Multiple epidermotropic melanoma metastases developing during *BRAF* and *MEK* inhibitor therapy

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INTRODUCTION

Since introduction of *BRAF* and *MEK* inhibition therapy, there has been a significant improvement in response rates, overall survival, and progression-free disease in melanoma patients.[1-3] Combined *BRAF* and *MEK* inhibition, compared with *BRAF* inhibition alone, has shown to delay the emergence of resistance in patients suffering from *BRAF V600*–mutated advanced melanoma. It has become the standard of care in patients carrying this mutation.[4] Several mechanisms of resistance to *BRAF* and *MEK* inhibition have been shown. Reactivation of the mitogen-activated protein kinase pathway is the major trigger in more than two-thirds of tumors.[5]

CASE REPORT

We report on a 63-year-old patient who had solely multiple eruptive verrucous epidermotropic melanoma metastases of the lower limb during *BRAF* and *MEK* inhibitor therapy with dabrafenib and trametinib. To our knowledge, this is the first description of a solely cutaneous progressive disease during *BRAF* and *MEK* therapy.

The patient had a primary nonulcerated melanoma of the left foot diagnosed in 2012. The Breslow tumor thickness was 2.5 mm. After the sentinel lymph node was diagnosed positive in the left groin, the patient underwent radical lymphadenectomy (2 of 12 lymph nodes positive). A mutational analysis revealed a *BRAF V600E* mutation. One year later, the patient presented to our ward with multiple liver and bone metastases.

Because of the *BRAF V600E* mutation, the patient was treated with dabrafenib and trametinib. The medication was tolerated well and without any adverse effects. Radiology images showed partial response over 14 months. The patient was closely monitored with computed tomography scans of the body and cerebral magnetic resonance imaging every 2 to 3 months using RECIST 1.1. criteria. Suddenly after 14 months of treatment with dabrafenib and trametinib, the patient developed multiple verrucous epidermotropic nodules of the left limb and lower abdomen in May 2014 as presented in Fig 1, *A*. The bone and liver metastases remained stable. Most lesions presented with a white halo around the dark central nodule. Histologically, the lesions presented as epidermotropic, pleomorphic melanoma metastases, as shown in Fig 2. Solar elastosis was also present, highly suggesting previous sun damage to the skin. Four large cutaneous metastases were excised. Others were treated with CO_2 laser

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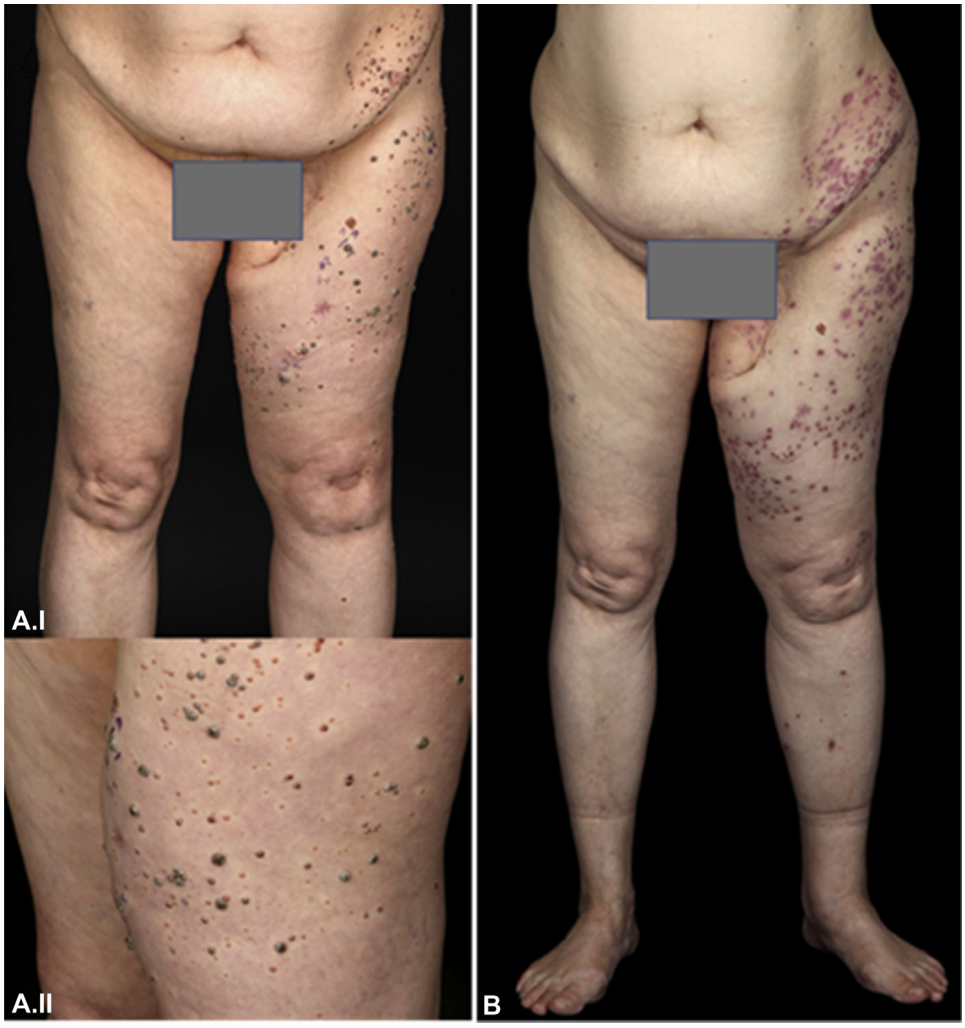

