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Case Report

Bilateral Upper Arm Granulomas Induced by Leuprorelin Acetate Injection Mimicking Malignant Soft Tissue Tumors: A Case Report

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Keywords

Leuprorelin acetate · Reactive granuloma · Intramuscular tumor · Fluorodeoxyglucose-positron emission tomography · Case report

Abstract

Leuprorelin acetate is a common anticancer medication used for prostate cancer treatment. One of the local adverse reactions after leuprorelin injection is the development of reactive granulomas, typically presenting as subcutaneous nodules. In this case report, we describe a 73-year-old patient with prostate cancer who developed unusually large sized intramuscular reactive granulomas, which mimicked malignant soft tissue tumors. The patient, who had been receiving leuprorelin acetate treatment for the past 12 months, noticed painful masses in both upper arms. Based on the findings of magnetic resonance imaging and fluorodeoxyglucose-positron emission tomography/computed tomography, a diagnosis of malignant soft tissue tumor was strongly suggested. However, further investigation through needle biopsy ultimately led us to the final diagnosis of reactive granuloma. The masses spontaneously resolved after discontinuation of leuprorelin injection. While reactive granulomas after leuprorelin injections are not rare, intramuscular cases are relatively uncommon. Despite using imaging studies as a rational initial approach in the diagnostic process, as we did in our case, their results turned out to be indistinguishable from those of malignant soft tissue tumors, thus highlighting the importance of pathological examination in confirming diagnosis, especially when a patient presents with atypical clinical manifestations.

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Introduction

Leuprorelin acetate, a superactive agonist analog of luteinizing hormone-releasing hormone, is indicated for hormone-dependent cancers such as prostate and breast cancer. Currently, three depot leuprorelin acetate formulations are available in Japan, to be administered at 1-month (3.75 mg), 3-month (11.25 mg), and 6-month (22.5 mg) intervals through subcutaneous injection. However, adverse reactions have been reported at the injection site, including pain, induration, redness, abscess, swelling, ulceration, granuloma formation, and necrosis [1].

The occurrence of reactive granulomas associated with leuprorelin acetate was first reported in a patient with prostate cancer by Whitaker et al. [2] in 2002. Since then, similar cases have been reported in the fields of dermatology and urology [3, 4]. These lesions typically present as non-tender subcutaneous nodules with a diameter ranging from 2 to 7 cm [2, 4–11]. Local skin changes, such as erythema or ulceration, are commonly present [3, 5, 7, 9]. These granulomas tend to resolve once leuprorelin injections are discontinued [2–13].

Herein, we report a case of a patient with prostate cancer who developed reactive intramuscular granulomas at injection sites in both upper arms due to leuprorelin acetate administration. The appearance of these lesions closely resembled that of malignant soft tissue tumors, making them indistinguishable without confirming their histology.

Case Presentation

A 73-year-old man was referred to our orthopedic department for an assessment of painful masses in both upper arms. He had a history of prostate cancer and had been receiving subcutaneous injections of leuprorelin acetate for the previous 12 months. Initially, he received the 3.75 mg formula monthly for the first 6 months, which was later switched to 3-month 11.25 mg injections. The patient noticed the masses after receiving the third injection of the 3-month formulation. On physical examination, we observed tender, firm but elastic, relatively immobile masses in both upper arms with no noticeable skin changes. Magnetic resonance imaging (MRI) of his left arm revealed a lobulated, 9-cm-long mass in the lateral head of the triceps. The lesion had iso-intensity on T1-weighted images (shown in Fig. 1a) and heterogeneous high intensity on T2-weighted images (shown in Fig. 1b), with strong enhancement with gadolinium (shown in Fig. 1c). Given the presence of a large intramuscular mass with strong gadolinium enhancement and nonspecific signal change patterns on MRI, a provisional diagnosis of malignant soft tissue tumor was made. To further investigate, we performed fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT), which revealed high uptake in the masses of both upper arms, with a maximum standardized uptake of 13.14 (shown in Fig. 2). However, no lesions suggestive of distant metastases were detected. Furthermore, blood tests showed no evidence of inflammatory reactions or elevated concentrations of tumor markers, including prostate-specific antigen and soluble interleukin-2 receptor.

