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CASE REPORT

Imaging of recurrent intramuscular granulomatous masses induced by depot injection of leuprorelin

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Abstract Leuprorelin is a luteinizing hormone-releasing hormone (LH-RH) agonist that is used as an agent of androgen deprivation in some patients with prostate cancer. When administered in depot form, local granulomatous reactions may occur at the injection site, which may mimic masses and which are associated with treatment failure. We present a patient who, over a period of 5 years, developed multiple intramuscular gluteal masses while receiving leuprorelin therapy via intramuscular depot injections; biopsy of one of the masses showed the specific histologic features of leuprorelin granuloma. To our knowledge, this entity has not been described in the radiology literature. Awareness of this entity is necessary to suggest the correct diagnosis in patients with a history of leuprorelin depot injections.

Keywords Prostate cancer · Leuprorelin (INN) · Leuprolide acetate (USAN) · Intramuscular granuloma · Sterile abscess · GnRH agonist · LH-RH agonist · MRI · PET

Introduction

Prostate cancer is the most common noncutaneous malignancy in men and is one of the leading causes of cancer deaths among men in the United States [1, 2]. Current treatment options include radical prostatectomy, external beam radiotherapy, brachytherapy, and hormonal therapy [1, 2]. Hormonal therapy, including androgen deprivation therapy, can be used in conjunction with radiotherapy in patients with localized disease and can also be used alone or with other modalities of treatment in patients with recurrent, metastatic, or progressive prostate cancer [1]. The most commonly used class of androgen deprivation therapy drugs are the luteinizing hormone-releasing hormone (LH-RH) agonists, which paradoxically decrease androgen levels when administered on a continuous basis; the successful use of this class of drugs may allow avoidance of orchiectomy [2, 3]. Leuprorelin, or leuprolide acetate, is a superactive synthetic LH-RH agonist commonly used in the treatment of prostate cancer. This potent LH-RH agonist, when administered repeatedly by either subcutaneous or intramuscular injection, induces chemical castration by inhibiting the biosynthesis of testicular hormones, thus reducing serum testosterone levels [2, 4]. In order to achieve and maintain low serum testosterone levels, LH-RH agonists must be delivered continuously and on schedule [3]. The development of depot formulations of the drugs, which are usually administered once every 3 or 4 months, significantly improved patient compliance in this endeavor [2, 3]. However, when administered in depot form, local granulomatous reactions may occur at the injection site. In many parts of the world, these formulations are administered subcutaneously, and the superficial local reactions associated with subcutaneous injections of depot forms of LH-RH agonist formulations have been described in the literature and include local induration and erythema, subcutaneous nodules, and sterile abscesses [4–18]. Deep intramuscular reactions resulting from intramuscular administration of these medications are not as well known. In addition to causing diagnostic confusion, these local soft tissue reactions are of clinical importance because of their reported association with treatment failure [5–10]. We present a patient who, over a

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period of 5 years, developed multiple bilateral intramuscular gluteal masses while receiving LH-RH agonist therapy via intramuscular depot injections; biopsy of one of the masses showed the specific histologic features of leuprorelin granuloma. To our knowledge, this is the first reported case of intramuscular leuprorelin granuloma formation in the radiology literature.

Case report

The patient, a 63-year-old man, underwent radical prostatectomy for poorly differentiated adenocarcinoma of the prostate, with a Gleason's score of 8. Pathology demonstrated positive surgical margins and seminal vesicle invasion. The patient did well following surgery, but 4 years later was diagnosed with biochemical evidence of recurrence due to a detectable serum prostate specific antigen (PSA) level, and shortly thereafter was started on androgen deprivation therapy with depot intramuscular injections of leuprorelin every 4 months; shortly thereafter, his PSA returned to undetectable levels, indicative of successful androgen deprivation. Nine months after this, a computed tomography (CT) scan of the pelvis was performed as part of a re-staging evaluation and revealed a small elongated fluid collection with peripheral enhancement in the right gluteus medius muscle (Fig. 1); the patient was asymptomatic in this region, and the finding was thought to represent a small hematoma by the patient's clinician. Three months later, a follow-up magnetic resonance (MR) imaging examination of the pelvis was performed and revealed that the right gluteus medius muscle abnormality had resolved; however, there was a new large, approximately 6 cm in greatest dimension, heterogeneous mass in the left gluteal musculature with thick, irregular peripheral enhancement, fluid signal intensity centrally, and edema in the surrounding musculature (Fig. 2). Because this mass developed over a very short time, it was also favored to represent a hematoma, versus less likely an abscess. The patient was asymptomatic in this region, and therefore the patient was followed clinically.

