

A Case of Foreign Body Granuloma Induced by Subcutaneous Injection of Leuporelin Acetate—Clinical Analysis for 335 Cases in Our Hospital—

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We experienced a case of granuloma formation by subcutaneous injection of leuporelin acetate for treatment of prostate cancer. This patient was an 80-year-old man visiting the clinic of gastroenterological surgery as an outpatient after gastric cancer surgery with a one-week's history of rash on the abdomen. Based on the history of gastric cancer and prostate cancer, though ultrasonography and CT were performed, the possibility of metastatic skin tumor could still not be ruled out. Finally, finding of a foreign-body granuloma in the subcutaneous adipose tissue was recognized histologically. Then, an interview with the patient revealed that he had received subcutaneous injection of a 3-month depot formulation of leuporelin acetate at the site of the lesion about two months earlier. Among urologists, as side effects for treatment, foreign body granuloma induced by subcutaneous injection of leuporelin maybe well known. Therefore, it is tried to analyze as to clinical findings, especially granuloma formation for 335 cases that received leuporelin acetate treatment at our hospital. In this report, we analyzed reported case and 335 cases that received leuporelin acetate treatment at our hospital and summarized the cases that developed the granuloma formation by it.

Key words: leuporelin acetate, foreign body granuloma, prostate cancer

INTRODUCTION

Leuporelin acetate is a luteinizing hormone releasing hormone (LH-RH) agonist; it depletes luteinizing hormone from the pituitary gland and indirectly inhibits the secretion of testosterone. It is the standard therapy for prostate cancer at present. The hormone is available for clinical use as 1-month and 3-month formulations; patients are often switched from the 1-month formulation to the 3-month formulation depending on the clinical course. We encountered a patient who developed a subcutaneous tumor, skin tumor, and ulceration at the injection site after receiving a subcutaneous injection of a 3-month depot formulation of leuporelin acetate for prostate cancer. We analyzed reported cases and 335 cases that received treatment with leuporelin acetate at our hospital and report it because we summarized the cases that developed granuloma formation thereby.

CASE REPORT

An 80-year-old man noticed a rash on the lower right abdomen about one week before he visited the department of gastroenterological surgery for follow-up as an outpatient after gastric cancer surgery. As skin metastasis from gastric cancer was suspected, he was referred to our department in January 2013. The patient had a history of gastric cancer (surgery at age

54 years) and prostate cancer (79 years). He did not have any relevant family history.

At the initial visit, he was found to have a subcutaneous mass in the right lower abdomen; on inspection, the mass appeared as a slightly ill-defined bulge measuring about 5 × 3 cm in size, with slight erythema but mostly normal in the right hypogastric region; on palpation, a well-defined mass, elastic-hard in consistency, was palpable; it was attached to the skin but not adherent to the underlying tissues (Fig. 1). There was no tenderness. As the patient had a history of gastric cancer and prostate cancer, ultrasonography and CT test were performed considering the possible clinical diagnosis of metastatic skin tumor. Ultrasonography was showed an ill-defined, lobulated, hypoechoic heterogeneous tumor in the subcutaneous tissue (Fig. 2). A Doppler study showed abundant blood flow. Based on the ultrasonography findings, metastatic skin tumor was suspected. CT was showed a soft shadow along the right lower abdominal wall. The boundary with the abdominal rectus muscle was maintained by adipose tissues, but it was unclear in parts (Fig. 3). As the possibility of metastatic skin tumor could still not be ruled out by these imaging examinations, skin biopsy was performed.

Histopathological finding was showed a non-caseating granuloma consisting of lymphocytes, epithelioid cells, and foreign body giant cells in the subcutaneous



Fig. 1 Clinical appearance: A subcutaneous mass in the right lower abdomen; on inspection, the mass appeared as a slightly ill-defined bulge measuring about 5×3 cm in size, with slight erythema but mostly normal in the right hypogastric region ; on palpation, a well-defined mass, elastic-hard in consistency, was palpable; it was attached to the skin but not adherent to the underlying tissues. There was no tenderness.