Our differential diagnoses comprise primary malignant soft tissue tumors, other malignant intramuscular lesions such as malignant lymphoma, and metastases from prostate cancer, as well as other tumor-like lesions such as reactive granuloma, nodular fasciitis, abscess, and hematoma. As neither imaging nor laboratory findings could definitively rule out the possibility of malignancy, we decided to perform a percutaneous CT-guided needle biopsy. The pathological examination of hematoxylin-eosin-stained sections showed granulomatous changes consisting of aggregations of epithelioid and multinucleated giant cells, accompanied by inflammatory infiltration of lymphocytes and eosinophils. The multinucleated giant cells

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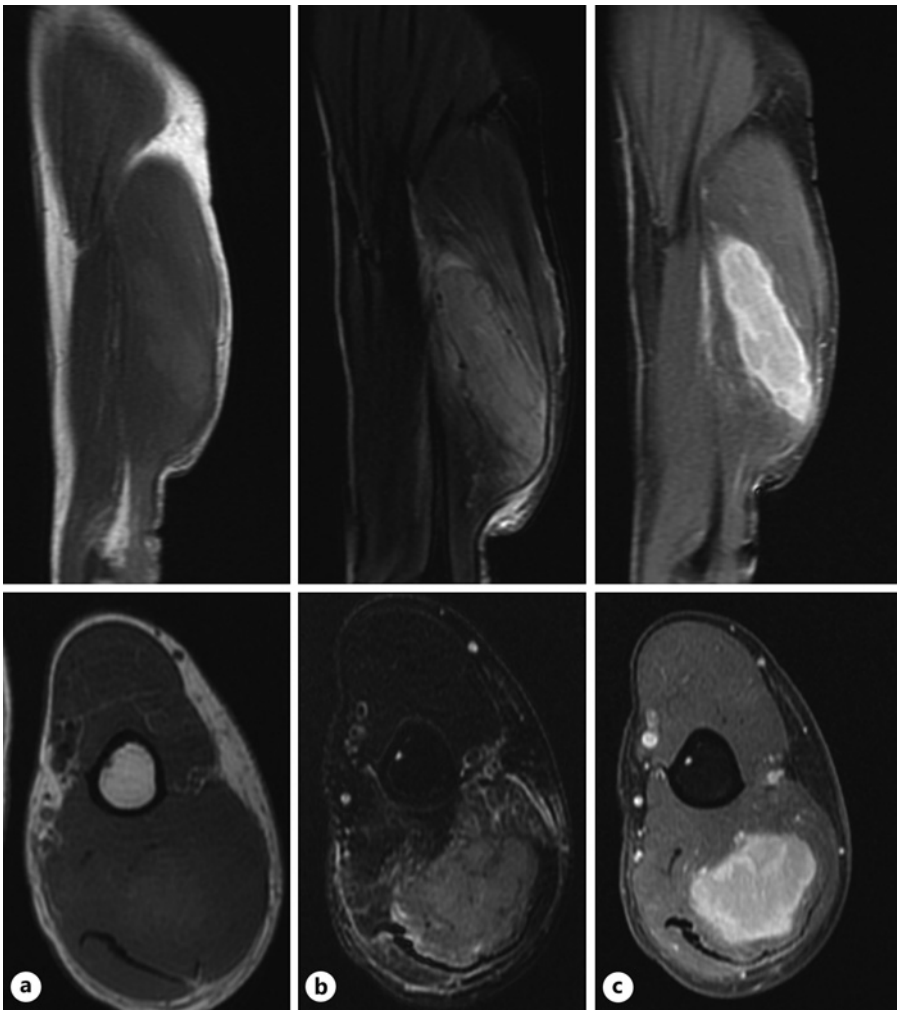

Fig. 1. MRI findings of an intramuscular mass in the left upper arm. Images show a 9-cm-long mass in the lateral head of the triceps with iso-intensity on T1-weighted images (**a**), heterogeneously high intensity on T2-weighted images with fat suppression (**b**), and strong enhancement with gadolinium (**c**).

contained cytoplasmic vacuoles of varying sizes (shown in Fig. 3). There was no evidence of malignancy, and we were able to exclude mycosis and tuberculosis based on the absence of detectable pathogens and negative cultures.

Considering these pathological findings and the location of the masses deep into the sites where leuprorelin acetate was injected, our final diagnosis pointed toward reactive granulomas induced by the leuprorelin acetate injections. Leuprorelin was discontinued immediately and replaced with oral antiandrogen therapy. Within 6 months, both masses and associated symptoms resolved completely, and there was no evidence of progression of our patient's prostate cancer.

