Diffuse granulomatous panniculitis associated with anti PD-1 antibody therapy

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INTRODUCTION

Melanoma is one of the deadliest type of skin cancer, with a dismal 5-year survival rate for patients with metastatic melanoma. However, in the last decade, the development of novel immune therapy and targeted therapy has significantly improved overall survival in patients with advanced melanoma, and these therapies have replaced cytotoxic chemotherapy as the mainstay of systemic treatment. Checkpoint inhibitors, such as anti CTLA-4 and anti–PD-1 antibodies, have shown durable tumor control among responders and have emerged as the front-line therapies in the treatment of metastatic melanoma.

The co-inhibitory checkpoint receptor molecule PD-1 is highly expressed on T lymphocytes. When PD-1 binds to its ligands (PD-L1 and PD-L2), it inhibits T-cell activation and proliferation in the tumor microenvironment.[1] Therefore, PD-1 binding to its ligands ultimately results in immune suppression against cancer cells. Nivolumab is an anti–PD-1 antibody that disrupts the binding of PD-1 to its ligands and restores T-cell activation and the body's immunologic response to cancer cells. It has demonstrated superior clinical efficacy, including significant improvements in overall survival and progression-free survival over anti–CTLA-4 antibody and cytotoxic chemotherapy drugs.[2,3] Common side effects associated with nivolumab include fatigue, nausea, and diarrhea but, more importantly, immune-related adverse events such as dermatitis, colitis, hepatitis, and endocrinopathies.[2] Here we describe a case of granulomatous panniculitis mimicking disease progression in a patient with metastatic melanoma who was treated with nivolumab.

Abbreviation used:

PET/CT: positron emission tomography/computed tomography

CASE REPORT

The patient was a 66-year-old man with a 1.15-mm thick, nonulcerated primary melanoma on the upper back diagnosed in October 2011 who had undergone wide local excision and left axillary sentinel lymph node dissection, revealing 1 lymph node positive for metastatic melanoma. In May 2015, he had a locoregional recurrence with 3 new hypermetabolic subcutaneous metastases in the left axilla and the left upper back confirmed by cytology. His tumor did not harbor a *BRAF* mutation. He started treatment with a combination of ipilimumab and nivolumab in July 2015. A positron emission tomography (PET)/computed tomography (CT) scan of the body in September 2015 showed resolution of the subcutaneous nodules in the left axilla. However, after 2 doses, a grade 3 diffuse papular skin rash and grade 3 hepatitis developed, and the combination therapy was discontinued. After his rash and hepatitis resolved with corticosteroid treatment, he started treatment with nivolumab alone in September 2015, without recurrence of the severe rash or hepatitis.

In December 2015, a PET/CT scan showed ill-defined subcutaneous fat stranding in the medial left lower extremity, without apparent skin

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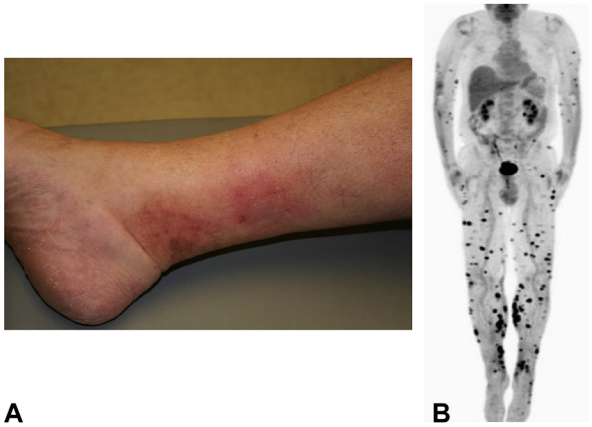

Fig 1. A, Photograph of granulomatous panniculitis in the patient's right medial leg. **B,** PET scan image of diffuse granulomatous panniculitis throughout the body, mostly notably in the lower extremities, mimicking widespread subcutaneous metastases.

