

Case Report/Case Series

Multiple *BRAF* Wild-Type Melanomas During Dabrafenib Treatment for Metastatic *BRAF*-Mutant Melanoma

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IMPORTANCE BRAF inhibitors have become the standard of care in metastatic *BRAF*-mutant melanomas. Compared with chemotherapies, BRAF inhibitors improve overall and disease-free survival and speed the recovery of symptomatic patients with metastatic disease. The most worrisome finding is the possible development of resistance to new malignant tumors.

OBSERVATIONS A patient in her 30s developed massive *BRAF*^{V600E} melanoma metastasis during her 30th week of pregnancy. After emergency cesarean delivery, oral dabrafenib treatment was initiated, and a partial radiologic response was confirmed within 1 month. At dermatologic digital follow-up aided by confocal microscopy 8 weeks after initiation of dabrafenib treatment, 4 melanomas were detected. Unfortunately, within the next month, the melanoma rapidly progressed. The 4 new melanomas were wild-type *BRAF* melanomas, whereas the new metastasis carried a different *BRAF* mutation (S467L).

CONCLUSIONS AND RELEVANCE Cutaneous malignant tumors are the most frequent adverse events of BRAF inhibitors; therefore, strict dermatologic surveillance in a referral center aided by digital follow-up is mandatory, especially when multiple nevi are present and these drugs are used in an adjuvant setting. In view of our findings, the pathogenesis of the development of new melanomas seems to be different from therapy resistance. Whether paradoxical *RAF* activation could explain these *BRAF* wild-type secondary malignant tumors is still unknown.

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BRAF inhibitors are one of the most relevant findings in melanoma therapy in the last 30 years, becoming first-line therapy for patients with *BRAF*^{V600}-mutant metastatic melanoma. Specific high-potency inhibitors of the BRAF protein exhibit high overall clinical response rates of up to 50% compared with 5% with dacarbazine chemotherapy and can achieve median progression-free survival of 6.3 vs 2.9 months, with a median overall survival in the dabrafenib group of 13.1 months.^{1,2}

Although cutaneous adverse events occur in approximately 50% of patients, BRAF inhibitors have a manageable toxicity profile.¹⁻³ Numerous publications are reporting new cutaneous adverse events of these drugs, but cutaneous squamous cell carcinomas have definitely been the most significant adverse effect in up to 35% of cases. Overall, approximately 1 in 3 treated patients experience a serious adverse event (grade III or IV), with most events being cutaneous.^{1,2}

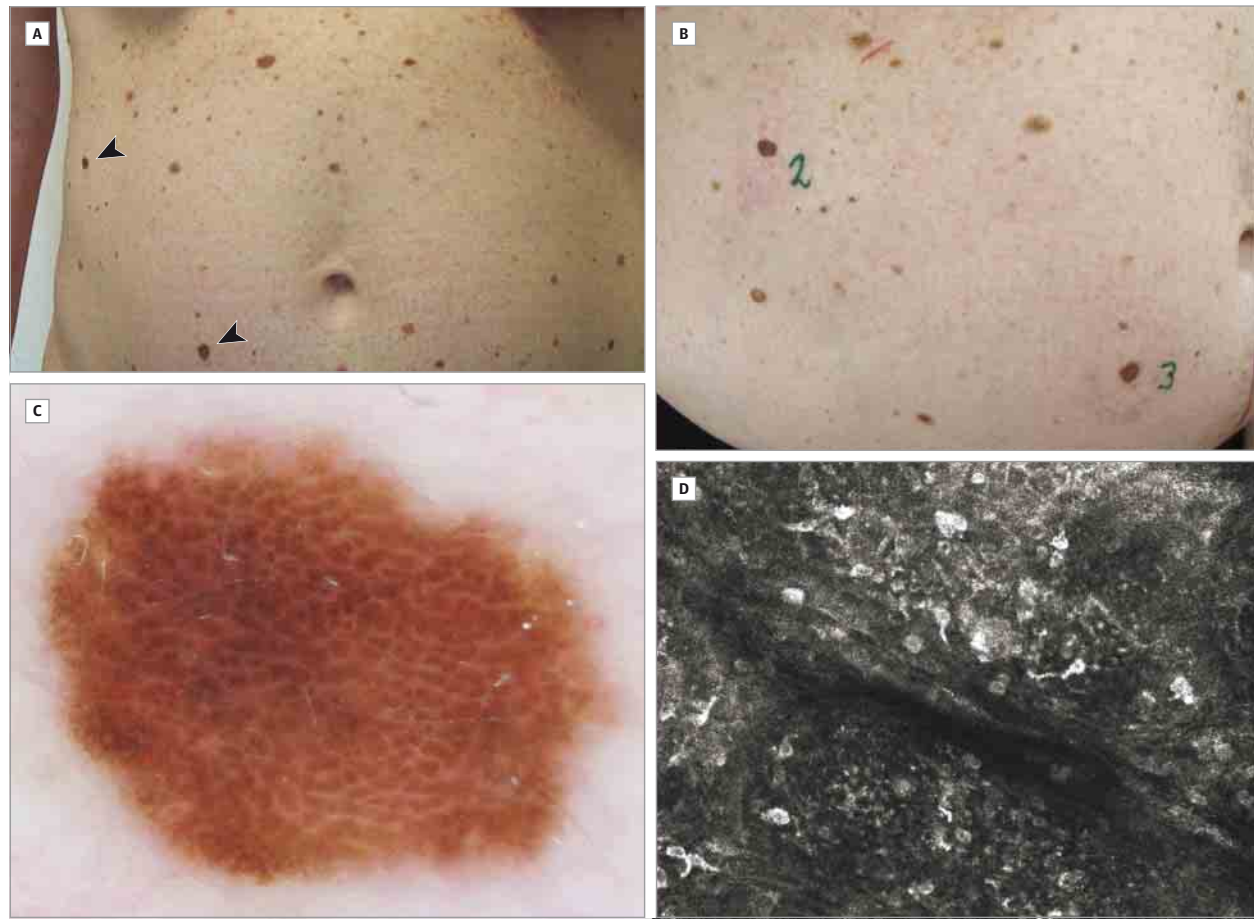
New primary melanomas have been reported during anti-BRAF treatment, especially in a vemurafenib series, which reported new primary melanomas in approximately 2% of patients.³⁻⁵ Dabrafenib appears to have an efficacy similar to vemurafenib, but it is associated with less cutaneous toxicity and photosensitivity and is generally well tolerated.^{1,2}

