

Correspondence

A case of delayed-type hypersensitivity to subcutaneously administered drugs during anticancer immunotherapy

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SIR, A 79-year-old man visited our dermatology outpatient clinic several times because of skin reactions after inclusion in a clinical trial with immunotherapy to treat hormone-sensitive prostate cancer. The trial consisted of bi-weekly vaccinations with GVAX immunotherapy for prostate cancer (500 million cells priming dose, followed by 300 million cells boosting dose) in a 24-week period (in total 13 times) in combination with monthly infusion of ipilimumab (3 mg kg^{-1}) in a 24-week period (in total five times).

In week 2 after inclusion he presented with a papular erythema on his chest and abdomen. An accompanying solid erythematous cutaneous nodule on the injection site of GVAX immunotherapy was considered an expected vaccination reaction, as seen in all patients. Haematoxylin and eosin stain of a biopsy of a papule from the chest showed a vacuolar interface dermatitis and a perivascular lymphocytic infiltrate mixed with eosinophilic granulocytes, suggestive for delayed-type hypersensitivity. Consequently, a drug exanthema was diagnosed. Temporary treatment with topical steroids and a systemic antihistaminic drug relieved the complaints.

In week 4, daily subcutaneous treatment was started with 0.6 cc low-molecular-weight heparin (nadroparin) because of a deep venous thrombosis. By way of precaution the (second) administration of ipilimumab was passed over. Shortly afterwards, nadroparin caused itching at the injection site.

In week 26 he developed hypophysitis, which is a known adverse side-effect of the trial. In week 38 he presented an ulcer with central necrosis and purple induration ($16 \times 5 \text{ mm}$) at the injection site of leuporelin (sixth injection) at the lower abdomen. Therapy with leuporelin had been started before inclusion in the trial. Haematoxylin and eosin stain of a biopsy from the indurated site surrounding the ulcer showed a dermis with a mixed infiltrate of lymphocytes, neutrophilic and eosinophilic granulocytes, histiocytes and giant cells. The superficial dermis showed several round, empty spaces surrounded by inflammatory cells and naked granulomas, with similar empty spaces in the epidermal layer (Fig. 1a). Antigranzyne B monoclonal antibody (GB7) stain showed a dense dermal infiltration of cytotoxic T lymphocytes (CTL) (Fig. 1b). Findings were interpreted as mixed giant cell dermatitis on foreign body material (empty spaces) in

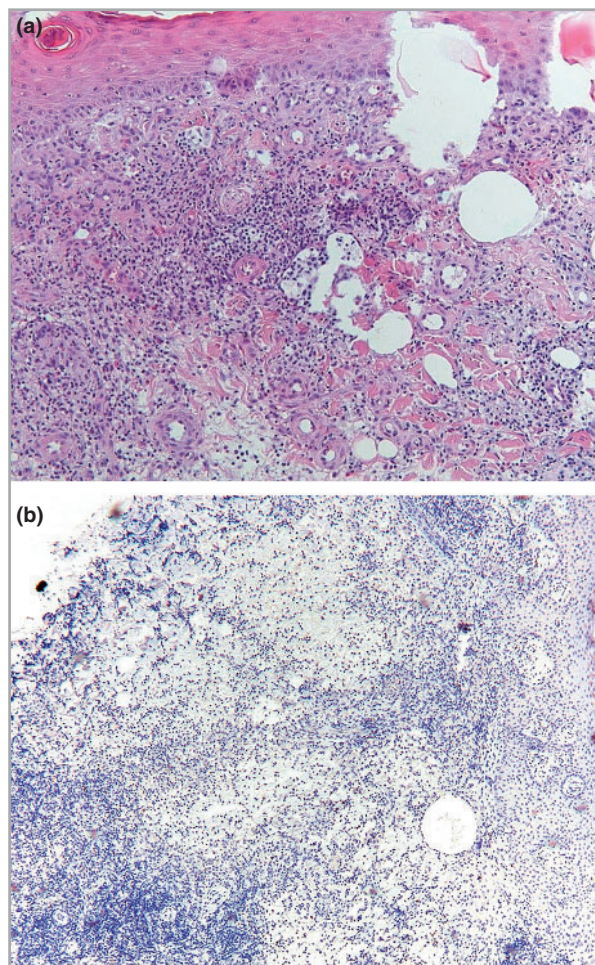


Fig 1. Histology of a 3-mm punch biopsy from the indurated side surrounding the ulcer at the injection site of leuporelin. Haematoxylin and eosin stain shows giant cell dermatitis on greasy material (a). Antigranzyne B monoclonal antibody (GB7) stain shows cytotoxic T lymphocytes (b). (a and b) Original magnification $\times 100$.

combination with delayed-type drug hypersensitivity (CTL and eosinophilic granulocytes).¹

Allergy tests with medication (nadroparin, dissolved leuporelin and solvent alone) were negative (Fig. 2a). However, after 24 h a positive reaction had developed at the intracutaneous test site of dissolved nadroparin and leuporelin. The test site of dissolved leuporelin worsened until a sterile ulcer with an indurated frame ($16 \times 20 \text{ mm}$) was seen after 4 weeks (Fig. 2b). Delayed-type hypersensitivity reaction was diagnosed to leuporelin and nadroparin. The skin was treated

