Chronic granulomatous reaction in patients receiving vaccine immunotherapy for metastatic melanoma

Alexander B. Aria, BS,[a] Leon Chen, MD,[b] Carlos A. Torres-Cabala, MD,[c] and Susan Y. Chon, MD[d]
Houston, Texas

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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 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.

Abbreviations used:

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

From Department of Dermatology,[b] University of Texas McGovern Medical School at Houston[a] and the Departments of Pathology[c] and Dermatology,[d] University of Texas, MD Anderson Cancer Center.
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Correspondence to: Susan Y. Chon, MD, 1400 Pressler Street, Unit 1452, Houston, TX 77030. E-mail: susanchon@mdanderson.org.

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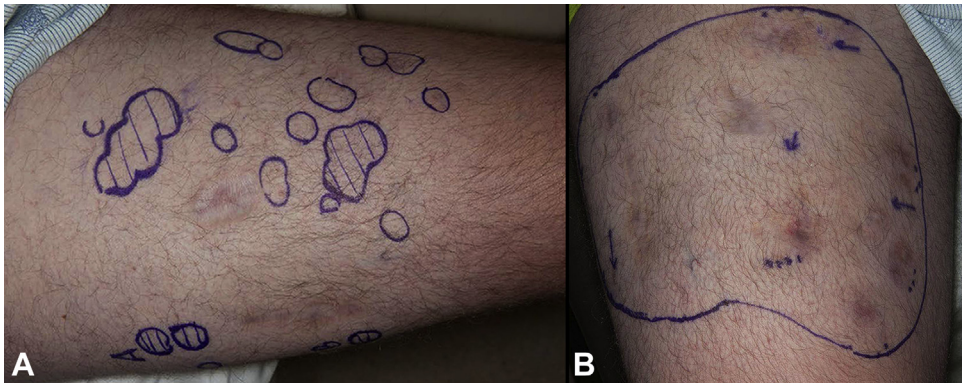

Fig 1. **A**, Numerous subcutaneous nodules present on the right thigh, which were also present on the left thigh. **B**, Atrophic scars after numerous subcutaneous nodule excisions on the right thigh.

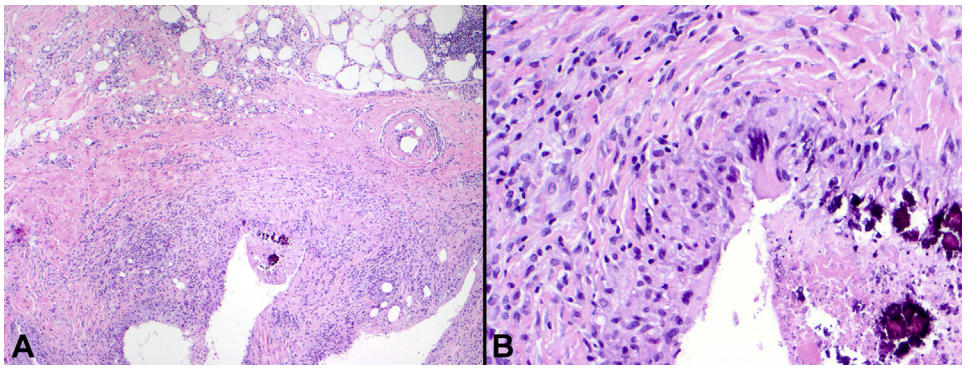

Fig 2. **A**, Necrotizing granulomatous inflammation. Peripheral fibrosis and fat necrosis with granulomatous reaction is also seen. **B**, At higher magnification, a histiocytic infiltrate with multinucleated giant cells surrounding necrosis with calcification is present. (**A** and **B**, Hematoxylin-eosin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

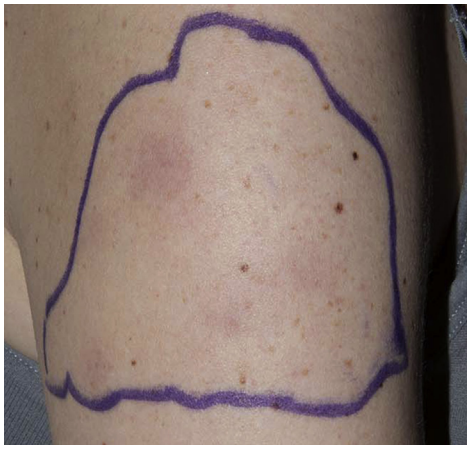

Fig 3. Numerous subcutaneous nodules present on the right shoulder, which were also present on the left shoulder.