Few reports have drawn attention to the difficult follow-up and treatment of these patients during BRAF inhibitor treatment. We describe 4 new primary melanomas in a patient in whom early detection was possible by means of digital follow-up.

Report of a Case

A patient in her 30s who was 21 weeks pregnant was diagnosed as having high-risk melanoma in her left submammary region (nodular ulcerated melanoma; Breslow index, 9.0 mm; Clark level, IV; and mitotic index, 6/mm²). She presented with a pathologic adenopathy on her axilla confirmed by ultrasonography and fine-needle aspiration, but no other evidence of distant metastasis was found on clinical laboratory testing (lactate dehydrogenase and S-100 protein levels below the reference range), thoracic computed tomography, and abdominal ultrasonography. She presented with multiple atypical nevi, which were monitored with total-body photography and digital dermoscopy. After surgical excision of an 8-cm conglomerate mass in diameter and wide-margin excision of primary melanoma, she was diagnosed as having resected stage IIIC disease.

Figure 1. New Concomitant Melanomas During BRAF Inhibitor Therapy



A, Clinical image after 8 weeks of dabrafenib treatment. Arrowheads are pointing to the suspicious pigmented lesions detected by digital follow-up. B, Note that the 2 lesions labeled 2 and 3 were not clinically suspicious. C, Dermoscopic image of lesion 2 showing a negative network pattern (whitish

lines with atypical irregular globules). D, Confocal examination revealed pleomorphic nucleated atypical cells with pagetoid spreading within the epidermis (500 × 500 μm). After excision, the lesions were diagnosed as melanoma arising in compound nevi, with Breslow indexes of 0.4 and 0.35 mm.

During the 30th week of pregnancy, she presented with malaise, liver failure, and multiple melanoma metastases in the bones, liver, and mesentery. She underwent emergency cesarean delivery and gave birth to a healthy, 1480-g, 31-week-old male infant who had no evidence of metastasis on the placenta. Because *BRAF*^{V600E} mutation was detected, oral dabrafenib treatment was initiated at 150 mg twice daily. After 7 days she recovered progressively, and a partial radiologic response was confirmed within 1 month.

