



# Chronic granulomatous reaction in patients receiving vaccine immunotherapy for metastatic melanoma

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## INTRODUCTION

Various agents such as melanoma-associated antigen 3 (MAGE-3), interleukin-2 (IL-2), gp100, and toll-like receptor agonists have been investigated as therapies for melanoma because of their ability to stimulate an immune response against melanocytes. We report on 3 patients with metastatic melanoma who, after receiving immunotherapy injections, had persistent subcutaneous nodules at their injection sites. One patient's nodules were shown to be a granulomatous reaction on histopathology.

## CASE 1

Our first patient is a 34-year-old white man with a history of metastatic melanoma with a positive lymph node at the base of the neck diagnosed in 2007, with no known primary lesion. He underwent wide local excision of the cutaneous skin on the left side of the neck with lymphadenectomy and adjuvant radiation therapy. In January 2008, the patient began a clinical trial with melanoma peptides and leuprolide. Based on his HLA-A0201 positivity, his therapy included a leuprolide 11.25-mg depot shot every 3 months (4 total) and a gp100/MAGE-3 injection in the anterior-medial aspect of each thigh every 3 weeks for 48 weeks (32 total injections). Afterwards, he had no evidence of disease recurrence but had persistent lymphadenopathy in the bilateral inguinal region. At the injection sites, the patient had soft tissue nodularity noted on positron emission tomography/computed tomography. In 2015, 6 years after completing his vaccine immunotherapy treatment, the patient

### Abbreviations used:

IL-2: interleukin-2  
MAGE-3: melanoma-associated antigen 3

received a 200-mg testosterone injection in his right lower back and within a few days noticed the development of around 10 to 14 extremely painful 1- to 3-cm subcutaneous nodules in his anterior left and right thighs, respectively (Fig 1, A). A computed tomography scan showed extensive subcutaneous fat stranding with interval calcification and nodules in the bilateral anterior thighs.

A right thigh nodule biopsy found fibroconnective tissue with dense fibrosis, granulomatous inflammation, fat necrosis, and calcification on histology (Fig 2, A and B). SOX10 and panmelanocytic cocktail (anti-homatropine methylbromide 45 and antityrosinase) immunohistochemical stains were negative. Two lesions on the patient's right thigh were excised with similar histologic findings. The patient was placed on oral cyclophosphamide, 150 mg daily, for 1 year and afterwards received intralesional triamcinolone injections; neither of these therapies improved his nodules. The patient has since had around 10 and 14 nodules surgically removed from the left and right leg, respectively, which has improved his pain yet has left significant atrophic scars (Fig 1, B). In the interim, the patient noted that 8 to 10 more nodules on each thigh had become symptomatic. The patient has severe pain that has rendered him unable to work or sleep through the night.

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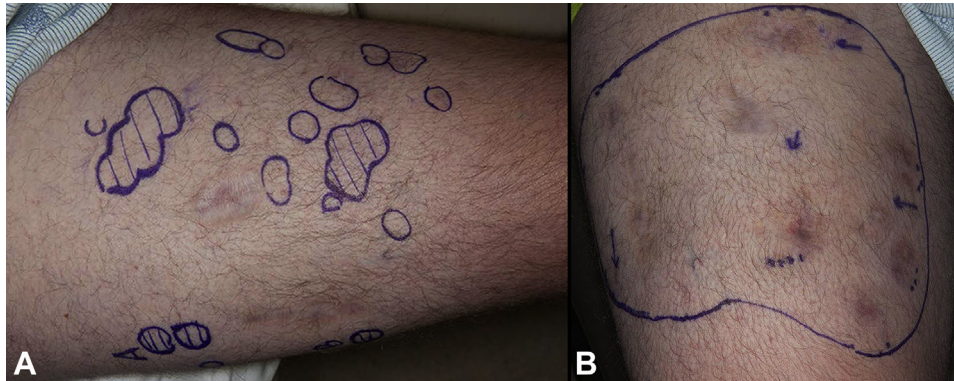
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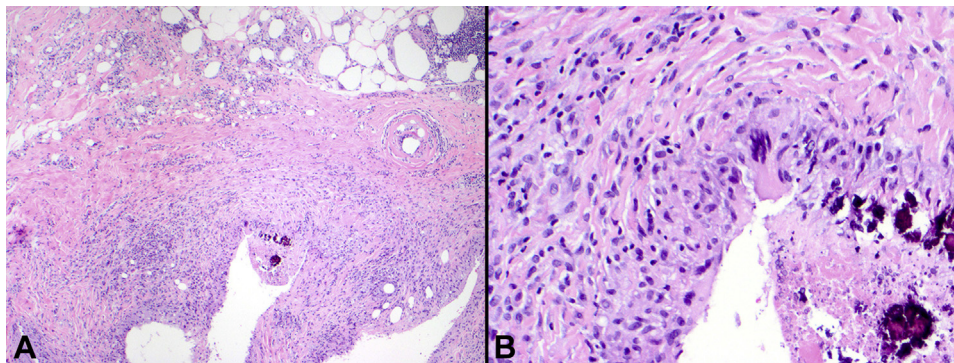
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**Fig 1.** **A**, Numerous subcutaneous nodules present on the right thigh, which were also present on the left thigh. **B**, Atrophic scars after numerous subcutaneous nodule excisions on the right thigh.



**Fig 2.** **A**, Necrotizing granulomatous inflammation. Peripheral fibrosis and fat necrosis with granulomatous reaction is also seen. **B**, At higher magnification, a histiocytic infiltrate with multinucleated giant cells surrounding necrosis with calcification is present. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 20$ ; **B**,  $\times 100$ ).

## CASE 2

Our second patient is a 30-year-old white woman with melanoma of the right shin, Breslow depth of 4.1 mm and 6 mitotic figures, diagnosed in 2011. She underwent a wide local excision and a sentinel lymph node biopsy with a subsequent partial right groin lymphadenectomy. She received carboplatin plus tamoxifen adjuvant therapy for 5 months. The patient later received adjuvant sargramostim therapy, which was discontinued after the discovery of an additional right groin mass. In July 2012, melanoma was found in the fibroadipose tissue of her right groin, leading to additional lymphadenectomy. She was enrolled in a melanoma vaccine trial and received 8 total treatments of gp100, MAGE-3, and resiquimod, a toll-like receptor agonist, over the course of a month. One month after completion of her trial in August 2012, the patient noted around ten 1- to 2-cm subcutaneous nodules on each of her upper arms at her immunotherapy injection sites (Fig 3). The patient's nodules become painful with strenuous activity. These subcutaneous nodules

haven't been biopsied per patient's request. The patient observed until April 2014, when she had a right anterior thigh soft tissue mass resected, revealing metastatic melanoma. She has been followed up without evidence of disease recurrence and her nodules are stable.

## CASE 3

Our third patient is a 60-year-old white woman with a 4.0-mm thick melanoma in the left popliteal area, diagnosed in 1999. She initially underwent wide local excision followed by a sentinel lymph node biopsy and left inguinal lymph node dissection. She then received immunotherapy with dendritic cells and IL-2 as part of a phase II clinical trial. In 2006, the patient underwent resection of a recurrence of metastatic melanoma on the left medial thigh. In 2007, she had metastatic disease to the lungs and was enrolled in another clinical trial consisting of 4 cycles of IL-2 and gp100 vaccine therapy. The patient subsequently had a metastatic tumor on the right thigh that was excised. She then had 4 cycles of

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