Metastatic melanoma with features of blue nevus and tumoral melanosis identified during pembrolizumab therapy

Matthew F. Helm, MD,[a] Michael J. Bax, MD,[b] Paul N. Bogner, MD,[c] and Catherine G. Chung, MD[a]
Hershey, Pennsylvania, and Buffalo, New York

Metastatic melanoma may exhibit clinical or histologic features of blue nevus. Pembrolizumab therapy is associated with regression and tumoral melanosis. We report on a man with widespread metastatic melanoma on pembrolizumab therapy in whom a blue-grey papule developed on the left side of his neck that clinically resembled a blue nevus and histologically showed features of both blue nevus and tumoral melanosis. The subtle melanocytic component and prominent changes of regression evident on biopsy suggest that his immunomodulatory therapy may have influenced the histologic findings noted on biopsy. Physicians that treat patients with metastatic melanoma should be aware of the spectrum of histologic findings evident on biopsy not only to allow for early diagnosis but to also better understand the effects of treatment. (J Am Acad Dermatol 2017;3:135-7.)

Key words: blue nevus; metastatic melanoma; pembrolizumab; programmed death 1; tumoral melanosis; tumor-infiltrating lymphocytes.

INTRODUCTION

Blue nevus–like metastases of melanoma can be difficult to identify.[1] Some metastases consist of slender dendritic bipolar melanocytes associated with a cell-poor infiltrate and eosinophilic stroma but only a sparse lymphocytic infiltrate.[1] Other blue nevus–like metastases may be markedly cellular.[2,3] Fluorescence in situ hybridization can help establish the diagnosis in difficult cases.[4] Blue nevi encompass a spectrum that includes heavily pigmented epithelioid melanocytomas and tumors with overlapping features that are difficult to classify,[5] and blue nevus–like metastatic melanoma also encompasses a broad histologic spectrum.[4,6] The introduction of chemotherapeutic agents that have the potential to trigger regression[7,8] may present additional histologic challenges in establishing the correct diagnosis.

CLINICAL CASE

A 70-year-old man with a history of metastatic melanoma had a blue-gray macule on the left side of his neck (Fig 1). A left preauricular melanoma with a depth of 2.9 mm (T3a) was treated with wide local excision 1 year before his current presentation. Positron emission tomography study 5 months after excision identified extensive local adenopathy and abnormalities of the bone and liver consistent with metastatic disease. Biopsy of the iliac crest found metastatic melanoma associated with marked melanosis (Fig 2). Genomic evaluation found that his melanoma had a *BRAFv600e* mutation. Treatment with pembrolizumab was initiated but was discontinued after 2 cycles because of disease progression. Combination dabrafenib/trametinib therapy was initiated but was soon discontinued because of side effects including nausea, vomiting, and rash. Vemurafenib therapy was subsequently started but was also discontinued because of an extensive drug eruption. Pembrolizumab treatment was restarted, and the patient remained on this treatment for the 3 months before the current presentation, during which time a new blue-grey macule was noticed on the left side of his neck.

Biopsy found numerous heavily pigmented melanophages in the dermis surrounding thickened collagen bundles (Fig 3) and a subtle proliferation

From the Department of Dermatology, Penn State Health Hershey Medical Center[a] and the Departments of Dermatology[b] and Pathology,[c] Roswell Park Cancer Institute.

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Correspondence to: Matthew F. Helm, MD, Penn State Health Hershey Medical Center, 500 University Drive HU14, Hershey, PA 17033. E-mail: mhelm2@hmc.psu.edu.

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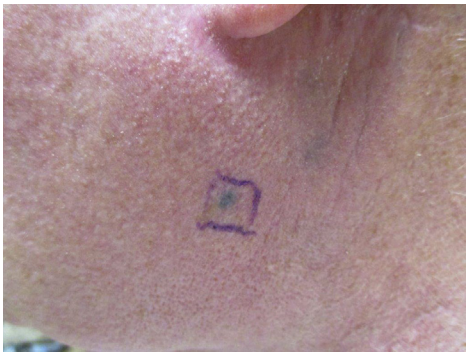

Fig 1. A new blue-gray papule was noted on the left side of the neck and was excised as outlined by gentian violet surgical marker.

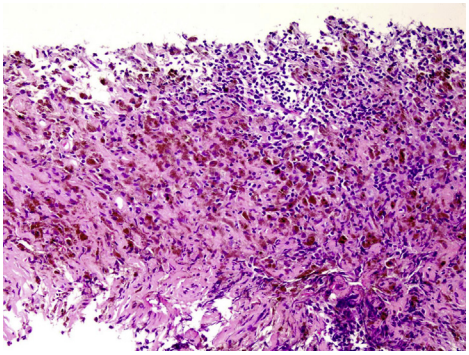

Fig 2. Trephine biopsy result of the iliac crest shows atypical melanocytes and marked melanosis. (Hematoxylin-eosin stain; original magnification: ×200.)