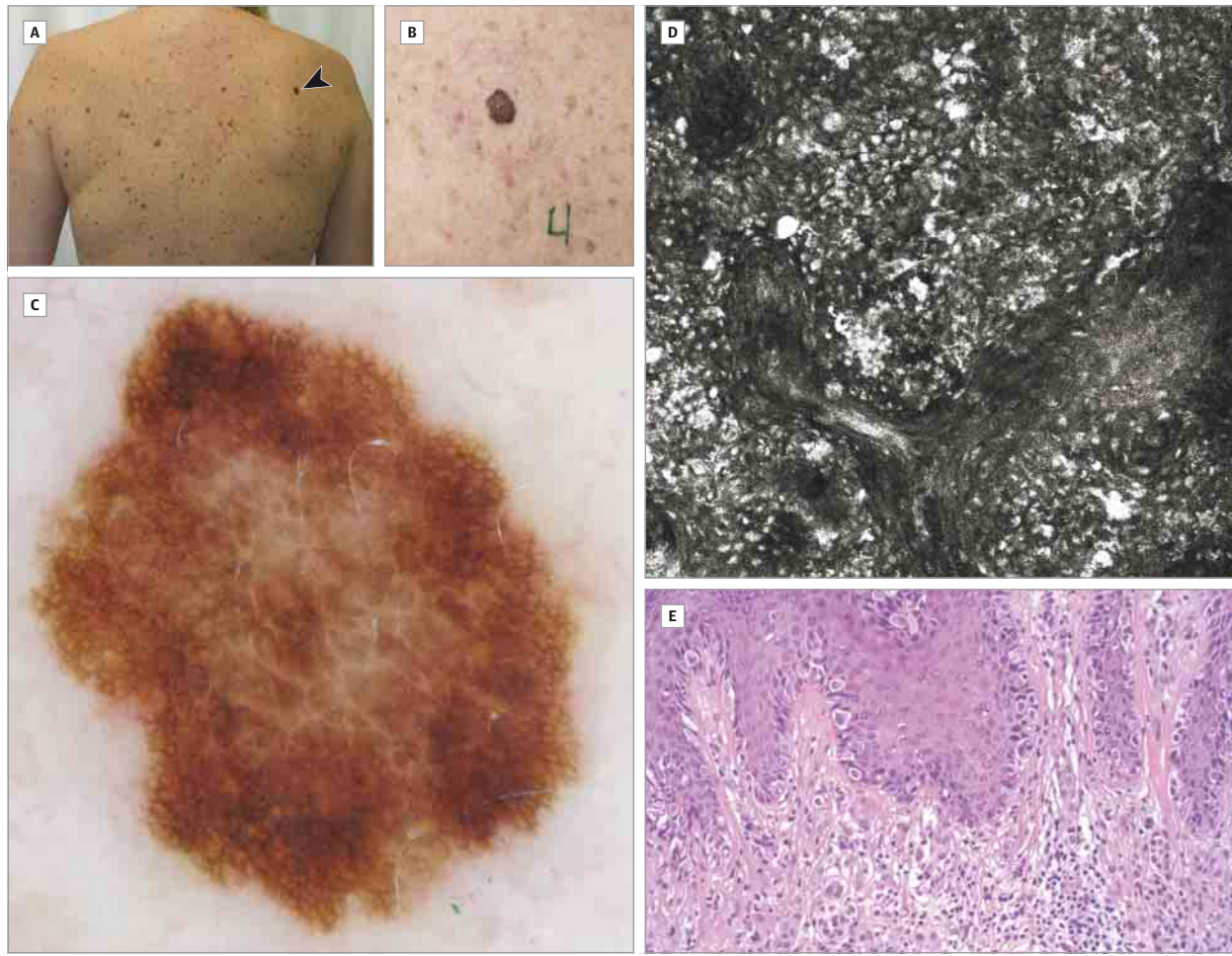
At dermatologic digital follow-up 8 weeks after initiation of dabrafenib treatment, 4 atypical lesions with equivocal features of melanoma were detected. One of them, located on the lateral aspect of the neck, had massive regression features, whereas the 3 other atypical melanocytic lesions, located on the trunk, had increased global pigmentation and a dermoscopic negative network pattern (Figure 1 and Figure 2). In vivo confocal microscopy was performed, and evident pagetoid pleomorphic cells within epidermal layers (Figure 1C and Figure 2D) were found in all 4 lesions. Simple surgical excision and histopathologic study by 2 experienced pathologists (A.G. and L.A.) were performed, and 4 superficial spreading

melanomas were diagnosed, in situ in melanoma specimen sample 1 and Clark level III associated with nevi with Breslow indexes of 0.62, 0.41, and 0.64 mm in melanoma specimens 2, 3, and 4, respectively. Regression features were found in all 4 melanomas, but none of the tumors had ulceration or mitotic figures.

Unfortunately, within the next month, melanoma rapidly progressed, new lung and pleura metastasis developed in a short period, and the patient died 5 months after initiation of dabrafenib treatment.

