Multiple Thick Nodular Melanoma: Differentiating Multiple Primaries from the Metastasis of a Previous Single Lesion

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To the Editor,
The rates of invasive melanoma have been rising for the past few decades with an estimated 96,480 new cases of melanoma in the United States and 7,230 deaths from the disease in 2019.

Nodular melanoma (NM) is the second most common type of melanoma after the superficial spreading type. The term ‘thick melanoma’ refers to a large malignant melanoma with a Breslow thickness of over 4 mm. Multiple primary melanomas (MPM) are defined clinically either by the presence of two or more primary melanomas at the time of diagnosis or by detecting multiple subsequent lesions occurring after the first primary melanoma. However, histologically is defined by the presence of in-situ component. Risk factors for MPM are Caucasian race, male sex, age >60 years, atypical and/or dysplastic nevi, family history of melanoma, pancreatic, colorectal or other cancers and germline mutations including CDKN2A, CDK4, MC1R, MITF, and PTEN. Here we present a multiple lesional thick melanoma that developed in the lower extremities. To our knowledge, this is the first case with a multiple primary nodular thick melanoma in the lower extremity with Breslow thickness of over 15 mm. A 63-year-old Hispanic woman presented to the emergency department with an atypical nevus on right calf, which was pruritic about 1 year previously and then started to grow about 4 months previously, initially slowly and then more rapidly. Her mother had had colon cancer and her sister ovarian cancer. Over a one-week period, the lesion started producing a copious purulent liquid and enlarged rapidly, followed by the appearance of two more raised lesions. Two weeks later, 2 of the 3 lesions started draining purulent discharge. On full skin examination, the patient had two ulcerated pigmented lesions measuring 5.5 x 4.0 x 3.6 cm and 4.5 x 4.0 x 2.9 cm (Panel A, B). Excisional biopsy revealed malignant melanoma in both lesions (Panel C, D), with tumor cells that were positive for a panel of melanocytic markers, including HMB45 (Panel E). Total body PET scan did not reveal any metastasis. The patient underwent a wide lesion resection and inguinal sentinel lymph node excision. Histopathologic examination showed melanoma, nodular type, Breslow thickness 18 and 15 mm, Clark’s level V, lymphovascular invasion (in the distal lesion only), and Stage pT4bN0. Molecular testing for BRAF mutation was negative. The patient returned two months later with two more nodules in her left leg, which was diagnosed as melanoma, nodular type, Breslow thickness 4 mm. A transition to metastasis was suspected and immunotherapy with Nivolumab was started.

Differentiating multiple primary melanomas (MPM) from the metastasis of a previous single lesion is crucial as the staging and management change dramatically. Many studies tried to compare MPM to single primary melanoma (SPM). Many significant differences were found between SPM and subsequent MPM. However, there were no differences between SPM and the first MPM. The Gene, Environment, Melanoma (GEM) study group reported lower mitotic activity; lower tumor thickness and Clark level; more frequent lentigo maligna melanoma subtype;
more frequent association with dysplastic nevi and more frequent location on the head/neck in subsequent MPM versus SPM and in subsequent MPM versus the first MPM. These results were challenged by others who reported no differences between SPM and the latest MPM with regard to mitotic activity, tumor thickness, Clark level, ulceration, melanoma subtype, anatomical site. However, they did not evaluate the presence of associated dysplastic nevi, which are a known risk factor for MPM. Moreover, Clark thickness is an important predictive marker for MPM and the subsequent appearance of primary melanomas in the same patient. Furthermore, MPM cohorts have reported that the 2nd and 3rd primary melanoma are prone to occur in the same anatomic location. Interestingly, our patient had been diagnosed with an atypical nevus long before she developed her melanoma. In addition, her family history was positive for colon cancer and ovarian cancer in her first-degree relatives along with the histopathologic findings of in-situ components suggested MPM diagnosis. These results pose a high risk of future development of melanocytic lesions and the need for extensive screening.

Conflict of Interest: No conflict of interest was declared by the authors.

References:
Figure 1. shows the clinical presentation of multiple primary melanoma in the leg (A, B) and the histopathologic diagnosis of nodular type (C, D) with positive tumor cells to a panel of melanocytic markers, including HMB45 (E).