Fig 1. A, Multiple verrucous epidermotropic melanoma metastases on the left leg/lower abdomen before therapy and **B**, 2 months after CO_2 laser therapy and topical imiquimod therapy.

therapy and topical imiquimod (Fig 1, *B*) showing complete resolutions after an initial inflammation owing to imiquimod treatment. The disease remained stable for another 7 months until February 2015, when the patient experienced a relapse with multiple para-aortal, parailiac, inguinal, and brain metastases. The treatment was switched to radiation therapy (brain and lymph node metastases) and ipilimumab. Because of progressive disease, the treatment was switched to pembrolizumab 3 months later. The patient deceased another 3 months later.

CONCLUSION

We present a rare case of multiple eruptive verrucous epidermotropic melanoma metastases during treatment with *BRAF* and *MEK* inhibitors. Visceral metastases regressed or remained stable during this therapy. This finding could be because of the reactivation of the mitogen-activated protein kinase pathway known as the major trigger of resistance,[5] solely in an epidermotropic melanoma cell subclone of our patient. Cutaneous metastases of malignant melanoma often represent the first sign of relapse of this fatal disease.[6] Clinically and histologically cutaneous metastases present in various forms. Most commonly, cutaneous metastasis is primarily composed of epithelioid cells. However, epidermotropic metastases as seen in our case are rare.[7]

Our case shows that CO_2 laser therapy and adjuvant imiquimod therapy[8,9] can be successfully applied to control the local appearance of epidermotropic melanoma metastases.

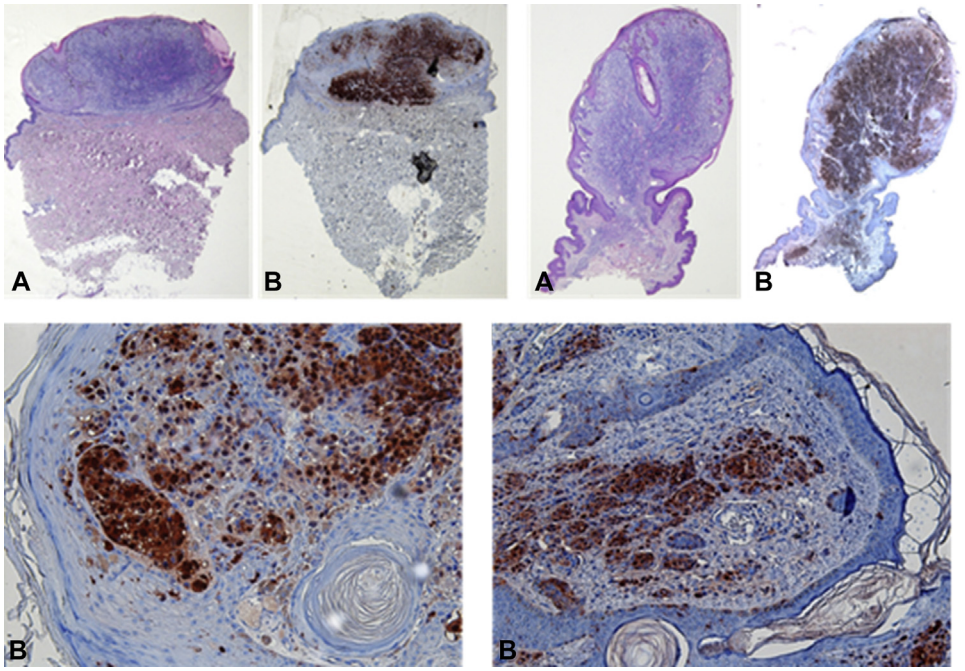

Fig 2. Histology of epidermotropic melanoma metastases. (**A**, Hematoxylin-eosin stain; **B**, anti-S100B stain.)

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