All pathologic samples, including the 4 newly developed melanomas, and pleural metastasis were further studied to investigate molecular *RAF* and *RAS* status. Melanoma and nevus cells were separately analyzed by means of laser capture microdissection. Molecular characterization included the genomic analyses of *BRAF* (exon 11 and 15) and *NRAS* (exon 2 and 3) by polymerase chain reaction and direct sequencing, and all investigated cell samples were wild type, except an unexpected different pathogenic *BRAF* mutation (S467L, exon 11) detected only in pleural metastasis cells. In addition, germline mutation analysis of melanoma susceptibility genes

Figure 2. Fourth Concomitant New Melanoma During BRAF Inhibitor Therapy



A and B, Clinical images of the fourth melanoma tumor (arrowhead and number 4, respectively) after 8 weeks of dabrafenib treatment. C, Dermoscopic image showing atypical pigmented network with focal hyperpigmentation and a central negative network pattern similar to the other melanomas excised after dabrafenib therapy. D, With confocal microscopy, roundish atypical nucleated

cells were detected within the whole epidermal layers and the subcorneal stratum (500 × 500 μm). Similar findings of pagetoid spreading of pleomorphic nucleated cells on the 4 lesions caused us to remove the 4 lesions.

E, Histopathologic analysis confirmed a melanoma with an associated nevus and a Breslow index of 0.4 mm (hematoxylin-eosin, original magnification ×10).

(*CDKN2A/CDK4/MITF*) and family history of the disease were assessed, and no increased risk of melanoma was identified.

Discussion

One of the most encouraging findings in the last decade related to oncologic dermatology is the development of new targeted therapies for metastatic *BRAF*-mutant melanomas. Despite well-tolerated cutaneous toxic effects, all selective *BRAF* inhibitor therapies are associated with the development of benign and malignant neoplasms, mainly squamous cell-derived skin tumors and keratoacanthoma-like squamous cell carcinomas, but recently new primary melanomas have also been reported.⁴ Case reports have included nonskin tumors as well, such as *RAS*-mutant leukemia, the metastatic recurrence of *RAS*-mutant colorectal cancer, and gastric and colonic polyps.⁶

The precise mechanism of this carcinogenesis is still under investigation, but the induction of squamous cell carcinomas has been theoretically attributed to paradoxical activation of the mitogen-activated kinase (MAPK) pathway managed by increased activity of *RAS* and MAPK kinase (MEK) downstream effectors when *BRAF* wild-type cells are exposed to a selective *BRAF* inhibitor.⁶ However, regarding melanocytic tumors, one study⁷ found that nevi that involute during *BRAF* inhibitor therapy possess the *BRAF*^{V600E} mutation, whereas others that grow or remain unchanged are wild type.

Few molecular studies are available regarding new melanomas; however, the trend toward increased MEK effectors and extracellular signal-regulated kinase signaling is suggestive of a role for the paradoxical MAPK activation as well. To date, only 2 new melanoma cases have been found to harbor the *NRAS* mutation, but they are generally supposed to be *BRAF* and *NRAS* wild type.^{4,8} Melanomas analyzed by laser microdissection in the 4 cases were all *BRAF/ NRAS* wild type. The unexpected dif-

ferent pathogenic *BRAF* mutation found only in the pleural metastasis cells, which was detected when resistance to therapy evolved to lethal outcome, supports the hypothesis of a double metastatic population even though a new mutation cannot be ruled out. However, none of the 4 secondary melanomas found in this study (which were *BRAF* wild type) presented it.

The new regimens of concomitant therapy with *BRAF* and *MEK* inhibitors could provide higher response rates and more durable clinical benefit than monotherapy, and they should abrogate the treatment-induced squamous cell carcinomas.^{9,10} However, in contrast to what was expected, the rate of melanomas and other noncutaneous cancers that developed during combined therapy seems to be the same as with *BRAF* inhibitors.⁶ Our molecular findings could depend on different pathogenic mechanisms to develop new secondary melanomas (likely related to paradoxical activation of wild-type cells) and to develop resistance to *BRAF* inhibitors (likely related to other pathogenic mutated cells), at least in our case.