Discussion

The incidence of leuprorelin acetate-related reactive granulomas has been reported to range from 3.2% to 9.5% for the 1-month formulation and 4.2–11.9% for the 3-month formulation [1, 7–9]. The incidence appears to be higher with the 3-month formulation (Table 1). Among the 54 reported cases where details of leuprorelin treatment were

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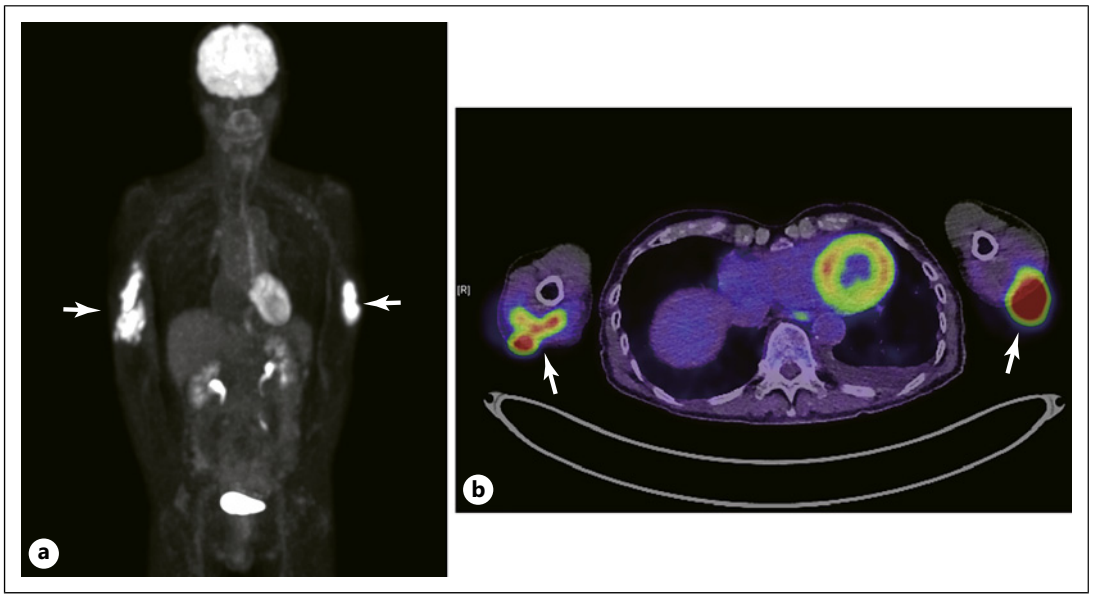

Fig. 2. Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) findings at the time of presentation. Both upper arm masses show high FDG uptake (arrows). Relevant parts of a whole-body scan (**a**) and an axial image (**b**) are presented.

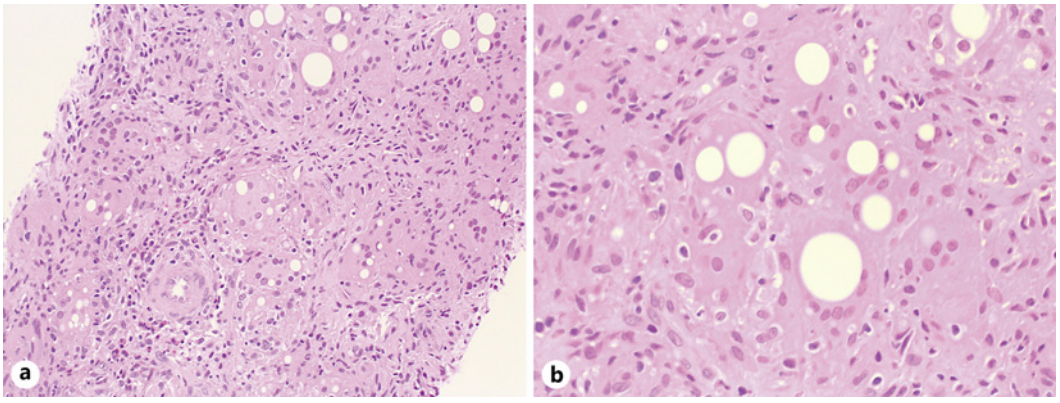

Fig. 3. Pathological findings on hematoxylin-eosin-stained sections of a biopsy specimen. Granulomatous changes consisting of epithelioid cells accompanied by inflammatory infiltration of lymphocytes and eosinophils, and multinucleated giant cells are apparent. The giant cells contain lucent cytoplasmic vacuoles of varying sizes. Magnification, ×100 (**a**), ×400 (**b**).