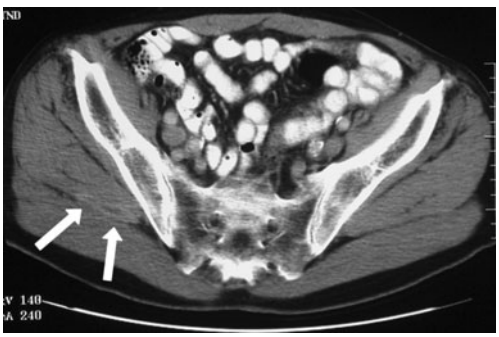

Fig. 1 Post-contrast axial CT image through the pelvis obtained 9 months after the initiation of LH-RH agonist therapy reveals a small elongated fluid collection with rim enhancement in the right gluteus medius muscle (*white arrows*)

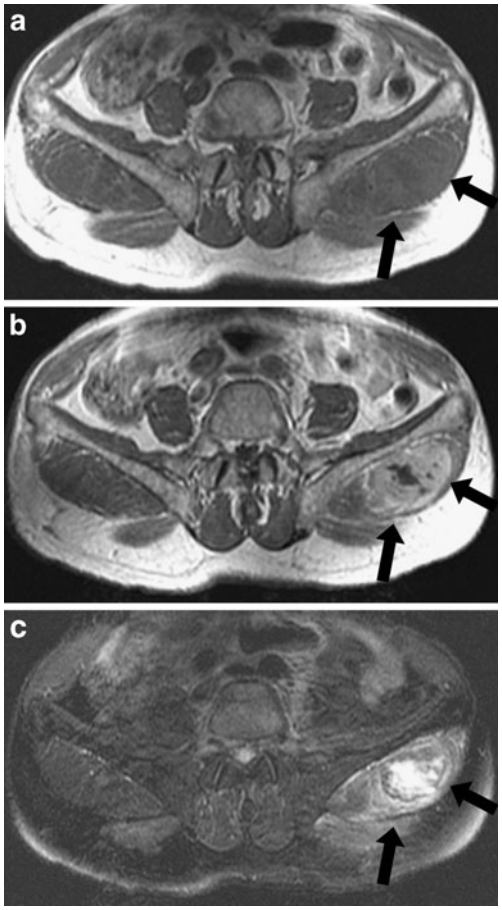

Fig. 2 Axial pre-contrast T1-weighted (**a**), post-contrast T1-weighted (**b**), and fat-suppressed fast spin echo (FSE) T2-weighted (**c**) images of the pelvis obtained 1 year after the initiation of LH-RH agonist therapy demonstrates a large mass in the left gluteus medius with a thick rim of peripheral enhancement, fluid signal intensity centrally, and surrounding edema (*black arrows*)

Six months later, the patient had biochemical evidence of progression of disease, with a detectable PSA level of 0.2 ng/mL (reference range, 0.0–4.0 ng/mL). The leuprorelin depot injections were continued at 4 month intervals. One-and-a-half years later, approximately 7 years after the patient's radical prostatectomy and 3 years after the initiation of depot LH-RH agonist therapy, the serum PSA level had increased again to 0.5 ng/mL, and serum testosterone was found to be at a nonsuppressed level of 74 ng/dL (reference range, 212–742 ng/dL). These laboratory results were consistent with failure of the androgen deprivation therapy, and therefore an antiandrogen medication (bicalutamide, a nonsteroidal antiandrogen) was added to the patient's ongoing regimen of leuprorelin depot injections.

