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Diverse cutaneous adverse reactions associated with encorafenib therapy

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To the Editor:

A 68-year-old woman, diagnosed over 10 years ago with stage IV *BRAF V600E*-mutated melanoma, was started on combination BRAF/MEK inhibitor therapy with encorafenib and binimetinib after development of recurrent brain metastases. One day after initiating combination therapy, the patient experienced central vision loss diagnosed as serous retinal detachment. Combination therapy was discontinued and subsequently, encorafenib alone was restarted. Upon initiation of encorafenib monotherapy, the patient quickly developed multiple 2-10mm pink and flesh-colored verrucous papules diffusely scattered on her scalp, back, chest, abdomen, and legs (**Figure 1**). A biopsy of four lesions was performed for histopathologic evaluation, revealing verrucous epidermal hyperplasia and hyperkeratosis along with an associated mild lymphocytic infiltrate (**Figure 2**). Additionally, the patient noticed significant worsening of her vitiligo with encorafenib therapy. She first developed mild vitiligo in response to prior ticilimumab therapy. However, this became much more extensive with initiation of encorafenib and the verrucous keratoses in areas of associated vitiligo were also noted to be depigmented. She developed a new pigmented lesion on her abdomen, found to be a compound dysplastic nevus with moderate atypia on histopathologic analysis. Lastly, she was noted to have palmoplantar hyperkeratosis (hand foot skin reaction), localized to pressure points (**Figure 3**). The diverse constellation of cutaneous findings is attributable to encorafenib monotherapy.

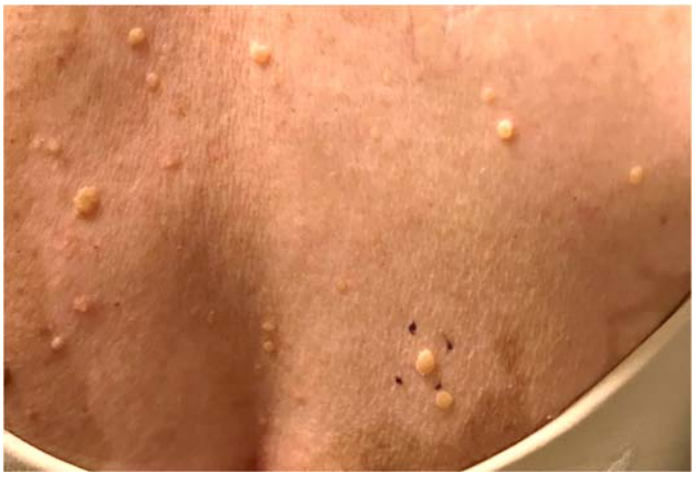

Figure 1. *Multiple verrucous keratoses on the back in a patient treated with encorafenib.*

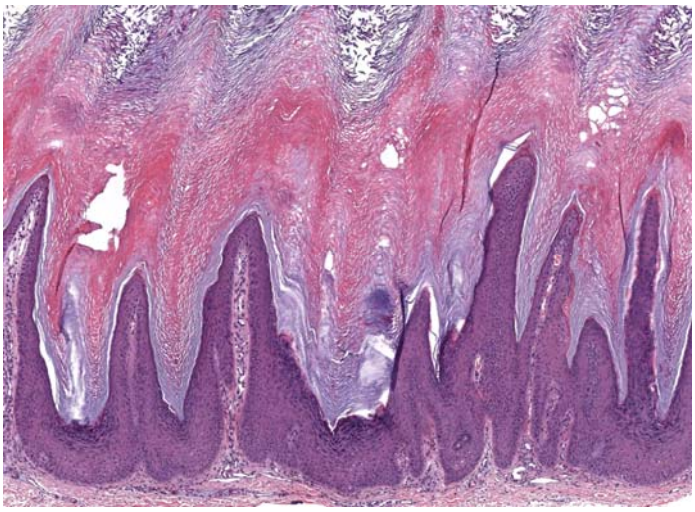

Figure 2. *Histopathology of a verrucous keratosis, showing prominent hyperkeratosis, papillomatosis and mild acanthosis of the epidermis. H&E, 55×.*