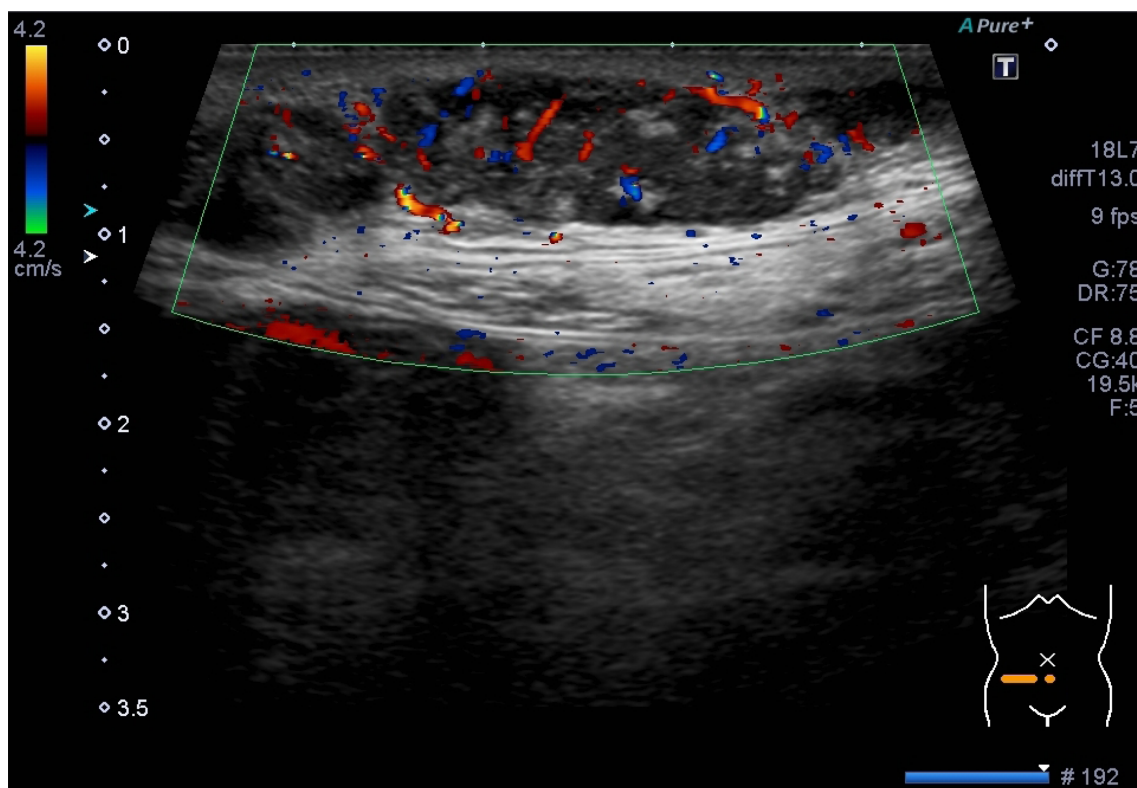


Fig. 2 Ultrasonography: An ill-defined, lobulated, hypoechoic heterogeneous tumor was observed in the subcutaneous tissue. A Doppler study showed abundant blood flow.

adipose tissue; numerous vacuoles were observed in the multinucleated giant cell (Fig. 4). No evidence of malignancy was observed. The diagnosis of foreign-body granuloma was considered as the most likely as pyogenic granuloma disease. The possibilities of sarcoidosis and subcutaneous granuloma annulare were considered in the differential diagnosis. An interview with the patient revealed that he had received subcutaneous injection of a 3-month depot formulation of leuporelin acetate at the site of the lesion about two months prior to his visit. Accordingly, the patient was diagnosed as having a foreign-body granuloma induced by subcutaneous injection of leuporelin acetate.

Avoidance of subcutaneous injection at the same site resulted in a reduction of subcutaneous tumor; however, subcutaneous mass appeared at other sites which received subcutaneous injection. A well-defined skin mass measuring 4×3.5 cm in size was observed at the site of the third injection of a 3-month depot formulation of leuporelin acetate; the mass appeared as an even bulge and had three oval ulcers up to 10 mm in diameter, with a dark red surface (Fig. 5). On palpation, it was elastic-hard in consistency, and not adherent to the tissues underneath. Histopathological examination of the skin biopsy revealed findings consistent with foreign-body granuloma. As for the patients, it was undergone surgical castration.



