

## Case report

**Bilateral injection-site granuloma by subcutaneous administration of luteinizing hormone-releasing hormone analogue: a case report**Riko Kitazawa<sup>1</sup>, Fukashi Yamamichi<sup>2</sup>, Toshiharu Hidaka<sup>3</sup>,  
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This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**Abstract**

We report a typical case of injection-site granuloma attributed to subcutaneous administration of leuporelin acetate, an LHRH agonist. A 70-year-old man who had undergone total prostatectomy and was subsequently given leuporelin injections for prostatic cancer presented with bilateral nodules in the lower abdominal wall. An excisional biopsy revealed a non-caseous epithelioid granuloma consisting of CD-68 positive histiocytic cells with infiltration of T-lymphocytes and eosinophils; skin metastasis from prostatic adenocarcinoma was ruled out through histological and immunohistochemical analysis. Generally, granulomas may be caused by delayed-type hypersensitivity to the constituents of leuporelin acetate injections.

**Introduction**

Although clinically localized prostatic cancer is treated by prostatectomy or radiotherapy (external beam radiotherapy or brachytherapy), endocrine therapy is chosen for advanced or metastatic cancer because most prostatic cancer cells depend on androgens for their growth. To deprive of androgens, synthetic agonists of luteinizing hormone-releasing hormone (LHRH) are administered instead of conducting an orchiectomy [1]. LHRH agonists, after the initial transient flare-up of LH secretion, suppress LH release and sex hormones by down-regulating the receptors of gonadotrophs of the pituitary gland and

ablating androgens. Although decrease of libido and osteopenia are well-known as the major side effects of LHRH agonists, we describe a rare case of injection-site granuloma (attributed to subcutaneous administration of an LHRH agonist) and emphasize its importance since it could mimic cancer metastasis, as in this case.

**Case presentation**

A 70-year-old Japanese man presenting with bilateral subcutaneous nodules in the lower abdominal region was referred to our hospital. He had undergone total prostatectomy 6 months earlier and had then received monthly

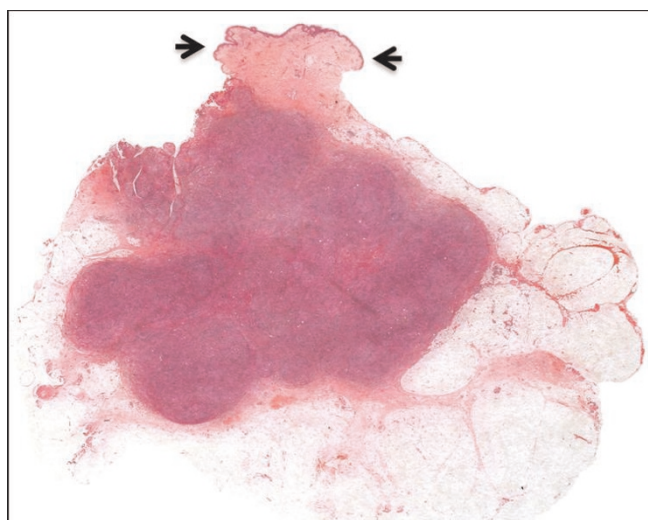
subcutaneous injections of 3.7 mg leuporelin acetate, a synthetic LHRH agonist. The bilateral nodules in the lower abdomen were located at the sites of the leuporelin injections. The nodules were excised to rule out skin metastasis from prostatic cancer.