Because of the biochemical evidence of disease progression, the patient underwent a re-staging CT examination of his chest,

abdomen, and pelvis. This revealed a tubular rim-enhancing lesion in the right gluteus maximus muscle, with stranding in the overlying subcutaneous fat. Again, this was suspected to represent either a hematoma or an abscess. The previously seen right gluteus medius and large left gluteus medius abnormalities had spontaneously resolved. The patient was continued on depot LH-RH agonist and antiandrogen therapies; serum PSA levels returned to an undetectable level, and serum testosterone returned to a suppressed level of <50 ng/dL.

One year and three months later, the patient's serum PSA level was again elevated at 0.4 ng/mL, and the patient was complaining of right posterior pelvic pain. A re-staging positron emission tomography (PET)-CT scan was performed due to biochemical evidence of disease progression. This revealed two adjacent hypermetabolic masses in the right gluteus maximus muscle in the region of the prior smaller mass, with expansion of the muscle belly and stranding in the overlying subcutaneous fat (Fig. 3). Based on correlation with the prior imaging, the differential diagnosis was hematoma, chronic abscess, primary soft tissue sarcoma, or less likely soft tissue metastatic lesion. Because of the history of pain, the patient underwent ultrasound-guided percutaneous biopsy of this lesion. Pathology revealed fragments of necrotic and fibrotic material interspersed with pieces of healthy and degenerating skeletal muscle. The fibrotic regions were largely bland and paucicellular with some histologic characteristics of early scar formation. Scattered throughout were numerous granulomatous foci comprised of a mixture of lymphocytes and plasma cells, with occasional eosinophils and polymorphonuclear cells. The multinucleate giant cells contained up to 10 nuclei, which were often peripherally arranged, consistent with a granuloma. They also had abundant eosinophilic and foamy cytoplasm. The most striking histologic feature was the presence of vacuoles within the giant cells; the vacuoles measured 10–60 μm in diameter and had sharply circumscribed borders (Fig. 4). The pathology findings were characteristic of a local granulomatous reaction secondary to intramuscular depot injection of leuprorelin. Histochemical stains for organisms (fungi, bacteria, and mycobacteria) were negative.

A CT scan of the pelvis performed 2 months later demonstrated that the right gluteal mass was spontaneously resolving, with a small residual area of enhancement in the right gluteal musculature (Fig. 5). A CT scan performed 1 year later revealed complete resolution of the right gluteal abnormalities, with a new, small, peripherally enhancing collection in the left gluteus maximus muscle (Fig. 6).

