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CASE REPORT

Granuloma caused by subcutaneous injection of leuprorelin acetate product: Case report and histopathological findings

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ABSTRACT

Leuprorelin acetate is a luteinizing hormone-releasing hormone (LH-RH) analog, which is used for chemical castration. Chemical castration treatment has an especially important role for prostate cancer. To ensure ongoing chemical castration, a novel sustained-action injection system using spherical microcapsules has been developed. We report a patient who had granuloma caused by administration of the 11.25 mg leuprorelin acetate product. Histological examination revealed many giant cells with vacuoles. On the basis of reported cases, these vacuoles are characteristic for the granuloma caused by leuprorelin acetate product. The vacuoles in the granuloma are the same size as the microcapsules, and their shape is almost spherical. We assume that the vacuoles in the granuloma are actually the microcapsules. We expect that there will be investigations regarding the procatarctic cause of granuloma formation.

Key words: granuloma, lactic acid, leuprorelin, subcutaneous injection, vacuoles.

INTRODUCTION

Leuprorelin acetate is a luteinizing hormone-releasing hormone (LH-RH) analog, which has approximately 100 times the biological activity of LH-RH. When administered repeatedly, it inhibits the biosynthesis of testicular and ovarian steroids; that is, it effects chemical castration.[1] Recently, hormone-dependent tumors (e.g. prostate cancer, breast cancer) and endocrinopathy (e.g. endometriosis) have been treated without surgery by using this LH-RH superagonist. For prostate cancer, which is particularly dependent on sex hormones, chemical castration by LH-RH superagonist treatment has an especially important role.

To ensure ongoing chemical castration, the concentration of leuprorelin acetate in the blood must be kept high over a prolonged period. To this end, a novel sustained-action injection system using microcapsules has been developed.[2] The microcapsules contain a high concentration of leuprorelin acetate. Biodegradable polymers are used for the microcapsule walls, and they are discharged as lactic acid, glycolic acid, carbonic acid gas and water after hydrolytic cleavage *in vivo*. This biodegradable material is assumed to be extremely safe and, accordingly, it is also used for absorbable surgical sutures.[1,3]

For chemical castration, a 3.75 mg dose of leuprorelin acetate (Leuprin, Takeda Chemical Industries, Osaka, Japan) is administered once every 4 weeks. Leuprin was released in Japan in September 1992. In August 2002, another leuprorelin acetate product was released in Japan; Leuprin SR (Takeda Chemical Industries, Osaka, Japan) contains a 11.25 mg dose, and is administered once every 12 weeks.

The incidence of dermatological problems caused by hypodermic injection of leuprorelin acetate has increased in Japan since the release of the 11.25 mg leuprorelin product. We report here a case of

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granuloma caused by administration of the 11.25 mg leuprorelin acetate product and consider the pathogenesis of leuprorelin acetate-related granuloma.

CASE REPORT

A 72-year-old Japanese man presented with a subcutaneous nodule with erosion on his right upper arm. The surface was smooth and slightly erythematous with light-brown pigmentation. The diameter of the nodule was approximately 6 cm, and he did not have any subjective symptoms (Fig. 1a). The patient had received, as treatment for prostate cancer, four 3.75 mg injections of leuprorelin acetate followed by two 11.25 mg injections. Urologist chose the injection site for both upper arms by turns. During the period of 3.75 mg injections, he had not noticed any symptoms at the injection sites. He noticed the nodule approximately 2 weeks after the second 11.25 mg injection. A biopsy sample was taken from the erosive area. The epidermis was absent. Dense granulomatous reaction consisting of many histiocytes and lymphoid cells occupied the dermis and upper fatty layer. The granuloma contained many giant cells with vacuoles (Fig. 1b). After this episode, the urologist discontinued the chemical castration and performed prostatectomy. The nodule resolved spontaneously by degrees over a few months.

DISCUSSION

In a published work search,[4–13] we found 29 reported cases of leuprorelin acetate-related granuloma. Only two reports were from outside Japan.[4,5] We consider that this geographical difference is caused by the different methods of injection in different countries: leuprorelin acetate is injected hypodermically in Japan, but intramuscularly in Europe and the US.

Among the reported cases, asymptomatic subcutaneous nodules were common, and they were sometimes accompanied by pus and ulcer formation. Histopathologically, granuloma with vacuolation was found in every case. Of the reported cases, there were six cases in which only the 3.75 mg leuprorelin acetate product was used (average no. injections: 15), 12 cases in which the 11.25 mg leuprorelin acetate product was followed by treatment with other drugs including Goserelin acetate and 3.75 mg leuprorelin acetate product (average no. injections: 1.5), nine cases in which the 11.25 mg leuprorelin acetate product was used alone (average no.