### Pathologic findings

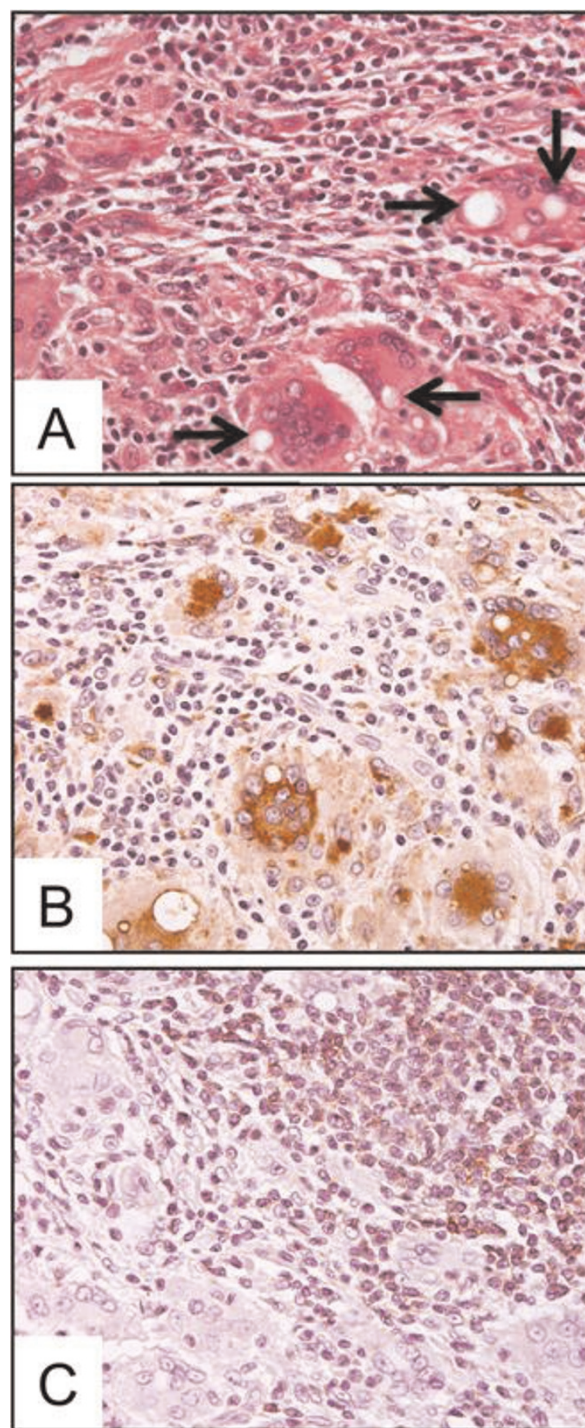
Grossly, the well-circumscribed nodules, approximately 20 mm in diameter, were located in the upper dermis of subcutaneous adipose tissue (Figure 1). Microscopically, they were non-caseous granulomatous lesions with multinucleated giant cells containing lipid droplets infiltrated with lymphocytes and eosinophils (Figure 2A). Ziehl-Neelsen, Periodic acid-Schiff (PAS) and Grocott staining showed no bacterial, fungal or protozoan component. Immunohistochemically, epithelioid cells were negative for cytokeratin 7, cytokeratin 20, low molecular weight keratin (CAM5.2) and prostate specific antigen (PSA), indicating that metastasis from prostatic cancer could be ruled out. Furthermore, epithelioid cells and multinucleated giant cells positive for CD68 (Fig. 2B) were histiocytic cells; infiltrating lymphocytes positive for CD-3 (Figure 2C), but negative for CD-20, were T-lymphocytes. These findings suggested that the granulomas at the injection sites were caused by delayed-type hypersensitivity to the leuporelin acetate.

### Discussion

Long-acting, synthetic LHRH agonists such as leuporelin and goserelin acetate have been widely used for advanced



**Figure 1.** Cross-section of the lesion excised from the right lower abdomen. Epidermis covering the lesion (arrows) was intact. The well-circumscribed nodules, 17 × 15 mm, were located in the upper dermis to subcutaneous adipose tissue (HE, X10).



**Figure 2.** Microscopic findings of non-caseous epithelioid granulomatous lesion. **(A):** High-power view of the nodule revealed epithelioid cells and multinucleated giant cells with droplets (arrows) and infiltration of eosinophils and lymphocytes (HE, X400). **(B):** Immunohistochemical staining for CD-68. Epithelioid cells and multi-nucleated giant cells were positive for CD-68. **(C):** Immunohistochemical staining for CD-3. (counterstained with Hematoxylin, X400).

prostatic cancer [2]. Major side effects of LHRH analogues are hot flashes, osteopenia and decreased libido due to androgen deprivation. Injection-site granuloma is associated with insulin and aluminum-containing tetanus toxoid vaccines [3]. Injections of LHRH analogue rarely cause skin lesion-mimicking metastasis of prostatic cancer [4-6]. In this case, histological and immunohistochemical analysis of the lesions at the injection sites ruled out skin metastasis and infection by microorganisms. Granulomas consisting of CD-68 positive histiocytes and CD3-positive T lymphocytes were compatible with those seen in delayed-type hypersensitivity reactions; droplet-containing phagosomes were also observed in mono- and multi-nucleated histiocytes. Since leuporelin acetate is combined with lactic acid, glycolic acid co-polymers or lactic acid polymers, the formation of granulomas may be related to the co-polymers or to the LHRH analogue itself. Indeed, Manasco *et al.* have demonstrated that the polymer, and not the diluent of leuporelin acetate, elicits a skin reaction, concluding that the causative agent is the polymer [7]. Therefore, in prostatic cancer patients treated with LHRH analogues, both the remission due to the expansion of testosterone-insensitive clones and the possible failure of leuporelin administration because of local skin reaction should be taken into consideration. In summary, we reported a case of bilateral injection-site granuloma by leuporelin administration.

### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for view by the Editor-in-Chief of the journal.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

RK performed the histological examinations and was the major contributor in writing the manuscript. SM, TH and FY were contributors in the clinical management of the patient. KM and TK assisted in immunohistochemical evaluations. SK supported the case analysis and the writing of the manuscript. All authors read and approved the final manuscript.

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