

Injection-Site Granulomas Resulting from the Administration of Both Leuporelin Acetate and Goserelin Acetate for the Treatment of Prostatic Cancer

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Abstract

Although injection-site granulomas caused by leuporelin acetate have been reported, there have been no reports of granulomas caused by both leuporelin acetate and goserelin acetate. An 81-year-old man presented with subcutaneous nodules of the abdominal wall and upper arm, where 11.25 mg of leuporelin acetate had been injected for the treatment of prostate cancer. Because of these nodules, treatment was changed to goserelin acetate. Nevertheless, he presented with another subcutaneous nodule at the injection site. Histological examination showed that these nodules consisted of numerous giant cells that were CD3-positive T lymphocytes and CD68-positive histiocytes associated with granulomatous changes. The granulomas had likely been caused by delayed-type hypersensitivity to leuporelin acetate injection. The granuloma that formed after goserelin acetate injection might thus have developed owing to the immunogenicity of the previous leuporelin acetate injections. The patient underwent surgical castration. The present case suggests that both leuporelin acetate and goserelin acetate can cause injection-site disorders.

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Key words: goserelin acetate, granuloma, luteinizing hormone-releasing hormone analogue, leuporelin acetate, prostatic neoplasms

Introduction

Luteinizing hormone-releasing hormone (LH-RH) analogues are widely used for the treatment of prostatic cancer, myoma of the uterus, breast cancer, central precocious puberty, and other conditions. In Japan, two LH-RH analogues have been approved for the treatment of prostate cancer: leuporelin acetate (Leuplin, Takeda, Osaka) and goserelin acetate (Zoladex, Astra Zeneca, London, UK). Both are marketed for use every month or

every 3 months. For monthly use, leuporelin acetate and goserelin acetate are given once every 4 to 5 weeks at doses of 3.75 mg and 3.6 mg, respectively, and for trimonthly use are given once every 12 to 13 weeks at doses of 11.25 mg and 10.8 mg, respectively. Leuporelin acetate is injected subcutaneously in the abdomen or arm, and goserelin acetate is injected in the abdomen only. Both drugs can cause adverse reactions, such as hot flushes, loss of libido, and osteoporosis. However, injection-site granulomas are rare with LH-RH analogues. Although injection-site granulomas have

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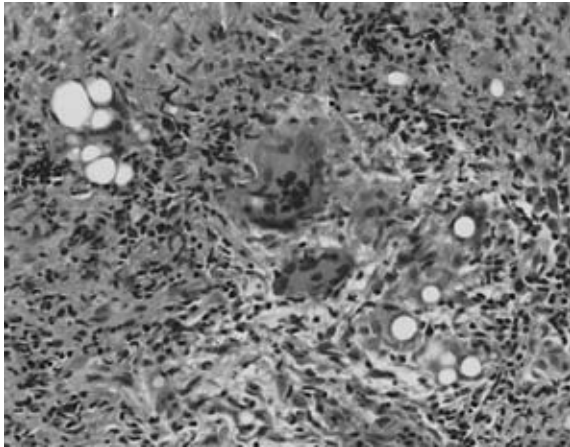


Fig. 1 A microscopic view of the nodule that developed after the administration of 11.25 mg of leuporelin acetate demonstrates giant cells associated with granulomatous changes. Hematoxylin and eosin $\times 100$.



Fig. 2 Gross examination of the subcutaneous nodule that developed after administration of 11.25 mg of leuporelin acetate demonstrates a 60×30 -mm, firm, elastic mass with pus discharge.

been reported with leuporelin acetate, there have been no reports of granulomas caused by both leuporelin acetate and goserelin acetate. We now report a case of injection-site granulomas induced by both leuporelin acetate and goserelin acetate.

Case Histories

An 81-year-old man visited our hospital with urinary retention and was found to have a locally advanced prostatic adenocarcinoma. Androgen deprivation therapy was started with an injection of 3.75 mg of leuporelin acetate for monthly use; an antiandrogen agent was not used and no adverse reactions were observed. Four weeks later, he received the first injection of 11.25 mg of leuporelin acetate for trimonthly use. Sixty days later, he presented with a subcutaneous nodule of the abdominal wall where he had received the first injection of 11.25 mg of leuporelin acetate. The nodule was painless, elastic, and firm and measured 60×30 mm. He had no history or findings of bronchial asthma, atopic dermatitis, other drug allergies, sarcoidosis, Crohn disease, syphilis, or tuberculosis. Biopsy showed that the nodule consisted of giant cells associated with granulomatous changes (**Fig. 1**). Twelve weeks after receiving the first injection of 11.25 mg of leuporelin acetate, he received a second injection of the same dose in the upper arm. Over the next 14 days, a mildly tender, elastic, firm subcutaneous nodule,

eventually measuring 50×40 mm, developed at the second injection site (**Fig. 2**). A bacterial culture of pus discharged by the granuloma was negative. The second injection-site granuloma was worse than the first one.