mentioned [2–12], a significant majority, 88.9% (48 cases), had granulomas following administration of a 3-month or longer formulation, whereas only 11.1% (6 cases) were associated with the 1-month formulation. Consistent with this, our patient developed upper arm masses after switching to the 3-month formulation. The observed disparity in incidence between the 1-month and 3-month formulations is likely attributable to differences in the molecular structure of the microcapsules used in these injections [5, 6]. Microcapsules play a crucial role in regulating the release and absorption of the active drug in all types of leuprorelin depot injections. These microcapsules are composed of synthetic biodegradable polymers of lactic acid, with or without glycolic acid, depending on the type of formulation used; 1-month versus 3-month, respectively [6]. While the exact reasons for the occurrence of

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Table 1. Formulas and doses of leuprorelin acetate prior to reactive granuloma formation and location of the lesions in reported prostate cancer cases

Formulas and doses of injection prior to granuloma formation	Location	Reference (year)
ND	SC	Whitaker et al. [2] (2002)
#1. 1-month × 6 times and 3-month × 3 times	SC	Yasukawa et al. [5] (2005)
#2. 1-month × 3 times and 3-month × 5 times	SC	
#3. 3-month × 3 times	SC	
1-month × 4 times and 3-month × 2 times	SC	Ouchi et al. [6] (2006)
ND	SC	Sakamoto et al. [11] (2006)
#1. 1-month and 3-month for 5 months in total (precise doses were not described)	SC	Shiota et al. [8] (2007)
#2. 1-month and 3-month for 13 months in total (precise doses were not described)	SC	
#3. 3-month × 2 times	SC	
#4. 3-month × 3 times	SC	
#5. 1-month × unknown times and 3-month × 9 times	SC	
<A report on 6 granuloma cases> 1-month; 1 case, 3-month; 5 cases Total duration of 150 days (mean of 6 cases, 35–350 days)	SC	Watanabe et al. [4] (2009)
4-month × 2 times	IM	Vinson et al. [12] (2012)
<A report on 13 granuloma cases among 335 patients with prostate cancer treated with leuprorelin acetate> 1-month only; 3 cases, 1-month and 3-month; 10 cases 1-month × 1.7 times (mean of 3 cases), 3-month × 2.4 times (average of 10 cases)	SC	Kawai et al. [7] (2014)
#1. 3-month × 1 time	IM	Thway et al. [3] (2015)
#2. 1-month × unknown times and 3-month × 1 time	SC-IM	
<A report on 21 granuloma cases among 180 patients with prostate cancer treated with leuprorelin acetate> 1-month only; 2 cases, 3-month; 19 cases Total duration of 22 months (median of 21 cases, 4–62 months)	SC	Fukui et al. [9] (2015)
6-month × 2 times	SC	Grimaux et al. [10] (2020)
1-month × 6 times and 3-month × 3 times	IM	Our case

ND, not described in the literature; SC, subcutaneous; IM, intramuscular.

reactive granulomas after leuprorelin injection have not yet been fully clarified, a widely accepted hypothesis points toward foreign body reactions triggered by the microcapsules [3–9, 12] and degenerated fat tissue because of leuprorelin's lipolytic activity [6, 8].

Reactive granulomas after leuprorelin acetate administration typically manifest as subcutaneous nodules, as summarized in Table 1, while only a few cases (three of 55 previously reported cases) have been documented to develop intramuscularly [2, 6]. Subcutaneous injections are

believed to have a higher likelihood of causing these reactive granulomas [4–8, 11, 13]. Some authors have suggested that intramuscular injections may be safer, as they are less likely to stimulate local granulomatous reactions [4, 11, 13]. However, there is no definitive evidence to support this contention. In Japan, leuprorelin acetate is generally administered subcutaneously to avoid complications from intramuscular injection. In our patient's case, the masses were intramuscular despite subcutaneous administration of leuprorelin acetate. This anomaly could be attributed to the possibility of the subcutaneous injections leaking into the triceps muscles, likely due to the thin subcutaneous layer observed on MRI and CT imaging (shown in Fig. 1, 2). Given the deep location of the granulomas in relation to the triceps fascia and their relatively large diameter (9 cm) on MRI, we initially considered the possibility of malignant soft tissue tumors, including soft tissue sarcoma. As a result, a correct diagnosis of reactive granuloma was only arrived at after comprehensive clinical evaluation, including an FDG-PET scan and biopsy.