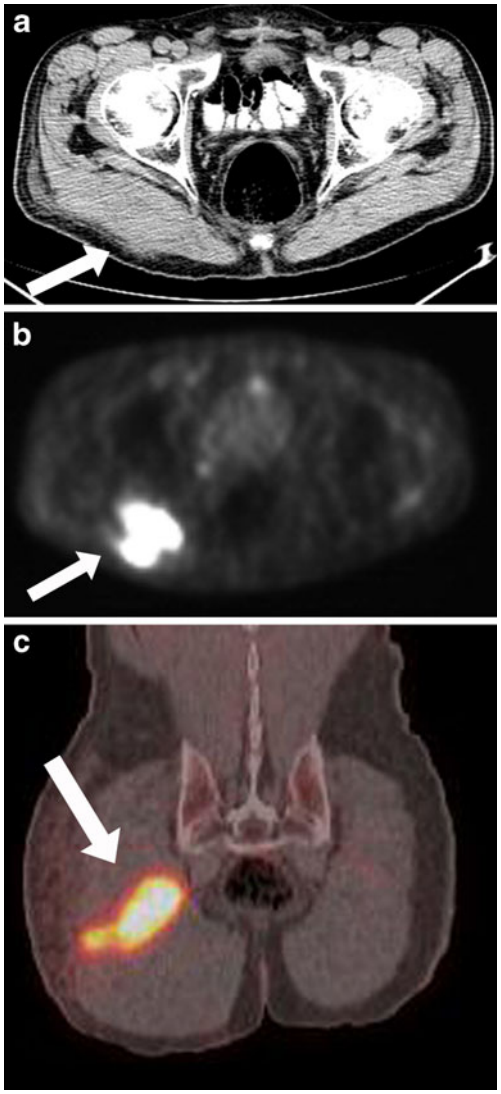

Fig. 3 Non-contrast axial CT image of the pelvis (**a**) obtained 4 years and 3 months after the initiation of LH-RH agonist therapy demonstrates two adjacent masses expanding the right gluteus maximus muscle, with stranding in the adjacent subcutaneous fat (*white arrows*). Corresponding axial FDG-PET image (**b**) and coronal PET-CT fusion image (**c**) demonstrate these masses to be hypermetabolic (*white arrows*)

Discussion

Androgen deprivation therapy, such as with LH-RH agonists, has become the mainstay of treatment for men with locally advanced or metastatic prostate cancer, and is also used as adjuvant therapy in some men with intermediate-risk or high-risk localized disease [1, 2]. The introduction of long-acting synthetic LH-RH agonists, such as depot formulations of leuprorelin, has led to ease of use and improved patient compliance by overcoming the need for daily injections with these therapies. In general, these agents have a favorable side effect profile and few complications, and several long-acting depot products have been approved for use in the United States [2, 3].

Local reactions to depot leuprorelin injections in the few cases described in the literature presented clinically as skin

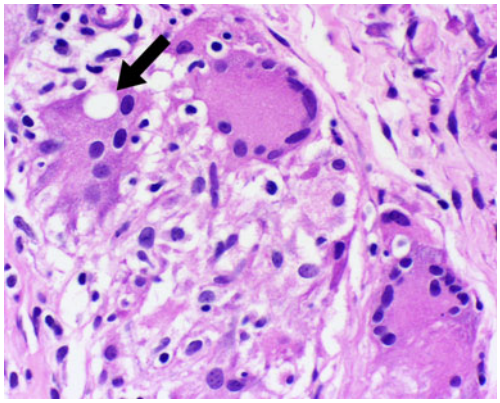

Fig. 4 Photomicrograph of tissue obtained from needle biopsy (hemotoxylin and eosin, magnification ×200) demonstrates granulomatous foci comprised of a mixture of lymphocytes and plasma cells, with occasional eosinophils and polymorphonuclear cells. The giant cells contain up to 10 nuclei, which are peripherally arranged, as well as abundant eosinophilic and foamy cytoplasm. Distinctive vacuoles with sharply circumscribed borders and measuring 10–60 μm in diameter are present within some of the giant cells (*black arrow*)

erythema and induration [5, 6, 8, 10], subcutaneous nodule formation [4, 11, 12, 14–19], or as necrotic masses with exudative centers that failed to yield an infectious organism, termed "sterile abscesses" [5–10, 13]. Some cases were accompanied by ulcers and skin breakdown [9, 18]. Although non-nodal soft tissue metastasis from prostate carcinoma would be an unusual finding, the presence of subcutaneous nodules or soft tissue masses on physical examination or on imaging studies may cause anxiety to the patient [12] and may be a cause of diagnostic error to the radiologist [11]. In the present case report, the patient was several times misdiagnosed on imaging exams with hematoma and possible abscess and required a percutaneous biopsy to have the diagnosis of leuprorelin granulomatous reaction confirmed by histopathology.