Because of these granulomas, treatment was changed to 10.8 mg of goserelin acetate every 3 months. However, 24 days after the injection of goserelin acetate, the patient again presented with a subcutaneous nodule of the abdominal wall where goserelin acetate had been injected. The histological features of this granuloma were similar to those of a previous granuloma that developed where leuporelin acetate had been injected, consisting of numerous giant cells that were CD3-positive T lymphocytes and CD68-positive histiocytes. Periodic acid-Schiff staining, Grocott staining, and Ziehl-Neelsen staining revealed no disease-causing substance (**Fig. 3–5**). Because of these granulomas, the patient underwent surgical castration.

Discussion

Injection-site granulomas are most often associated with insulin and with aluminum-containing tetanus toxoid vaccines¹. Injection-site granulomas due to leuporelin acetate are rare but have been reported^{2–4}. However, we believe that our case of injection-site granuloma is the first to be caused by both leuporelin acetate and goserelin acetate.

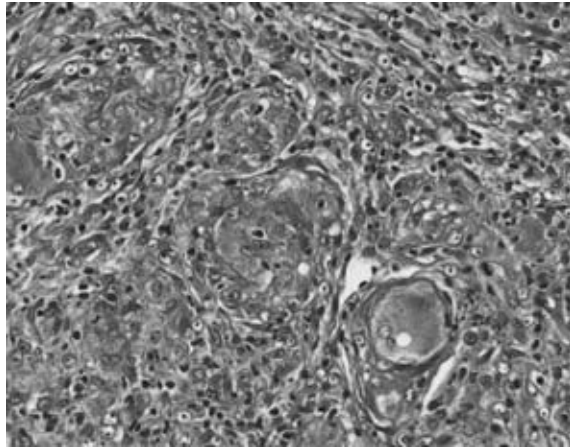


Fig. 3 On microscopic examination the nodule that developed after administration of goserelin acetate demonstrates an appearance similar to that of the nodule that developed after administration of leuporelin acetate. Hematoxylin and eosin $\times 100$.

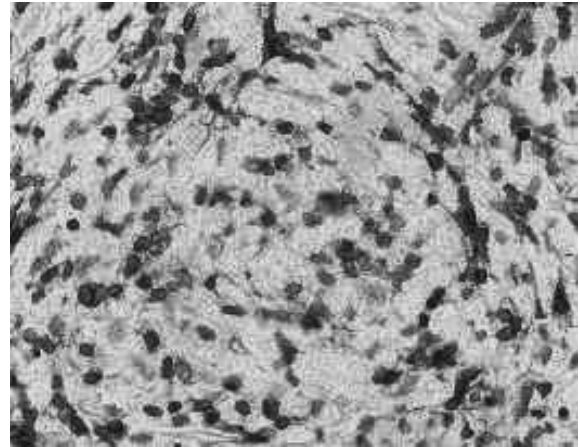


Fig. 4 Inflammatory cells are mainly CD3-positive T lymphocytes, which suggest delayed-type hypersensitivity, $\times 200$.

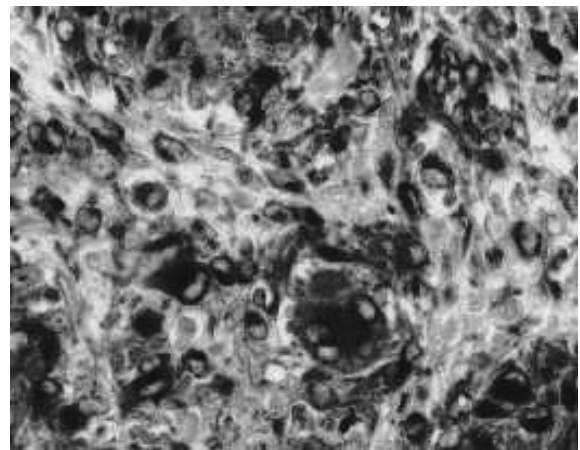


Fig. 5 Inflammatory cells are mainly CD68-positive histiocytes, which suggest delayed-type hypersensitivity, $\times 200$.

Leuporelin acetate is combined with lactic acid/glycolic acid co-polymers or lactic acid polymers. Goserelin acetate is also combined with lactic acid/glycolic acid co-polymers. The formation of granulomas might be related to such co-polymers/polymers combined with the LH-RH analogue or to the LH-RH analogue itself. These granulomas were likely caused by delayed-type hypersensitivity to leuporelin acetate injection, as shown in **Figures 4 and 5**. In addition, delayed-type hypersensitivity is also suggested by the greater severity of the second injection-site granuloma, which was due to leuporelin acetate. Until now, there has been no report concerning granuloma caused by both leuporelin acetate and goserelin acetate. Why did these injection-site granulomas develop after injections of both leuporelin acetate and goserelin acetate in this patient? The subsequent granuloma might have developed rapidly after injection of goserelin acetate owing to the strong immunogenicity of leuporelin acetate, which may prevent the use of other LH-RH analogues in such patients.

There are no definitive treatments or preventative measures for this problem. We should therefore keep in mind that both leuporelin acetate and goserelin acetate may cause injection-site disorders and that such patients have limited therapeutic options, such as surgical castration.

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