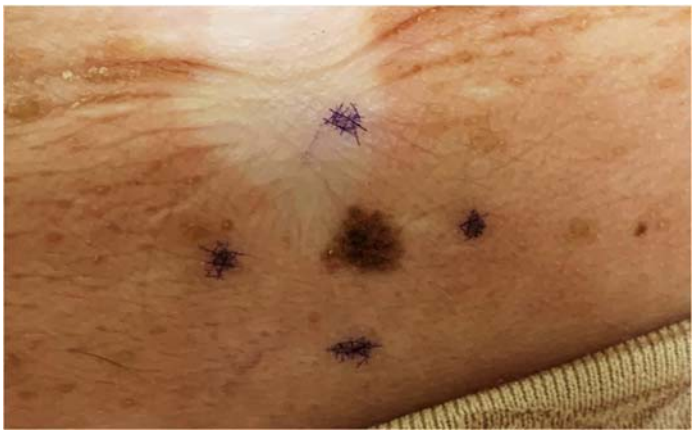

Figure 3. *Focal hyperkeratosis on the foot on encorafenib therapy, representing hand-foot-skin reaction.*

For patients with *BRAFV600*-mutated metastatic melanoma, combination BRAF/MEK inhibitor therapy is a first line treatment option [1,2]. Many adverse cutaneous effects of first-generation selective BRAF inhibitors such as vemurafenib and dabrafenib are well-noted in the literature [3,4]. Malignant and benign growths, including verrucous keratoses, have been attributed to the MAPK signaling pathway's paradoxical activation during BRAF inhibition [4]. In studies of first-generation BRAF inhibitors, verrucous keratoses, which are benign wart-like growths without apparent viral cytopathic changes, are the most commonly reported cutaneous side effect, but others include palmoplantar hyperkeratosis (hand-foot-skin reaction), transient acantholytic dermatosis, and squamous cell carcinoma [3,4]. Notably, combined BRAF/MEK inhibition appears to have a lower prevalence of cutaneous side effects than BRAF inhibitor monotherapy [3].

Although the correlation of appearance of verrucous keratosis and other cutaneous proliferations with vemurafenib and dabrafenib monotherapy is well-established, their correlation with encorafenib remains nascent. Encorafenib, a second-generation BRAF inhibitor, was approved for treating metastatic melanoma in 2018 after demonstrating better efficacy, tolerability, and progression-free survival rates than vemurafenib, particularly when in combination with MEK inhibitor binimetinib [2]. Interestingly, encorafenib showed a lower incidence of verrucous keratoses (skin papillomas), (10%) than vemurafenib (19%) in the initial COLUMBUS trial [1].

Our patient demonstrates a diverse array of encorafenib-related cutaneous adverse reactions. The patient transitioned to encorafenib monotherapy after experiencing serous retinopathy (a side effect associated with encorafenib/binimetinib combination therapy), [1] and it was only upon monotherapy initiation that she experienced diffuse eruption of verrucous keratoses, as well as hand-foot-skin reaction, a new atypical nevus, and worsening vitiligo. The clinical promise of encorafenib is certainly supported by the greater efficacy and tolerability that it offers compared to first-generation BRAF inhibitors [1,2]. However, as the clinical use of encorafenib/binimetinib and encorafenib monotherapy increases, we expect that additional cutaneous adverse reactions will be observed.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Gogas HJ, Flaherty KT, Dummer R, et al. Adverse events associated with encorafenib plus binimetinib in the COLUMBUS study: incidence, course and management. *Eur J Cancer*. 2019;119:97-106. [PMID: 31437754].
2. Koelblinger P, Thuerigen O, Dummer R. Development of encorafenib for BRAF-mutated advanced melanoma. *Curr Opin Oncol*. 2018;30:125-133. [PMID: 29356698].
3. Carlos G, Anforth R, Clements A, et al. Cutaneous Toxic Effects of BRAF Inhibitors Alone and in Combination With MEK Inhibitors for Metastatic Melanoma. *JAMA Dermatol*. 2015;151:1103-1109. [PMID: 26200476].
4. Chu EY, Wanat KA, Miller CJ, et al. Diverse cutaneous side effects associated with BRAF inhibitor therapy: a clinicopathologic study. *J Am Acad Dermatol*. 2012;67:1265-1272. [PMID: 22609219].