biochemotherapy: IL-2, interferon, cisplatin, vinblastine, and temozolomide. Unfortunately, she had posterior reversible encephalopathy syndrome complicated by seizures and discontinued treatment. In 2008, the patient had another recurrence on the right posterior thigh, which was resected followed by adjuvant radiation therapy to the posterolateral thigh. She later had 3 new primary melanomas, all of which were treated with wide local excision. In April 2016, the patient had erythema and subcutaneous nodules of the right anterior thigh at the vaccine sites from 2007. The patient also had mild postsurgical and radiation changes in the right posterolateral thigh, not overlapping with the nodules. An ultrasound scan performed in March 2017 found architectural distortion of the subcutaneous soft tissue along her right lateral thigh scar as well as superficial subcutaneous foci of posterior acoustic shadowing in the right midanterior thigh, most likely representing foci of fat necrosis. These subcutaneous nodules haven't been biopsied per patient's request.

DISCUSSION

All 3 of our patients received vaccine immunotherapy containing a combination of gp100 and other agents for the treatment of metastatic melanoma and subsequently had subcutaneous nodules; only our first patient has histopathology results that show granulomatous reaction. Our second and third patients' nodules are presumed to be caused by a similar adverse granulomatous reaction given their clinical appearance and the patients' histories of vaccine immunotherapy, but a definitive diagnosis cannot be confirmed without a biopsy. The time span to the development of painful, chronic subcutaneous nodules after immunotherapy was between 1 month and 9 years. Our first patient's granulomatous reactions didn't become painful or enlarged until he received his testosterone injections 6 years after completing his immunotherapy. An immunohistochemical study for androgen receptor was performed on our patient's skin biopsy. No positive nuclei for androgen receptor were identified. Additionally, no reports describing testosterone-induced granulomatous reaction could be found in the literature.

At this point, it is difficult to ascertain what specific agent or combination of agents is responsible for the adverse subcutaneous nodules that developed in our patients. A list of the components of the immunotherapy vaccines received by our second patient include 0.5 mg of MAGE-3 peptide, 1 mg of gp100, 1 mL of saline, and 1.5 mL Freund's incomplete adjuvant formulated as Montanide ISA-51. Montanide ISA-51 is a blend of mineral oil and a mannide monooleate surfactant that creates a water-in-oil emulsion when mixed with water-based antigenic media. Data gathered from 25 clinical trials consisting of greater than 4000 patients and 40,000 injections showed that granulomas, in addition to local pain, tenderness, and erythema, are possible side effects of this adjuvant.[1] van Doorn et al[2] found that injection site reactions were reported in 67% and 80% of clinical trials of Montanide ISA-51 with subcutaneous injection and intramuscular injection, respectively.

Reports of granulomatous reaction after vaccine immunotherapy for melanoma exist in the literature. One of the earliest reported cases was a granulomatous reaction to Bacillus Calmette–Guérin vaccine immunotherapy for malignant melanoma.[3] Gibney et al[4] conducted a trial investigating the safety and efficacy of a combination of nivolumab, an anti–programmed death-1 antibody, NY-ESO-1, gp100 and Montanide ISA-51 for the treatment of metastatic melanoma. Injection site reactions, some of which were granulomas, occurred in 94% of the patients.[4] A study of an immunotherapy vaccine combination of resiquimod, NY-ESO-1, and Montanide ISA-51 reported that 100% of the study patients had adverse granulomatous injection site reactions (n = 26).[5] Further investigation is necessary to determine whether Montanide ISA-51, gp100, resiquimod, or a combination of some of these agents may be responsible for the adverse cutaneous reactions seen in our patients.

Schaefer et al[6] found that when given a 6-week course of weekly melanoma-associated peptide vaccinations, study participants were found to have areas of granulomatous reaction in the subcutis of

their injection sites. It is possible that changing to a new vaccination site at the time of peak inflammatory cell infiltration may minimize adverse effects caused by repeat peptide injections.[6] On the other hand, changing sites may also result in less-effective therapy if peptides are injected into immunologically "unprimed" environments.[6] Whether the severity of granulomatous formation is indicative of a strong response to therapy has yet to be verified. These three cases show the irreversible painful adverse effects of melanoma vaccines and point to a possible cost-benefit ratio between favorable therapy outcomes and chronic adverse effects to the point of causing physical debilitation. Future studies of the formulation, timing, and location of immunotherapy vaccines are necessary to decrease the risk of harm to patients.

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