These local reactions to depot LH-RH agonist injections have been reported both in children being treated for central

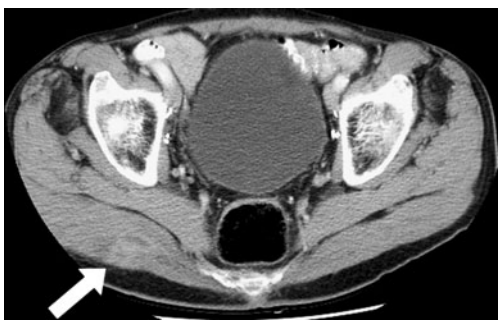

Fig. 5 Axial post-contrast CT image of the pelvis 4 years and 6 months after the initiation of LH-RH agonist therapy demonstrates interval decrease in size of the right gluteus maximus mass, with mild residual enhancement (*white arrows*)

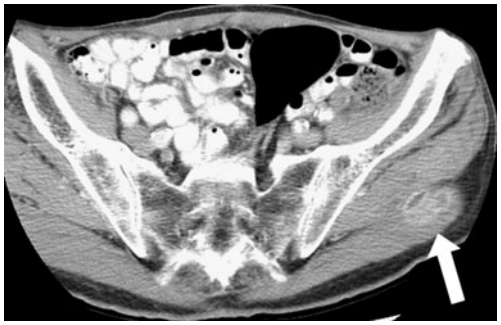

Fig. 6 Axial post-contrast CT image of the pelvis 5 years and 3 months after the initiation of LH-RH agonist therapy demonstrates a new, small rim-enhancing fluid collection in the left gluteus maximus (*white arrow*)

precocious puberty and in men being treated for prostate cancer in the pediatric, dermatology, and urology literature. In 1992 Neely et al. described the clinical occurrence of local reactions following the intramuscular injection of depot leuprorelin formulations in a paper detailing the results of depot leuprorelin therapy in children with central precocious puberty. Two patients in that report experienced local reactions to the injections. In one of these patients, the reaction described consisted of the formation of what the authors described as a sterile abscess. The occurrence of this sterile abscess reaction was coincident with treatment failure in that patient, as evidenced by biochemical evidence of cessation of hormone suppression [5]. Others have also reported the formation of local reactions including sterile abscesses in children undergoing intramuscular injections of depot formulations of leuprorelin and have speculated that the response, at least initially, may be a foreign body reaction to the inert copolymer of lactic and glycolic acid used in the preparation [6, 8] or to the vehicle used [13]. Some of these reports also include descriptions of treatment failure in some of the patients with local reactions to the injections [6, 8], and one speculates that local reactions, especially when recurrent, may somehow hinder the effectiveness of the drug at suppressing hormone levels [6].

Subsequent to those reports, several publications emerged detailing similar local reactions in men undergoing therapy for prostate cancer. Many of these detailed single or recurrent subcutaneous nodules at the injections sites of depot forms of leuprorelin [4, 11, 12, 15, 16], reflective of the fact that the injection, while most commonly administered intramuscularly in the United States, is often administered subcutaneously in other parts of the world [11]. Some of these reports also describe treatment failure coincident with the occurrence of local reactions [7, 9].

The precise mechanism of the local reaction to leuprorelin injection has not been elucidated. The depot form of leuprorelin utilizes synthetic biodegradable microcapsules, which contain a high concentration of the medication. The

microcapsule walls are made of biodegradable polymers, which are discharged in vivo as lactic acid, glycolic acid, carbonic acid gas, and water following degradation. The material is considered extremely safe and is also used for bioabsorbable surgical sutures [4, 11]. Foreign body reactions to suture material, similar to those described here, are well known to surgeons [20]. This has led to speculation that the granulomatous reactions seen in depot injections of leuprorelin are due to the biodegradable microcapsules. However, it has also been suggested that leuprorelin acetate alone can stimulate the granulomatous reaction [11]. Allergy testing in children being treated with depot LH-RH agonist therapy for precocious puberty who suffered injection site reactions has been performed, with variable results. Some patients show allergic reactions to the LH-RH agonist alone, and others react to the vehicle contents alone [13]. Some authors speculate that after an initial idiosyncratic reaction to the drug-copolymer combination leading to a local foreign body reaction, additional interaction with the drug itself is possible [20].

