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CASE REPORT

Granulomas induced by subcutaneous injection of leuprorelin acetate

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ABSTRACT

Leuprorelin acetate, a chemotherapeutic agent used to treat prostate cancer, is a synthetic luteinizing hormone-releasing hormone (LHRH) agonist. We report a 75-year-old man who presented with several large subcutaneous nodules at the site of leuprorelin acetate injections for his prostatic cancer. A biopsy of the nodules disclosed epithelioid granulomatous inflammation and resulted in a diagnosis of drug-induced granulomatous reaction to leuprorelin acetate.

Key words: granuloma, leuprorelin acetate, prostate cancer.

INTRODUCTION

Patients whose prostate cancer has spread beyond the prostate or recurred after treatment are often treated with hormone therapy. Orchiectomy to suppress plasma testosterone is often rejected by these patients. Long-acting, synthetic luteinizing hormone-releasing hormone (LHRH) agonists have been used in cases with advanced prostate cancer for more than 15 years.[1] At present, LHRH agonists such as leuprorelin and goserelin acetate comprise 70% of administered hormone therapy treatments.[2]

We describe a prostate cancer patient with granulomas induced by the s.c. injection of leuprorelin acetate and provide a review of the published work.

CASE REPORT

A 75-year-old man was referred to our clinic in September 2004. He had developed subcutaneous nodules that caused him to fear metastasis from prostate cancer. In 1998, he had undergone surgery for prostate cancer and had received monthly injections of leuprorelin acetate since that time. Leuprorelin acetate is delivered as a microsphere-type depot injection; synthetic biodegradable polymers, poly(lactic/glycolic) acid, are the wall materials of the leuprorelin polycore microcapsules.[3] The nodules developed at the injection sites after the first injection. A general surgeon excised one of the nodules and made a diagnosis of cryptogenic granulomas.

On physical examination, we noted several scars from his prostate cancer surgery and the resection of subcutaneous nodules on the lower abdomen. The nodules were located in the subcutaneous fatty tissue; they measured 25–30 mm in diameter and were freely movable, firm, irregular and painless (Fig. 1). The skin covering the nodules was normal. Biopsy specimens revealed epithelioid and multinucleated giant cells with large lipid droplets gathered to form granulomas (Fig. 2). In the granulomatous tissue, there was infiltration by many eosinophils (Fig. 3). There was no evidence of metastatic tumor. Periodic acid-Schiff (PAS) and Ziehl–Neelsen staining revealed no bacterial or fungal elements.

Based on these findings, a diagnosis of granulomas induced by injected leuprorelin acetate was made.

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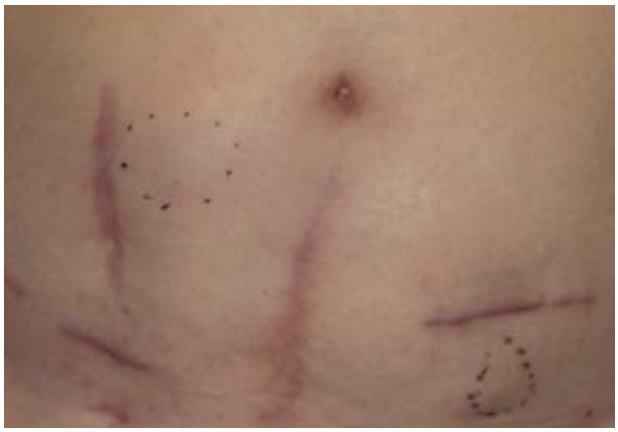

Figure 1. Two large subcutaneous tumors (dotted areas) and two long scars made by their excision close to the subcutaneous nodules.

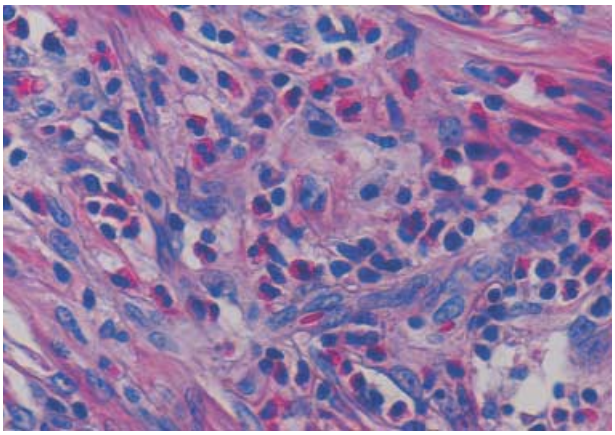

Figure 3. Infiltration by many eosinophils into the interstitial area (HE stain, magnification: ×200).