Fig. 3 CT: A soft shadow was observed along the right lower abdominal wall. The boundary with the abdominal rectus muscle was maintained by adipose tissues, but it was unclear in parts.

Fig. 4 Histopathological findings: A non-caseating granuloma consisting of lymphocytes, epithelioid cells, and foreign body giant cells was observed in the subcutaneous adipose tissue; numerous vacuoles were observed in the multinucleated giant cell. No evidence of malignancy was observed.

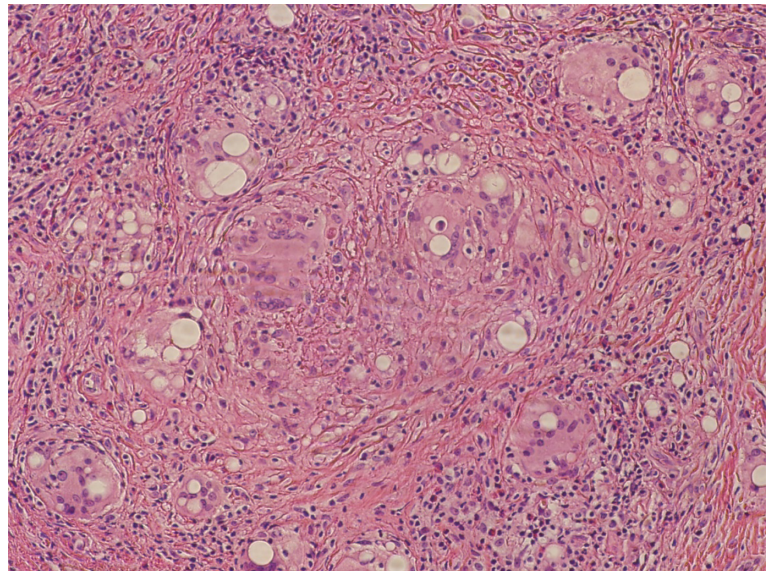


Fig. 5 The site of the third injection of a 3-month depot formulation of leuporelin acetate: A well-defined skin mass measuring 4 × 3.5 cm in size was observed; the mass appeared as an even bulge and had three oval ulcers up to 10 mm in diameter, with a dark red surface. On palpation, it was elastic-hard in consistency, and not adherent to the tissues underneath. Histopathological examination of the skin biopsy revealed findings consistent with foreign-body granuloma.

Table 1 Foreign body granuloma induced by subcutaneous injection of leuporelin acetate

Age	77 y/o (60~90 y/o)
Disease	Prostate cancer 37cases
Site of Lesion	Injection site 37cases
Clinical appearance	Subcutaneous induration 18cases
	Subcutaneous nodules 13cases
	Subcutaneous mass 6cases
	Accompanying ulceration 11cases
Treatment	1-month depot formulation 5cases
	3-month depot formulation 32cases

Summary of 37 cases of Japan reported cases of 1999 to 2012 (1,4-21)

DISCUSSION

Leuporelin acetate is a luteinizing hormone releasing hormone (LH-RH) agonist; as it depletes luteinizing hormone from the pituitary gland and indirectly inhibits the secretion of testosterone, it is used in the treatment of sex hormone-dependent diseases [1].

LH-RH agonist formulations indicated for prostate cancer and used in Japan include leuporelin acetate and goserelin acetate. Depot formulations of leuporelin acetate are composed of microspheres with a mean diameter of 20 μ m, with the drug contained in carriers of lactic acid/glycol acid copolymers or a lactic acid polymer. Both 1-month (3.75 mg) and 3-month (11.25 mg) depot formulations are available. Goserelin acetate is a solid cylindrical depot formulation prepared by heating and pressurizing the drug/copolymer mixture of lactic acid/glycolic acid and goserelin acetate. This drug is also available in 1-month (3.6 mg) and 3-month (10.8 mg) depot formulations [2]. Both formulations release active ingredients in a sustained manner following subcutaneous injection [3]. Leuporelin acetate is administered by subcutaneous injection into the upper arms, abdomen or buttocks, while goserelin acetate is administered by subcutaneous injection into the abdomen [4]. According to the package insert of the pharmaceutical company, in the post-marketing surveillance, injection site disorders are found in 13%.

