RESIDENT ROUNDS: PART III

Metastatic Melanoma Patient on Vemurafenib Develops Multiple Primary Cutaneous Melanomas

Jeffrey Brackeen MD, Jordan Jamerson BS, and Amy Brackeen MD
Texas Tech University Health Sciences Center, Lubbock, TX

CASE REPORT

A 45-year-old Caucasian female with a history of melanoma, 1.0mm in depth, Sentinel lymph node biopsy negative, 11-years prior, presented for routine skin exam and was noted to have lymphadenopathy of the right side of her neck. A subsequent CT scan revealed 10cm lesions in both the liver and spleen. Biopsies demonstrated metastatic melanoma; no cutaneous manifestations were present. Interferon treatment was initially used with no response. Genetic analysis revealed a positive $BRAF^{V600E}$ mutation, and vemurafenib therapy was initiated. One month after starting vemurafenib, two superficial spreading melanomas on the left mid back and left upper abdomen were discovered, depth 0.25mm and 0.60mm, respectively. The visceral tumors responded well, each shrinking to less than 2cm. Over the next 11 months four additional superficial spreading melanomas emerged, on the left upper and left superior upper arm, depth 0.32mm and 0.80mm, and the mid back and mid upper back, 0.27mm and 0.50mm. All six primary melanomas were confirmed by two dermatopathologists at separate institutions. Two of the six melanomas occurring while on vemurafenib were tested and were BRAF mutation negative. The patient is currently closely monitored. She continues to be treated with vemurafenib and more recently taxol, as 3 years after starting vemurafenib therapy, the tumors have grown back to their original diameters of 10cm. In addition to the aforementioned melanomas, 2 atypical melanocytic proliferations, 9 dysplastic nevi some with moderate cytologic atypia, and 5 compound melanocytic nevi were removed. In summary, a total of 6 superficial spreading melanomas, each uniquely located, developed after vemurafenib initiation.

Unresectable or metastatic melanoma has a poor prognosis with a 1-year survival rate of 25.5%.[1] For years, dacarbazine or interferon was the standard care for these patients. In phase III clinical trials (BRIM-3), vemurafenib compared to dacarbazine demonstrated significant reduction in risk of death, clinical superiority in median overall survival, 13.6 to 9.7 months, and a significant increase in progression free survival, median of 5.3 to 1.6 months.[2] Vemurafenib is an inhibitor for mutated $BRAF^{V600E}$, which is a common mutation found in up to 66% of metastatic melanomas[3] and constitutively activates a specific RAF kinase involved in the MAPK cellular proliferation pathway. While vermurafenib specifically inhibits proliferation in BRAF-mutated cells, it can paradoxically activate wild-type cells with mutated or activated RAS, previously found in potentially precancerous actinic keratoses.[4] Cutaneous squamous cell carcinomas (cSCCs) or keratoacanthomas (KAs) may occur in approximately 25% of patients.[4] Often, they occur in the first 2-3 months after starting therapy on sun-exposed areas.[4] Oberholzer et al found that squamous cell tumors treated with a RAF inhibitor had higher rates of HRAS mutations, despite similar rates of total mutations. Increased RAS mutation rates in these cutaneous cancers plus its preferential development in sun-exposed locations on older patients rapidly following treatment initiation supports the theory of an underlying mutational predisposition that is unmasked due to a RAF inhibitor pro-proliferative state.[4] RAS-mutated tumors in BRAF wild type cells allow inhibitor binding to cause RAF dimerization, permitting transactivation of the drug-free promoter and activating the MEK substrate.[5] Aside from the risk of cutaneous carcinomas, RAS mutations in BRAF positive cells may be a mechanism for BRAF inhibitor resistance as well as potentially increase the risk of extracutaneous cancer, since RAS mutations are seen in many types including colon, pancreatic, and lung, although this not been seen.[4]

FIGURE 1. Melanoma of mid-back, clinical photo.

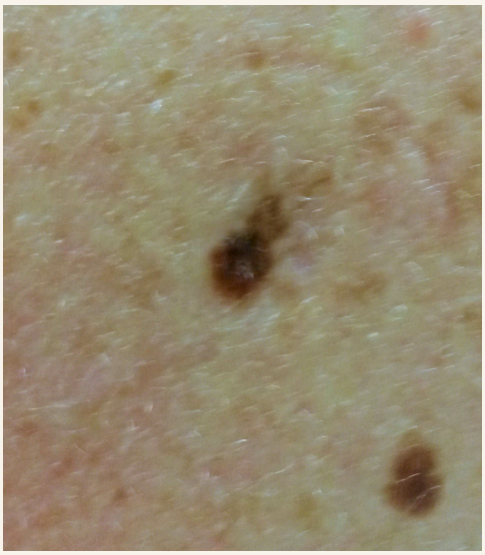


FIGURE 2. Histopathology of melanoma mid-back.