The differential diagnoses for soft tissue masses in prostate cancer patients are abscess, tuberculosis, hematoma, sarcoidosis, and soft tissue metastases [2, 3, 7, 11, 12]. When the lesions are intramuscular, especially when they exceed 5 cm in diameter, both primary and metastatic soft tissue tumors should be considered [14]. In such cases, a multimodal clinical evaluation is essential to confirm the diagnosis, as described in the present report. Imaging findings of leuprorelin-related reactive granulomas have been described in three published reports (Table 2) [3, 5, 12]. Typically, MRI shows low signals on T1-weighted images and high signals on T2-weighted images with contrast enhancement, resembling characteristics seen in various types of malignant soft tissue tumors. Our patient's contrast-enhanced MRI presented a similar pattern (shown in Fig. 1). While there is only one report of FDG-PET findings [12], the authors reported FDG uptake in a reactive granuloma after leuprorelin injection, which is similar to our observations (shown in Fig. 2). It is challenging to definitively rule out the possibility of malignant soft tissue tumors based solely on imaging studies, even with contrast-enhanced MRI or FDG-PET. Pathological findings are crucial for definite diagnoses in all previously reported cases as well as in our own (shown in Fig. 3) [2–13]. Hematoxylin-eosin-stained sections show granulomatous changes comprising epithelioid cells, inflammatory cell infiltration, and giant multinucleated cells with clear cytoplasmic vacuoles of various sizes. Microscopic examination has identified the cytoplasmic vacuoles, approximately 20 μm in diameter, as the microcapsules themselves [4], while electron microscopic studies have identified both smaller and larger lucent vacuoles as degenerated lipid droplets [4]. The giant multinucleated cells with intracytoplasmic vacuoles are commonly found in leuprorelin injection site granulomas. Special stains, such as Ziehl-Nielsen and periodic acid-Schiff, are required to exclude tuberculosis and fungal infection. Immunohistochemistry can also be helpful in ruling out malignant diseases.

Reactive granulomas induced by leuprorelin acetate injections are relatively common in patients with prostate cancer receiving this treatment. However, many medical practitioners outside of urology or dermatology may not be familiar with this condition. In some instances, granulomas can present as intramuscular masses due to technical errors during leuprorelin injection. Consequently, patients with such granulomas are often referred to the orthopedic department for diagnostic purposes. Living in the so-called "cancer era," there is increasing societal demand for orthopedic surgeons to attend to musculoskeletal symptoms related to cancer or its treatment [15]. Considering the large number of patients with prostate cancer receiving leuprorelin acetate, orthopedic surgeons who may have limited experience caring for patients with cancer could encounter cases like the one we presented. Medical practitioners who are aware of this potential adverse effect of leuprorelin acetate injection can readily suspect this condition based on the patients' clinical presentation. It is essential to note that reactive granuloma is benign and typically resolves with the discontinuation of leuprorelin injections. Therefore, invasive procedures like surgical resection may not be necessary if the correct diagnosis is made. Nevertheless, confirming the diagnosis through

Table 2. Findings of imaging studies in reactive granuloma cases after leuprorelin acetate injection – summary of the past reports

Modality	Findings	Reference
MRI	• High intensity on T2-weighted images • Enhanced by gadolinium contrast	Yasukawa et al. [5] (2005)
MRI	• Iso-intensity on T1-weighted images • High intensity on T2-weighted images • Enhanced by gadolinium contrast	Vinson et al. [12] (2012)
FDG-PET	• FDG uptake (+)	
MRI	• High intensity on T2-weighted images • Enhanced by gadolinium contrast	Thway et al. [3] (2015)
MRI	• Iso-intensity on T1-weighted images • High intensity on T2-weighted images • Enhanced by gadolinium contrast	Our case
FDG-PET	• FDG uptake (+)	

MRI, magnetic resonance imaging; FDG, fluorodeoxyglucose; PET, positron emission tomography.

histological examination, such as a needle or incisional biopsy, may be strongly advisable, particularly when the clinical presentation raises concerns about malignant soft tissue tumors, as was the case with our patient. The authors have completed the CARE Checklist for this case report, which is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533924).

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Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study has been granted an exemption from requiring ethics approval by the Institute's Committee on Human Research and the Ethical Committee of Keio University School of Medicine. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Data collection and assembly: Sakura Yamaguchi, Sayaka Yamaguchi, and T. Hirozane; manuscript writing: Sakura Yamaguchi, Sayaka Yamaguchi, and R. Nakayama; and data analysis, data interpretation, and final manuscript approval: Sakura Yamaguchi, Sayaka Yamaguchi, T. Hirozane, T. Mori, N. Asano, H. Okita, R. Nakayama, M. Matsumoto, and M. Nakamura.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of the patient but are available from the corresponding author (S.Y.) upon reasonable request. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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