Case 2. A man in his 60s presented with a 1-year history of an 8 × 7-cm tumor on his left back associated with fever and left axillary lymphadenopathy (Figure). Histologic sections of the surgical resection revealed a nodular proliferation of atypical and epithelioid melanocytes that extended into the reticular dermis to a depth of 2.4 cm. Sixteen mitoses/mm² were identified, and the margins were negative. Two sentinel lymph nodes in the left axilla were negative for metastasis by S-100 and MART-1 immunostains. A chest, abdomen, and pelvis CT scan and subsequent whole-body PET scan were negative for metastatic disease. The patient died 4 months after diagnosis due to chronic cardiac disease.

Discussion | Cases of giant primary melanoma, defined as lesions at least 10 cm in diameter or 48 mm in thickness, are almost exclusively associated with extensive metastatic disease. To our knowledge, only 2 other cases of giant primary melanoma without extensive metastasis have been described in the literature. Studies have illustrated that certain primary melanoma subtypes are associated with favorable prognostic outcomes. Desmoplastic melanoma is a rare variant with variable presentation that is marked histologically by fusiform melanocytes in a sclerotic stroma. Investigators have found that patients with pure desmoplastic melanoma (desmoplasia found throughout the tumor) have a more advanced Breslow depth and less regional metastasis than patients with conventional melanoma. Primary dermal melanoma, a more recently described variant that is confined to the dermis and may histologically resemble cutaneous metastasis, also appears to have improved survival compared with metastatic melanoma or primary nodular melanoma of equal Breslow thickness.

These cases challenge the current belief that large primary cutaneous melanoma of long duration connotes extensive metastatic disease and/or rapid death. Although our conclusions are somewhat limited by the inability to assess long-term outcomes in patient 2, both patients reported a prolonged duration of symptoms and had negative findings on metastatic workup, suggesting a less aggressive biology for these tumors. With the discovery of various genetic mutations in primary melanomas, there has been a recent movement to reclassify melanoma subtypes based on genetic profile, which may predict pathologic behavior and therefore outcome more accurately than histopathologic features. We propose that these cases may represent a distinct genetic subtype of giant melanoma that, while locally aggressive, lacks propensity for metastasis.

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Spindle Cell Squamous Carcinoma During BRAF Inhibitor Therapy for Advanced Melanoma: An Aggressive Secondary Neoplasm of Undetermined Biologic Potential

Secondary cutaneous squamous cell carcinomas (cSCCs) are adverse effects of BRAF inhibitor targeted therapy for advanced melanoma. The histologic type most commonly reported during vemurafenib and dabrafenib mesylate BRAF inhibitor therapy is well-differentiated keratoacanthoma-like cSCC (cSCC-KA). Lesions of cSCC-KA in BRAF inhibitor therapy are considered to have a low biologic potential (ie, infrequent metastasis or recurrence). Whereas the early follow-up (<3 years) in most patients seems to support this claim, it is unproven. Furthermore, optimal intervention for secondary BRAF inhibitor cSCC is not established. We report multiple biphasic
spindle cell squamous carcinomas, also known as sarcomatoid squamous cell carcinomas, in a patient receiving BRAF inhibitor therapy.

**Report of a Case** | A woman in her 50s with no history of cSCC presented in 2004 with a left lower extremity Clark level IV, 1.3-mm Breslow depth melanoma with no disease found in a sentinel lymph node biopsy (T2aN0 stage IB). She presented in 2009 with upper extremity weakness and had multiple brain metastases and adenopathy. A resected pelvic node harbored V600E BRAF-mutant metastatic melanoma, and she was treated with whole brain and stereotactic radiation. In 2011, a brain lesion grew and she was enrolled in a BRAF inhibitor (dabrafenib [GSK2118436]; clinicaltrials.gov Identifier: NCT01266967) clinical trial. Within 1 week of starting therapy (150 mg, twice daily), she developed facial and extremity acrochordons and new nevi on her torso and axillae, along with fever, chills, and fatigue. She experienced enlarging, tender and bleeding lesions on the trunk and extremities. On examination at 4 weeks, she had more than 100 new cutaneous squamous proliferations throughout her body (Figure 1). New verrucous red lesions also erupted on the shoulders, as well as rough lesions on the face. Seven large, tender and indurated lesions were removed for histopathologic assessment using “deep scoop” shave biopsy.