abnormalities on physical examination. In January 2016, he presented with small skin nodules in the left calf that were mildly tender to palpation. In March 2016, he noted an increasing number of diffuse erythematous nontender subcutaneous nodules on his bilateral lower extremities (Fig 1, *A*). A PET/CT scan at that time showed interval development of approximately 50 hypermetabolic subcutaneous nodules in the upper extremities, pelvis, and lower extremities, mostly concentrated in the lower extremities below the knees (Fig 1, *B*), raising a high suspicion for disease progression in the subcutaneous tissue. Results of blood tests at the time showed elevated erythrocyte sedimentation rate at 100 mm/h (normal range, 0-20 mm/h), slightly elevated rheumatoid factor at 17 IU/mL (normal, <15 IU/mL), and C-reactive protein at 9.0 mg/L (normal, 0-8.0 mg/L). Complete blood counts, liver function results, and serum creatinine level were within normal limits, and antinuclear antibody titer was negative. Excisional biopsy of 3 of the subcutaneous nodules on his lower extremities and the forearm found a robust lobular, septal, and paraseptal lymphohistiocytic infiltrate that was overtly granulomatous in nature in some areas in which multinucleate histiocytes were noted. No vasculitis was observed, and no bacterial, fungal, or mycobacterium tuberculosis DNA was detected in the samples. On the basis of pathologic evaluation, a diagnosis of granulomatous panniculitis was made.

Nivolumab treatment was discontinued at the time of panniculitis diagnosis, and the patient was observed clinically without corticosteroid treatment. However, by May 2016, an increasing number of subcutaneous lesions developed throughout his body, more prominently in the lower legs. Although some of the existing lesions had resolved, some of the lesions became tender. C-reactive protein was further elevated (36.1 mg/L), but erythrocyte sedimentation rate was normal. A PET/CT scan showed further progression of the subcutaneous nodules throughout the body. He was started on 20 mg of oral prednisone daily, and his subcutaneous nodules regressed quite rapidly. Prednisone was slowly tapered off over the next 3 months. A follow-up PET/CT scan performed in August 2016 showed near complete resolution of the subcutaneous lesions.

DISCUSSION

Panniculitis, inflammation of the subcutaneous fat, is a relatively rare condition that is generally associated with infection, trauma, malignancy, or inflammatory states. The diagnosis of panniculitis can be difficult to make on physical examination, as the subcutaneous nodules or plaques can resemble other conditions, such as vasculitis or tumors. Although a presumptive diagnosis is frequently made clinically, histologic evaluation is required for a definitive diagnosis. Histologic assessment is especially valuable when malignant conditions, such as metastatic cancers or subcutaneous lymphomas, need to be excluded and distinguished from panniculitis, such as in our patient. Although the exact pathophysiology is unknown, panniculitis is generally considered a type IV delayed hypersensitivity cellular reaction primarily to viruses, bacteria, fungi, or other antigens. The reaction is lymphohistiocytic in part, and granuloma formation is a natural end product of a heightened cellular immune response.[4]

In our case, the finding of the erythematous skin nodules showed a lobular, septal, and paraseptal lymphohistiocytic infiltrate that was overtly granulomatous in nature, with the presence of multinucleate histiocytes (Fig 2, *A* and *B*). The findings were reminiscent of those of erythema nodosum, the most common type of panniculitis, which typically involves inflammation of the septa in the subcutaneous tissue, usually without associated vasculitis.[5] However, our sample involved lobular, septal, and paraseptal lymphohistiocytic infiltrates and was not limited to the septa as in erythema nodosum. Furthermore, our patient had nodules extending from his lower extremities to his trunk and upper extremities, and erythema nodosum is typically confined to the lower legs. Our patient also did not have fever or arthralgia, which are commonly associated with erythema nodosum. Lipodermatosclerosis/sclerosing panniculitis, another subtype of panniculitis, is typically