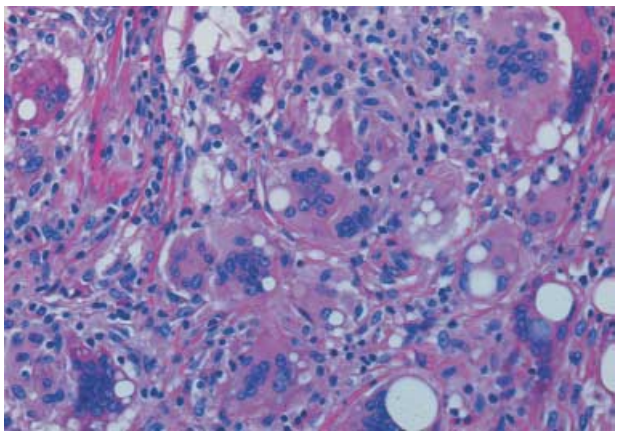

Figure 2. Epithelioid granuloma with multinucleated giant cells with lipid droplets (HE stain, magnification: ×100).

DISCUSSION

Leuprorelin acetate, a superactive LHRH agonist, has about ten times the biological activity of native LHRH.[3] The prolonged administration of LHRH and its agonists, especially at high concentrations, leads to downregulation of receptors and desensitization of gonadotrophs. The administration of depot preparations of LHRH agonists suppresses the secretion of gonadotrophins and sex hormones, and has proven efficacious in the treatment of prostate cancer, endometriosis, breast cancer and central precocious puberty.

Granuloma formation as an adverse effect of leuprorelin acetate injections has rarely been reported in the field of dermatology. In our patient, pathological examination revealed that collections of epithelioid and giant cells had formed granulomas. We postulate that his subcutaneous nodules were the result of the injection of a leuprorelin acetate depot and that the subcutaneous nodules were foreign body reactions to the polymer. Leuprorelin acetate per s.c. is unstable in body fluids and is excreted rapidly; in contrast, the polymer remains for 1 month.[3] Erythema, induration, tenderness and sterile abscesses at the injection site have been reported as local reactions to leuprorelin acetate.[4–12] Most were encountered in children treated for central precocious puberty.[4–7] Manasco *et al.*[4] described three children presenting with "sterile abscesses". When they tested one of their pediatric patients for reactions to the diluent of leuprorelin acetate and the polymer used as vehicle, only the vehicle elicited a reaction. Therefore, they concluded that the sterile abscess was probably a response to the polymer. Neely *et al.*[5] also encountered two children with local reactions to depot leuprolide injections; one had a sterile abscess, the other erythema. No complications ensued when their treatment was changed to daily leuprolide, suggesting that the observed reactions[4,5] were in fact polymer-induced, because polymer is absent in leuprolide. Nakai *et al.*[8] who injected rabbits s.c. with TAP-144-SR, also found that the polymer elicited a reaction.

On the other hand, intradermal tests with leuprorelin and goserelin acetate produced a granulomatous reaction in a patient with prostate cancer

who also developed subcutaneous nodules after leuprorelin acetate injection.[9] This patient did not react to the vehicle.

Goserelin acetate is homogeneously dispersed in the polymer, poly(lactic/glycolic) acid, as well as leuprorelin. However, no granulomatous reaction induced by goserelin has been reported. Leuprorelin is applied utilizing a microcapsular depot, whereas a cylindrical rod is employed for goserelin. We postulate that the likelihood of whether granulomatous reaction is induced or not might be affected by the distinct form of the depot.

These contradictory findings make it necessary to further investigate the agents responsible for the induction of the adverse reactions seen in patients treated with LHRH agonists. Before the inception of leuprorelin acetate therapy, patients should be informed of the possibility of a local reaction. In addition, a local injection reaction should alert the physician to a possible failure of hormone suppression.[7] Studies are underway in our laboratory to identify the causative agents of adverse reactions in patients treated with LHRH agonists and to assess the possible therapeutic implications of these reactions.

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