Since Dalle et al¹¹ reported the first 5 cases of new primary melanomas during vemurafenib therapy, more attention has focused on early diagnosis and the important role of the dermatologist during follow-up. One limitation in the estimated incidence rates is the different protocol and training of the physician (ie, the rate of secondary melanomas can range from 2% [by naked eye in published clinical trials] to 20% [by digital monitoring as reported by Perier-Muzet et al⁵]). It is well known that digital follow-up by total-body photography and digitalized dermoscopy is the most efficient strategy for the early detection of melanomas in a high-risk population.¹² However, during *BRAF* therapies, more than 50% of lesions can have substantial changes during digital follow-up; therefore, additional data should be taken into account to determine whether excision is necessary.^{4,5,13} Early melanomas detected by der-

moscopy were suspected because they presented relevant changes in short-term follow-up that consisted of a negative network pattern and changes in pigmentation. In vivo reflectance confocal microscopy allowed us to improve our biopsy rate index in doubtful lesions, as recently reported.¹⁴ The observation of large atypical dendritic and roundish cells within epidermal layers was consistent in all cases. According to Debarbieux et al,¹⁵ these confocal features are suggestive of melanoma after but not before *BRAF* inhibitor treatment.

Our 4 incipient cases were diagnosed by the consensus of 2 experienced pathologists (A.G. and L.A.). The unresolved question about the malignant potential of such early cases must be taken into account. However, to date, the surgical excision of any melanocytic lesion that looks like a melanoma on dermoscopy, confocal microscopy, and pathologic examination is mandatory.

Conclusions

Perhaps the most worrisome toxic effect of *BRAF* inhibitors is the emergence of secondary malignant neoplasms. Awareness of all potential adverse effects of these agents is mandatory, especially if a role as an adjuvant therapy is approved after ongoing trials. Further investigations are needed to clarify the pathogenic mechanism and whether *MEK* inhibitors could abrogate the subjacent oncogenic mechanism. Because cutaneous squamous cell carcinomas and new primary melanomas are the most frequent severe adverse events reported, strict dermatologic surveillance in a referral center with well-trained staff aided by digital follow-up is mandatory, especially when multiple nevi are presented and if these drugs are used in an adjuvant setting in the future.

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NOTABLE NOTES

Fashionable Pathology

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Morphological descriptions of cutaneous lesions lend themselves to comparisons with the world around us, such as the realms of food,¹ animals, or plants.² Over the ages, the dermatology literature has also been draped with descriptive terms that conjure up ideas of style and fashion.

Mycosis fungoides is often described as having a bathing suit distribution, as are the lesions of angiokeratoma corporis diffusum in Fabry disease. Giant congenital melanocytic nevi were called garment nevi, and hypertrichosis lanuginosa acquisita has been likened to a downy coat. Coxsackie virus may manifest as papular-purpuric gloves and socks syndrome, and this distribution is also observed in the peripheral neuropathy of patients with diabetes mellitus. The shawl sign and holster sign are well reported in dermatomyositis, and venous ulcers are typically found over the gaiters' area. The mitten deformity is observed in recessive dystrophic epidermolysis bullosa, and the distribution of lesions in allergic contact dermatitis naturally draws on the culprit garb, such as belt buckle or shoe dermatitis. Cylindromas are also known as turban tumors, chloasma is sometimes called the mask of pregnancy, and patients with keratosis pilaris rouge appear to be wearing blusher. Morphologically, the buttonhole sign is classically observed in neurofibromas and anetoderma, and the boutonnière deformity is seen in advanced rheumatoid arthritis.

The photosensitive nature of pellagra gives rise to a characteristic gauntlet on the forearms as well as Cassal's necklace over the décolletage. Similarly, the hypomelanotic macules of secondary syphilis are known as the necklace of Venus and the term *monilethrix* is derived from the Latin term for necklace. The periungual papules of reticulohistiocytosis have been likened to coral beads, and the annular bullae of linear IgA bullous dermatosis are often described as a crown of jewels.

Tactile descriptions of cutaneous diseases also draw on comparisons with fabric. In tuberous sclerosis, the description shagreen patch

likens pathognomonic hamartomas to leather. Acanthosis nigricans is said to feel like velvet, and woolly hair is observed in a number of genodermatoses. The reticulate pattern of Wickham striae in lichen planus is often described as lacy, as is the exanthem of erythema infectiosum.

Beyond the realm of the naked eye, trichoscopic examination of patients with loose anagen syndrome demonstrates a characteristic “floppy sock” appearance. Dermoscopically, numerous references to fashion are reported, such as the blue-gray veil seen in melanoma or the hairpin vessels of keratinizing tumors.³ Pathologists are well versed in the findings of perivascular cuffing, the coat sleeve changes of erythema annulare centrifugum, and the signet ring cells of adenocarcinoma metastases.

The dermatological literature brims with descriptions derived from the sartorial world. Given the visual nature of our specialty, it is little wonder that such descriptions came into vogue.

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