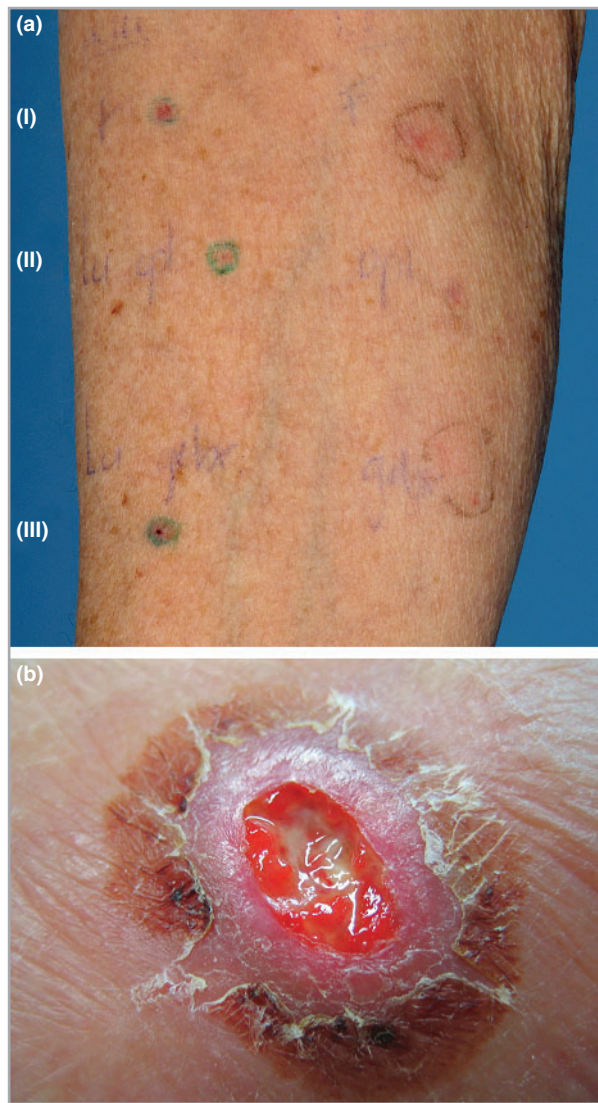


Fig 2. Allergy tests. Immediate skin reaction 15 min after intracutaneous prick test (left) and scratch test (right) for nadroparin (Fraxodi®) (I), solvent alone (II) and dissolved leuporelin (Lucrin®) (III) (a). Four weeks later the intracutaneous prick-test side for dissolved leuporelin (Lucrin®) (III) showed delayed-type hypersensitivity of the skin (b). The positive control test is not displayed in this figure.

with intralesional steroid injections. Treatment with luteinizing hormone-releasing hormone (LHRH)-agonist leuporelin (Lucrin®, Abbott) was replaced by goserelin (Zoladex®, AstraZeneca) and low-molecular-weight heparin nadroparin (Fraxodi®, GlaxoSmithKline) was replaced by the coumarin derivative acenocoumarol (Sintrom®, Novartis). Under this regime, all skin complaints disappeared gradually.

GVAX immunotherapy for prostate cancer is a cellular vaccine consisting of two allogeneic prostate cancer cell lines, which have been genetically modified to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF).²⁻⁴ GM-CSF recruits and activates dendritic cells (DCs) at the injection site (especially in the first weeks after vaccination), which is

important for the initiation of an immune response. This may not only lead to a better immune response to tumour cells, but also might induce unwanted immune reactions, in particular towards drugs administered in the DC-rich subcutaneous tissues. In this case, the local co-administration of the subcutaneous drugs after GVAX immunotherapy injection might have promoted the hypersensitivity reactions. Based on these experiences, administration of subcutaneous drugs at the injection site of GVAX immunotherapy is no longer practised at our departments. On the other hand, these side-effects have never been reported in GVAX immunotherapy trials in prostate cancer, including hundreds of patients of whom the majority were treated simultaneously with subcutaneous LHRH agonists.

It is difficult to determine what contribution ipilimumab had in this case. Ipilimumab consists of antibodies against CTLA-4, an activation-induced T-cell surface molecule. CTLA-4-mediated signals are inhibitory and attenuate T-cell-dependent immune responses. *In vivo* blockade of CTLA-4, using antibodies, induced enhanced antitumour immune responses and regressions of established tumours. This potent experimental treatment induces relatively frequent immune-mediated toxicities such as enterocolitis, hypophysitis, dermatitis (not further qualified), arthritis, uveitis, hepatitis and nephritis.^{5,6} These so-called immune breakthrough events are associated with antitumour response and are usually well controlled with immunosuppressive agents.

Subcutaneous leuporelin is widely used and generally well tolerated by patients. The normal user dosage was tested in allergy tests, which makes an irritant skin reaction highly improbable. A few case reports describe granulomas (similar to our case) at the injection site of leuporelin.^{7,8}

We conclude that physicians should be aware that patients exposed to GVAX immunotherapy for prostate cancer in combination with ipilimumab might develop delayed-type hypersensitivity to subcutaneously administered drugs such as leuporelin and/or nadroparin.

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