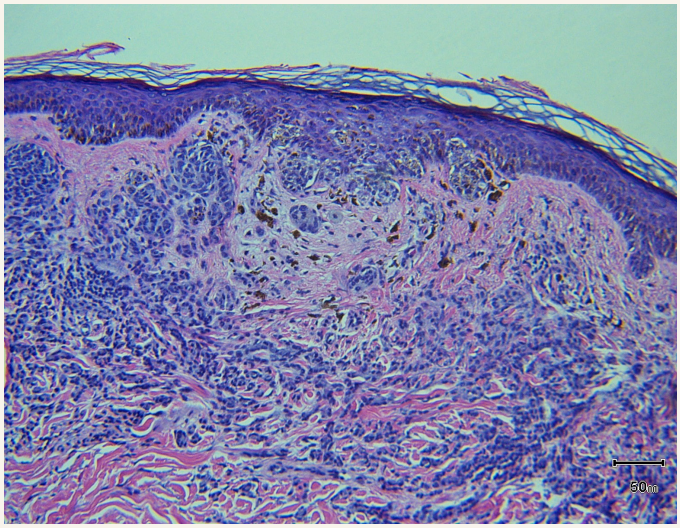


FIGURE 3. Melanoma of left upper arm, clinical photo.

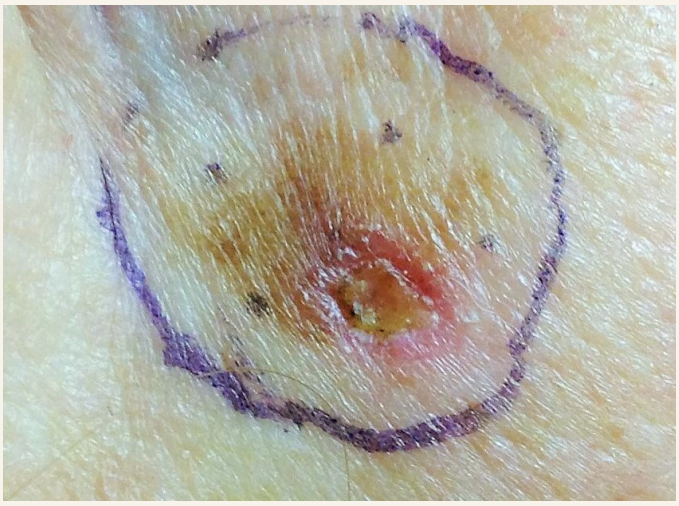
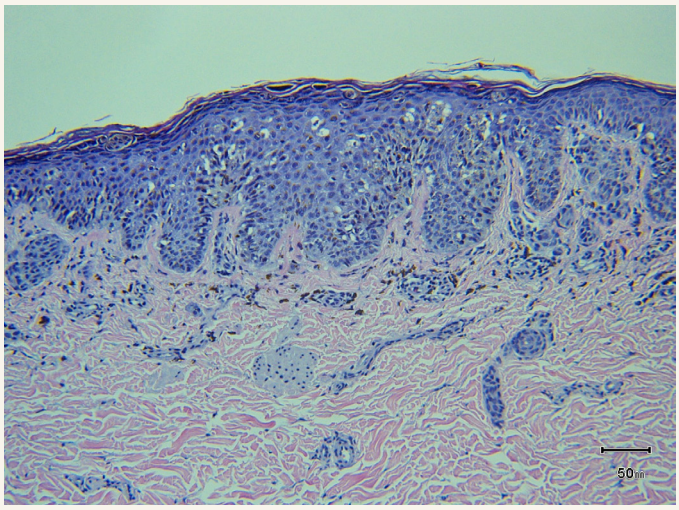


FIGURE 4. Histopathology of melanoma left upper arm.



A less common but more serious cutaneous manifestation following BRAF inhibitor therapy is the induction or differentiation of melanocytic lesions considered to arise via wild type paradoxical MAPK pathway stimulation by increased activity upstream. Dalle et al reported on 5 BRAF wild type melanomas and one dysplastic nevus in four patients undergoing BRAF inhibitor treatment.[6] Chapman et al documented 5 cases in 464 patients undergoing treatment with a RAF inhibitor.[7] Zimmer et al investigated 19 patients with 22 changing melanocytic lesions or secondary melanomas treating with a RAF inhibitor, and their genetic investigation of the new primary melanomas were found to be BRAF negative with increased levels of cyclin D1 and pAKT, which may suggest other proliferative pathways aside from MAPK may be involved.[5] Early detection and treatment of melanoma is vital as it imparts a greatly improved prognosis.

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The patient’s 3-year progression free survival is evidence of exceptional therapeutic benefit. Prior treatment with dacarbazine gave a median overall survival prognosis of slightly more than 6 months.[3] Unfortunately, monotherapy for these cancers limits the therapeutic window of susceptibility and leads to resistance with multiple mechanisms upstream and downstream

in play. Several trials investigating different immunologic and MAPK enzyme combination therapies show promise. One example is a study of dabrafenib, a selective BRAF inhibitor, and trametinib, a MEK inhibitor, showed improvement of combination therapy over BRAF monotherapy in overall survival as well as a decrease in the rate of cutaneous SCC development.[8] This treatment combination was recently granted accelerated approval from the FDA.

Interestingly, in this case, a single patient developed 6 primary melanomas, as well as 2 atypical melanocytic proliferations and 9 dysplastic nevi over less than a year's time after initiating vemurafenib with no significant skin findings in the preceding 11 years of routine skin exams. Although cSCCs and KAa are expected complications of vemurafenib therapy and frequent monitoring is recommended, this case helps highlight the importance of a high degree of suspicion for melanocytic lesions as well, of which there may be multiple. Photographs and dermoscopy may be helpful in evaluating new, changing, or suspicious lesions, especially since findings may be subtle.[6]

DISCLOSURES

None of the authors have a conflict of interest.

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AUTHOR CORRESPONDENCE

Jeffrey Brackeen MD
E-mail:.....jeffrey.brackeen@ttuhsc.edu