In 1999, leuporelin acetate-induced granuloma was reported for the first time in Japan; thereafter, 37 cases have been reported, including our case reported herein [1, 4-21]. In many patients, the symptom developed when the patients began to receive the 3-month depot formulation (Table 1). One case of goserelin acetate-induced granuloma has been reported [4].

In the cases that the symptom developed when the patients began to receive the 1-month depot formulation, there was it until the case that the symptom developed after 6-year treatment from the case that the symptom developed with the first injection. Of the 5 patients, the rash of 3 was relieved naturally, the passage of the other 2 was unknown.

In the cases that the symptom developed when the patients began to receive the 3-month depot formulation, there was it until the case that the symptom developed after the injection of seven times from the case that the symptom developed with the first injection.

The mean number of times was approximately 2.5 times. The case which the symptom developed with the first injection was 12 of 32 cases. The case that the number of times was unidentified was 4 cases.

There were steroid external use and the resected cases, but there were the most spontaneous relieved cases with 15 of 37 cases. The treatment of prostate cancer later, 20 cases was changed to goserelin subcutaneous injection, 4 cases were undergone surgical castration, 1 case was the end of treatment, 12 cases were unknown.

Over the last five years, 335 patients have received treatment with leuporelin acetate for prostate cancer at Tokai University Hospital, and onset of a rash at the site of injection was observed in 13/335 (3.88%) of these patients. Of the 13 patients, 10 developed the rash after switching from the 1-month depot formulation to the 3-month depot formulation. The patient described in this paper was the only one who visited the clinic of dermatology. Consistent with previous reports, in many patients, the rash developed when they began to receive the 3-month depot formulation (Table 2). The mean number of times before the symptom developing when the patients began to receive the 1-month depot formulation was approximately 1.7 times. The mean number of times before the symptom developing when the patients began to receive the 3-month depot formulation was 2.4 times.

The precise reason for the granuloma formation induced by leuporelin acetate, particularly the 3-month depot formulation, and the mechanism of formation of the granuloma have not yet been clearly elucidated. The difference between the 3-month formulation of leuporelin acetate and 1-month formulation or goserelin acetate lies in the amount of the base compound and base components [2]. While a number of studies have been carried out, Yamada *et al.* [3] carried out a morphological examination of the granuloma using a transmission electron microscope (TEM) and confirmed the occurrence of foreign body-type reaction in the adipose tissues denatured by microcapsules and drugs.

Two cases of granuloma formation at sites of intramuscular injection of leuporelin acetate have been reported from overseas [21, 22]. The reason for the lower number of reports from overseas than that from Japan is that the mode of administration in Japan is different from that used overseas; that is, the primary

Table 2 Foreign body granuloma induced by subcutaneous injection of leuporelin acetate

	Onset of a rash at the site of injection 13/335cases (3.88%)
1-month depot formulation (95cases)	Subcutaneous induration 3cases (3.16%)
3-month depot formulation (240cases)	Subcutaneous induration 8cases (3.33%) Ulceration 1case (0.42%) Subcutaneous mass and ulceration 1case (0.42%)

Summary of 335 cases of leuporelin acetate treatment in cases of prostate cancer for the past five years in Tokai University Hospital

route of administration in Japan is the subcutaneous route, while the intramuscular route is used more frequently overseas [2]. With the goal of preventing muscle and nerve damage, the intramuscular route for leuporelin acetate injection is not employed in Japan [5].

As leuporelin acetate is frequently used in the treatment of prostate cancer, attention should be paid to the possibility of granuloma formation at the injection sites. Based on past reports, it is presumed that a change in the administration method from the subcutaneous route to the intramuscular route might reduce the frequency of granuloma formation. It is considered necessary to review the mode of administration of this drug product in Japan.

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