Regardless of the mechanism of the local reaction, an important complication associated with these local reactions is subsequent treatment failure [4, 7–9, 11, 12, 14, 17]. Many of those patients with subcutaneous nodules and sterile abscesses have developed insensitivity to the LH-RH agonist therapy, indicated by a rise in serum androgen levels, though they previously experienced adequate suppression. Some patients may return to a previous status of treatment success after the resolution of the local reaction, but other patients may even experience subsequent failure of different LH-RH agonists, such as goserelin and triptorelin [5–10]. It is thought that the development of a local granulomatous reaction may impair drug absorption, leading to biochemical failure of treatment [16]. Local inflammation may induce hastened release of the drug from the depot, or the drug may become sequestered within a sterile abscess, and either of these could result in treatment failure [7]. Alternatively, local inflammation in the area of the granulomatous reaction may stimulate a humoral response that somehow affects drug efficacy, though to date no such antibodies have been detected [7].

In a small case series, Yasukawa et al. in 2005 reported histopathology in three patients with local reactions to subcutaneous injections of depot leuprorelin. In all three patients, histology showed a granulomatous reaction with numerous giant cells containing translucent vesicles [11]. Ouchi et al. in 2006 described the histopathology of injection site reactions occurring in the subcutaneous tissues as granulomas consisting of many giant cells containing vacuolation. The diameter of each vacuole was approximately 20 μm, similar to the diameter of the injected microcapsule itself [4]. Watanabe et al. in 2009 studied biopsy specimens in six patients with local reactions to depot leuprorelin with routine haematoxylin and eosin staining as well as electron microscopy. Histology revealed epithelioid granulomatous inflammation with foreign body giant cells, with or without central necrosis, with intracytoplasmic vacuoles and degenerated fat tissue in the granulomas. Round bodies of 5–25 μm diameter, thought to represent the microcapsules, and degenerated lipid droplets were present within the granuloma cells on electron microscopy. The fat degeneration was thought to be induced by the leuprorelin acetate itself. The authors speculated a foreign body reaction to both the microcapsules and to degenerated fat tissue, and that the involvement of degeneration of fat tissue in granuloma formation may explain the apparent increased incidence of local reactions in subcutaneous depot injections compared to intramuscular injections [15]. The sharply demarcated vacuoles within the giant cells seem to be the most consistent and specific histology feature in the reported cases, and this feature was also evident on the histology of this current case.

To our knowledge, there are no prior reports on the imaging appearance of deep intramuscular reactions to depot leuprorelin injections. Our patient demonstrated waxing and waning lesions in both the right and left gluteal regions on imaging studies, at the sites of intramuscular administration. On post-contrast CT imaging, the lesions usually appeared as crescent and oval shaped areas of central hypodensity with rim enhancement. MR imaging of one of the lesions showed a heterogeneous mass-like lesion with thick peripheral enhancement and central non-enhancing material that was as hyperintense as fluid on T2-weighted images, most likely representing a large granulomatous reaction with central necrosis. PET imaging demonstrated an area of increased radiotracer uptake corresponding to the lesion consistent with hypermetabolism.

In conclusion, this case report demonstrates that patients undergoing treatment with leuprorelin by depot injection, whether via subcutaneous or intramuscular injection, may develop local reactions at the injection site. These reactions may present as erythema and induration, or as subcutaneous or intramuscular mass-like granuloma with or without central necrosis. Histopathologically, the granulomas are characterized by the presence of vacuolation. The appearance of these local reactions on imaging studies is nonspecific. When an intramuscular mass, with or without necrosis, is encountered in the soft tissues on an imaging study (such as CT, MRI, or PET), the differential diagnosis typically includes a primary soft tissue sarcoma, a metastatic lesion, an abscess, or a hematoma. In patients with a treatment history of depot leuprorelin injection, an injection granuloma is an important additional consideration. Radiologists and treating physicians alike should be aware of this complication, as it may be a cause of diagnostic error on imaging examinations and, perhaps most importantly, these reactions are associated with subsequent LH-RH agonist treatment failure.

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