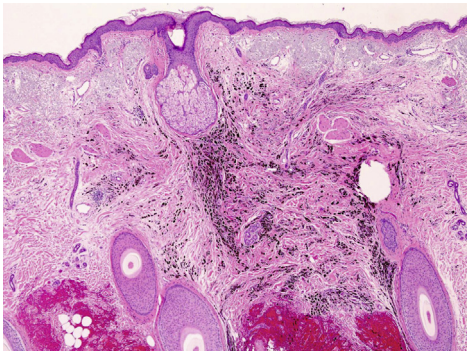

Fig 3. Biopsy result of the left side of the neck shows large numbers of heavily pigmented melanophages along with spindle cells on markedly sun-damaged skin. (Hematoxylin-eosin stain; original magnification: ×200.)

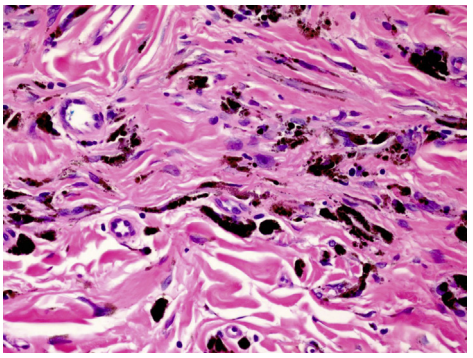

Fig 4. Some spindle cells exhibit slight nuclear pleomorphism, are associated with eosinophilic stroma, and are surrounded by numerous melanophages. (Hematoxylin-eosin stain; original magnification: ×400.)

of spindled cells, some of which were characterized by nuclear atypia and pleomorphism (Fig 4). Lymphocytes, histiocytes, and a few plasma cells were noted, but eosinophils and neutrophils were not identified, nor were mitotic figures encountered. Some melanophages and spindle cells were loosely arranged around blood vessels. An S100 immunostain highlighted the sparse proliferation of spindled cells. Additional faint blue-grey lesions were noted beneath and posterior to the left ear lobule but were not biopsied because they were stable and not noted to change by the patient or his physicians. Whole-body 18F-fludeoxyglucose positron emission tomography/computed tomography found interval progression with a T7 lytic lesion and other nonspecific changes. Pembrolizumab therapy was continued, and no additional blue nevus–like metastases developed over the following 5 months, nor has there been persistence or recurrence at the neck biopsy site or change in the subtle pigmented areas beneath and posterior to the left ear lobule.

DISCUSSION

The increased incidence of melanoma coupled with the longer survival of those affected with metastatic disease has created situations in which previously uncommon presentations may be encountered with greater frequency. Although most metastatic melanomas are readily discernible by their histologic features, including atypical melanocytes, marked pleomorphism, and high mitotic activity, blue nevus–like metastatic melanoma may histologically mimic common blue nevi and exhibit minimal to no pleomorphism.[6] In these situations, the clinical scenario usually aids in establishing the correct diagnosis. In situations in which the diagnosis is unclear, fluorescence in situ hybridization studies maybe a valuable tool in clarifying the diagnosis. The histologic similarity to the iliac crest metastasis, the proximity to his primary tumor site, and the radiologic evidence of distant metastases developing concurrently with the tumor on the left side of his neck led us to conclude that the neck lesion was a manifestation of his metastatic melanoma. If not for the subtle melanocytic component, the histologic findings might be classified as an example of tumoral melanosis. Other entities in the

differential diagnosis could be excluded on histologic grounds. An incidental newly formed blue nevus would not typically be associated with inflammatory cells or show localization around blood vessels. A regressed new and incidental primary melanoma usually is associated with papillary dermal fibrosis and a bandlike lymphocytic infiltrate along with attenuation of the overlying rete ridge pattern.[9]

The findings noted in our patient suggest that immunotherapy with pembrolizumab, a humanized antibody against the programmed death 1 receptor, likely contributed to the marked regression noted. Tumoral melanosis was previously reported in a series of patients treated with pembrolizumab,[8] and the heightened immune response modulated by pembrolizumab therapy may account for these changes. Although melanoma immunotherapy would be expected to alter microscopic findings, these changes have not yet been well characterized. Targeted and immune response—related therapy can be associated with an increase in tumor-infiltrating lymphocytes.[10] Neoplastic melanocytes may have been present in the skin of our patient and only became apparent secondary to melanosis prompted by pembrolizumab therapy. We suspect that over time, our patient's lesion would have regressed into tumoral melanosis. Pathologists should be aware of subtle histologic findings associated with metastases of melanoma and seek clinical information in suspicious cases. As the incidence of cutaneous metastases from melanoma increases and as patients with metastatic melanoma live longer and receive novel immunomodulating therapies, most physicians involved in the care of patients with metastatic melanoma can expect to encounter unusual biopsy findings such as the one from our patient.

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