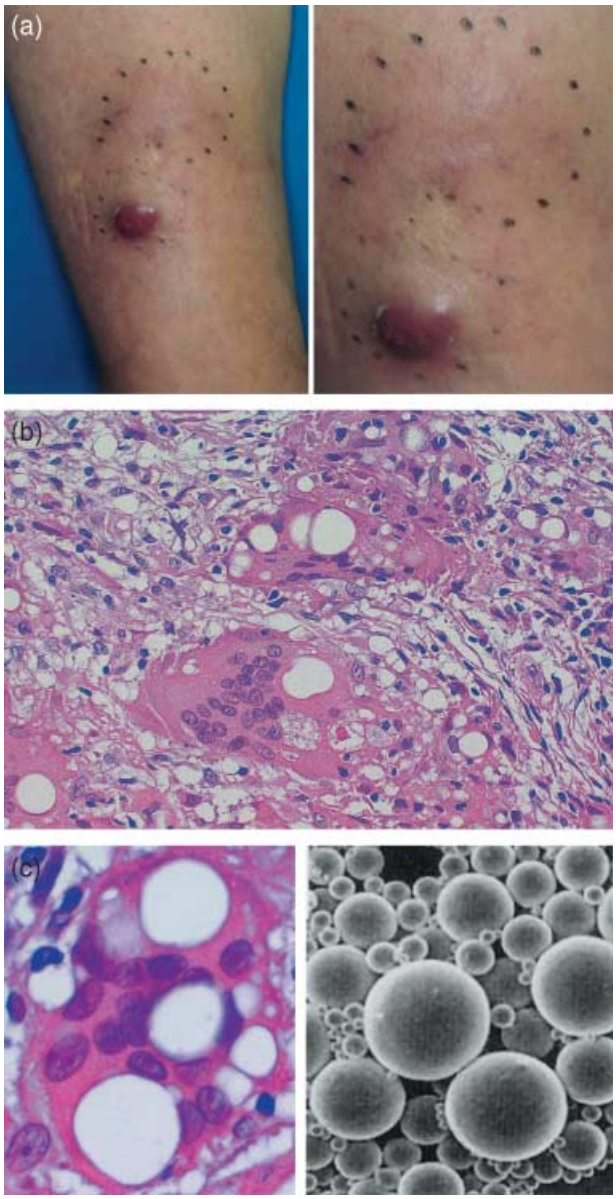

Figure 1. (a) Clinical appearance: Subcutaneous nodule with erosion. (b) Many giant cells with vacuoles are seen (original magnification ×200). (c) Left: Foreign body giant cell containing vacuoles on HE staining (original magnification ×1000). The diameter of the vacuoles is approximately 20 μm. Right: Microcapsules taken by scanning electron microscopy. The average diameter of them is 20 μm (The photograph was provided by Takeda Chemical Industries, Osaka, Japan).

Table 1. Comparison of Leuprin and Leuprin SR

	Leuprin	Leuprin SR
Leuprorelin acetate	3.75 mg	11.25 mg
Raw material of MC	Random copolymer of the lactic acid and glycolic acid	Polymer of the lactic acid
Molecular weight of raw material	10.000	14.000
Total amount of MC	33.1 mg	99.3 mg

MC, micro capsules.

injections: two), and two cases in which the details of treatment were uncertain.

According to this information, we can make some general observations:

1. Approximately 70% of these cases were caused by the 11.25 mg leuprorelin acetate product.
2. The 11.25 mg leuprorelin acetate product forms granuloma faster than the 3.75 mg product.
3. Histopathologically, the granulomas are characterized by vacuolation.

It should be possible to deduce the pathogenesis of the granuloma formation on the basis of information about the two products, and the histopathological findings.

The 11.25 mg product contains three times as much leuprorelin acetate as the 3.75 mg product. A random copolymer of lactic acid and glycolic acid is used as the raw material for the 3.75 mg product microcapsule, whereas a polymer of lactic acid is used for the 11.25 mg product microcapsule. The raw material of the 11.25 mg product microcapsules has a greater molecular weight than that of the 3.75 mg product and as in whole amounts (Table 1).

The average diameter of the microcapsules is 20 μm,[3] and their shape is almost spherical according to scanning electron microscopy.[1] On average, the vacuoles in the giant cells are the same size as the microcapsules, and their shape is almost spherical (Fig. 1c). Therefore, we assume that the vacuoles are actually the microcapsules and cause the granuloma reaction.

Mizoguti reported the intracutaneous test of leuprorelin acetate product and the raw materials of microcapsules.[8] According to their report, granulomatous reaction with vacuoles appeared only at the intracutaneous injection site of leuprorelin acetate product (both 3.75 mg and 11.25 mg product). The intracutaneous test of independent raw materials presented non-specific inflammatory process. This report supports our deduction.

On the basis of these observations, we presume that the excessive granuloma reaction is caused by many microcapsules remaining in the subcutaneous tissue layer, with unknown procatarxis (possibly injection site or rubbing). The 11.25 mg leuprorelin acetate product has more microcapsules with much molecular weight. Hence, it is supposed to cause granulomatous reaction easily and rapidly. We expect that there will be investigations regarding the procatarctic cause of granuloma formation.

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