LA depot (Leuplin) in September 2001. He had no history of allergies to medications or foods. At the sixth injection, local skin reaction with erythema and induration was observed at the injection site, but resolved without any treatment. Because a similar course followed with the seventh and eighth injections, the injections were discontinued, although the prostate-specific antigen (PSA) level decreased from 368 ng/mL to 0.1 ng/mL 8 months after the first LA depot injection. Then, the patient was given



Fig. 1 Generalized urticaria (abdomen).

low-dose estramustine phosphate (EMP; 140 mg daily) for 4 years without an increase in PSA level. Thereafter, the serum PSA level gradually increased up to 4 ng/mL. Injection of 1-month LA depot was started again in April 2006 based on his request. Local skin reaction appeared again 5 days after the injection. One month later, LA depot was injected subcutaneously. Approximately 30 min after the injection, the patient lost consciousness on his way back home, and was brought to our emergency room by ambulance. In the emergency room, he was cyanotic with generalized urticaria (Fig. 1). His blood pressure and oxygen saturation by pulse oximetry (SpO_2) were 76/48 mmHg and 92%, respectively. Based on the diagnosis of anaphylactic shock by LA depot injection, he was immediately treated with fluids, hydrocortisone sodium succinate and monoammonium glycyrrhizinate. Although the patient recovered successfully by conservative treatment, he was hospitalized for monitoring of his vital signs. On hospital day 2, he was discharged without any further events. One month later, we carried out a drug-lymphocyte stimulation test (DLST),⁷ which is used to detect the sensitization drug. The stimulation index (SI) is calculated from the ratio of radioactivity in the lymphocytes with LA, PLGA (which is the vehicle of 1-month LA depot), and polylactic acid (PLA; which is the vehicle of 3-month LA depot) versus that without the drug. Based on the criteria that a SI over 180% is considered positive for DLST, LA (SI, 225%) and PLGA (SI, 217%) were positive, and PLA (SI, 175%) was negative, suggesting that the patient was sensitized to both LA and PLGA, but not to PLA. Thereafter, until December 2010, the patient was treated with EMP (280–560 mg daily) again followed by dexamethasone (1 mg daily) with stable PSA levels less than 12 ng/mL. During this period, he received docetaxel (DTX) monotherapy (70 mg/m² q21d) in January 2009, although it was discontinued immediately after the first course of DTX monotherapy because of severe myelosuppression, and irra-

diation to the prostate for the palliative control of hematuria in December 2009. Because PSA levels increased up to 146 ng/mL in January 2011, he received the treatment with oral cyclophosphamide (100 mg daily). However, PSA levels had risen to 521 ng/mL by April 2011. The patient died of cancer in May 2011, 5 years after the anaphylaxis.

Discussion

Review of the literature showed five case reports of anaphylaxis to GnRHa depot (Table 1).^{2–6} Thus, this is the sixth case to develop anaphylaxis to GnRHa depot, but the first case of a Japanese man to develop anaphylaxis to LA depot in the treatment of prostate cancer. Although the number of cases is small in the literature (Table 1), there was no clear relationship between anaphylaxis and clinical factors including age, sex, disease, race, allergic history, preparation type of GnRHa depot, injection route, treatment period, and local skin reaction at the injection site. In three out of six cases, anaphylaxis occurred at the first injection of GnRHa depot. These findings suggest that there is no parameter to predict the anaphylaxis to GnRHa depot at present.

Skin testing is indeed a simple method for determining which drugs a patient is sensitive to. However, we used DLST instead of skin testing, because Letterie *et al.* reported that skin testing for GnRHa depot induced acute symptoms that required treatment with subcutaneous epinephrine.² DLST in the present case could show that not only LA itself, but its vehicle PLGA, might be responsible for the anaphylaxis to LA depot. Thus, DLST would be a better option to determine the drugs causing anaphylaxis in terms of its invasiveness. Of the six cases in Table 1, four cases showed anaphylaxis to LA depot, one did to goserelin acetate (GA) depot, and one did to both of them. Present results of DLST in addition to these case reports suggest that not only GnRHa itself, but vehicles could be the cause of anaphylaxis. As a vehicle, PLGA is contained in 1-month depot LA and all forms of GA including 1-month and 3-month depots, whereas PLA is contained only in 3-month depot LA. Because GA has structural homology with LA and their depots, except 3-month depot LA, have a common vehicle, cross-sensitivity could develop between LA depots and GA depots.⁵ Therefore, once a patient shows anaphylaxis to GnRHa depot, any other preparation of GnRHa depot should be avoided for further therapy.

Anaphylaxis is usually observed within 30 min after the exposure. However, three out of six cases in Table 1 showed anaphylaxis over 6 h after the injection of GnRHa depot. This delayed reaction and/or recurrence of anaphylaxis might be explained by the slow and continuous release of GnRHa depot. Thus, surgical excision of GnRHa depot in case of GA depot is a choice of treatment for prolonged symptoms and the recurrence of anaphylaxis.⁵

Table 1 Anaphylaxis to gonadotropin-releasing hormone analog depots in the literature

Author	Age (years)	Sex	Disease	Allergic history	GnRHa depot injected	Treatment duration with GnRHa depot	Onset time of anaphylaxis after injection of GnRHa depot	Local skin reaction	Skin test	DLST
Letterie <i>et al.</i> ²	27	F	Endometriosis	n/a	Leuprolide acetate depot 7.5 mg i.m.	0	6 h	NA	Leuprolide acetate depot (+)	NA
Taylor ³	74	M	Prostate cancer	Sulfonamides	Leuporelin acetate depot 7.5 mg s.c.	0	5 min	NA	NA	NA
Raj <i>et al.</i> ⁴	36	F	Endometriosis	Asthma	Goserelin acetate depot 3.6 mg s.c.	6 months	8 h	(+)	Goserelin acetate (+) Leuprolide acetate depot (+)	NA
Lam <i>et al.</i> ⁵	8	F	Precocious puberty	Allergic rhinoconjunctivitis	Leuprolide acetate depot 7.5 mg i.m.	7 months	14 days	(-)	Leuprolide acetate (+)	NA
					Goserelin acetate depot 3.6 mg s.c.	8 months		(-)		
					Goserelin acetate depot 10.8 mg s.c.	3 years	5 days	(-)		
Grant <i>et al.</i> ⁶	66	M	Prostate cancer	None	Leuprolide acetate depot 22.5 mg s.c.	0	2 min	NA	NA	NA
Fujisaki <i>et al.</i>	68	M	Prostate cancer	None	Leuporelin acetate depot 3.75 mg s.c.	9 months	30 min	(+)	NA	Leuporelin acetate (+) PLGA (+)

DLST, drug-lymphocyte stimulation test; GnRHa, gonadotropin-releasing hormone analogue; NA, not available; PLGA, poly(lactic and glycolic acids).

Although all the patients shown in Table 1 successfully recovered by conservative treatment including fluids, drugs (epinephrine, hydrocortisone), oxygen inhalation, and/or airway management, anaphylaxis can be lethal. Therefore, one should bear in mind the possibility of anaphylaxis in all patients who receive GnRHa depot and monitor such patients carefully. Furthermore, we must provide sufficient information of adverse reactions, including anaphylaxis, to patients.

Conflict of interest

None declared.

References

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