Histologically, lesions revealed a biphasic malignant growth pattern. The superficial portion demonstrated conventional cSCC-KA features of hyperkeratosis, epidermal acanthosis, and central core of glassy eosinophilic keratin with pseudopapillomatosis and a base with focal invasive lobules of cytologically atypical keratinocytes (Figure 2A), consistent with previously reported cSCC-KA. In stark contrast to prior reports, the deep aspects of 6 of 7 lesions showed invasive spindled and epithelioid cells with monomorphic elongated nuclei with condensed chromatin and mitoses (Figure 2B and eFigure 1 in Supplement) consistent with spindle cell squamous carcinoma, an aggressive subtype of squamous cell carcinoma.

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**Figure 1. Malignant and Benign Squamous Proliferations During BRAF Inhibitor Therapy**

A squamous proliferation with keratoacanthomatos appearance in a patient with melanoma treated with BRAF inhibitor therapy. Representative lesion shown from the mid-upper back (circled left). Numerous hyperkeratoses are evident in the surrounding skin with uncertain biologic potential.

**Figure 2. Invasive Histopathologic Features of Spindle Cell Squamous Carcinoma During BRAF Inhibitor Therapy**

A, Spindle cell squamous cell carcinoma with superficial hyperkeratosis, central glassy eosinophilic keratin, and a pseudopapillomatous growth pattern (hematoxylin-eosin [H&E], original magnification, ×4). B, Atypical spindled and epithelioid keratinocytes with mitoses (arrowhead) invade the deep dermis (H&E, original magnification, ×40).
Superficial and spindled tumor cells were strongly immunoreactive for cytokeratin CK5/6 and CK903 (eFigure 2A and 2B in Supplement). Both squamous and spindled components were vimentin reactive (eFigure 2C in Supplement) and displayed increased proliferative index (Ki-67/MIB-1) (eFigure 2D in Supplement). The tumor cells lacked immunoreactivity with CD68, actin, SMA, or factor XIIa (not shown), supporting a diagnosis of spindle cell squamous carcinoma in the setting of BRAF inhibitor therapy. Unlike the expected pattern of a spindle cell melanoma, the spindled tumor cells were also MART-1 and S100 negative (not shown). The patient elected to discontinue the BRAF inhibitor therapy and has had no recurrence of, or new, cSCCs. She had a single melanoma recurrence in her thigh that was resected in early 2013. She is presently disease free.

Discussion | Cutaneous squamous cell carcinomas with features of keratoacanthoma are common during BRAF inhibitor targeted therapy. These lesions are generally considered indolent and are conservatively managed with electrodesiccation and/or curettage, topical fluorouracil, or photodynamic therapy.5 In BRAF inhibitor-related cSCC-KA, the mitogen-activated protein kinase (MAPK) cascade signaling is paradoxically increased and augmented by mutant RAS.6

Because the clinical appearance of cSCC-KA and the spindle cell squamous carcinomas in our patient are indistinguishable, histologic evaluation of the entire lesion (via saucization biopsy or incisional biopsy) is vital to prevent inadequate treatment of a deeply invasive process with a probable higher malignant potential. To our knowledge, this is the first report of an invasive spindled cSCC to occur during BRAF inhibitor therapy that clinically mimics cSCC-KA. It serves as a cautionary tale for dermatologists, dermatopathologists, and medical oncologists caring for these patients.

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Author Contributions: Drs Cohen and Zwerner had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cohen, Lumbang, Zwerner.

Acquisition of data: All authors.

Analysis and interpretation of data: Cohen, Lumbang, Zwerner.

Drafting of the manuscript: Cohen, Lumbang, Sosman.

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, and material support: Lumbang, Boyd, Sosman.

Study supervision: Zwerner.

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Correction

Incorrect Information in Text and Table: In the Original Investigation entitled “International Prevalence of Indoor Tanning: A Systematic Review and Meta-analysis” published in the April 2014 issue of JAMA Dermatol (2014;150[4]:390-400. doi:10.1001/jamadermatol.2013.6896), incorrect information appeared. In the Results section Population Proportional Attributable Risk, the second and third sentences should have read: “The population proportional attributable risk for the 3 regions ranged from 3.0% to 10.8% for basal cell carcinoma, from 6.7% to 21.8% for squamous cell carcinoma, and from 2.6% to 9.4% for melanoma, corresponding to 419 245 cases of skin cancer in the United States, 26 484 in Northern and Western Europe, and 18 441 in Australia. Overall, we estimate 452 796 cases of basal and squamous cell carcinoma (NMSC) and 11 374 cases of melanoma each year attributable to indoor tanning.” In Table 2, the Total skin cancer cases for Cases Attributable to Ever Exposure under the heading of United States should have appeared as 419 245 (327 997 - 504 914) and under the heading of Northern and Western Europe should have appeared as 26 484 (19 231 - 33 195). This article was corrected online.