Multiple palpebral syringomas occurring after initiation of BRAF inhibition therapy in a patient with metastatic melanoma

Rastine Merat, MD, PhD,[a] Olivia Seyde, MD,[b] Eugenio Fernandez, MD,[c] and Gürkan Kaya, MD, PhD[a]
Geneva, Switzerland

Key words: BRAF inhibitor; melanoma; side effects; syringomas.

INTRODUCTION

Several skin lesions resulting from keratinocyte hyperproliferation have been observed in melanoma patients receiving BRAF inhibitor monotherapy. The most common of these lesions are verrucal keratosis, Grover disease, plantar hyperkeratosis, actinic keratosis, cutaneous squamous cell carcinoma,[1-4] and keratosis pilaris. More rare types of keratinocyte hyerproliferation occurring within the eccrine glands, as in eccrine syringometaplasia, have also been reported.[5] Most of these side effects are thought to result from the paradoxical activation of the mitogen-activated protein kinase (MAPK) pathway. Here we present the case of a patient treated with BRAF inhibitors for metastatic melanoma who subsequently had multiple palpebral syringomas that lasted during the monotherapy periods and regressed after the addition of a MAPK/ERK kinase (MEK) inhibitor.

Abbreviations used:

MAPK: mitogen-activated protein kinase
MEK: MAPK/ERK kinase

CASE REPORT

A 61-year-old man with lymph node, lung, pancreas, and adrenal gland metastatic melanoma disease carrying a *BRAF V600E* mutation, with an initial progressive disease under ipilimumab therapy, was treated with dabrafenib BRAF inhibitor. The monotherapy was maintained during a 1-month period of waiting before combined therapy could be initiated.

After the first 2 weeks of monotherapy, he presented with a sudden bilateral palpebral skin eruption characterized by small papules (Fig 1). Histologic examination found a dermal cystic epithelial proliferation with tadpole appearance and abundant cytoplasm, consistent with syringoma with clear cell aspect (Fig 2).

Within the 3 months of combined therapy that followed the initial monotherapy period, most of the lesions had vanished (Fig 3). Subsequently, because of a grade 4 fever, the treatment had to be interrupted. Considering that the patient experienced radiologic stability of his systemic metastases, targeted therapy was gradually reintroduced with an initial 2-month period of vemurafenib monotherapy before being combined again with the MEK inhibitor cobimetinib. During this second period of monotherapy, the palpebral lesions reappeared and disappeared again within 3 months of combined therapy.

DISCUSSION

Cutaneous adverse proliferative events known to occur during BRAF inhibitor therapy for melanoma range from keratinocyte squamoproliferative disorders to melanocytic proliferations as in eruptive nevi and second primary melanoma. The most frequently seen squamoproliferative disorders under BRAF inhibition therapy are verrucal keratosis, Grover disease, plantar hyperkeratosis, actinic keratosis, cutaneous squamous cell carcinoma, and keratosis pilaris.[1-4] More rare types of BRAF inhibitor–induced proliferation affecting eccrine glands

From the Divisions of Dermatology,[a] Pathology,[b] and Oncology,[c] University Hospital of Geneva.
Funding sources: None.
Conflicts of interest: None declared.
Correspondence to: Rastine Merat, MD, PhD, Department of Dermatology, University Hospital of Geneva, Rue Gabrielle-Perret-Gentil 4, CH-1205 Geneva, Switzerland. E-mail: rastine.merat@hcuge.ch.

JAAD Case Reports 2016;2:482-4.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2016.09.003

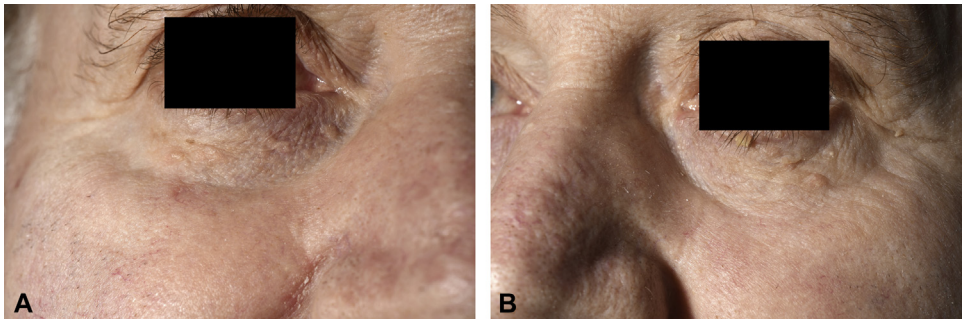

Fig 1. A and **B**, Skin eruption characterized by small papules on the both lower eyelids occurring after 2 weeks of dabrafenib monotherapy. Note the concomitant eruptive warts and milia lesions.

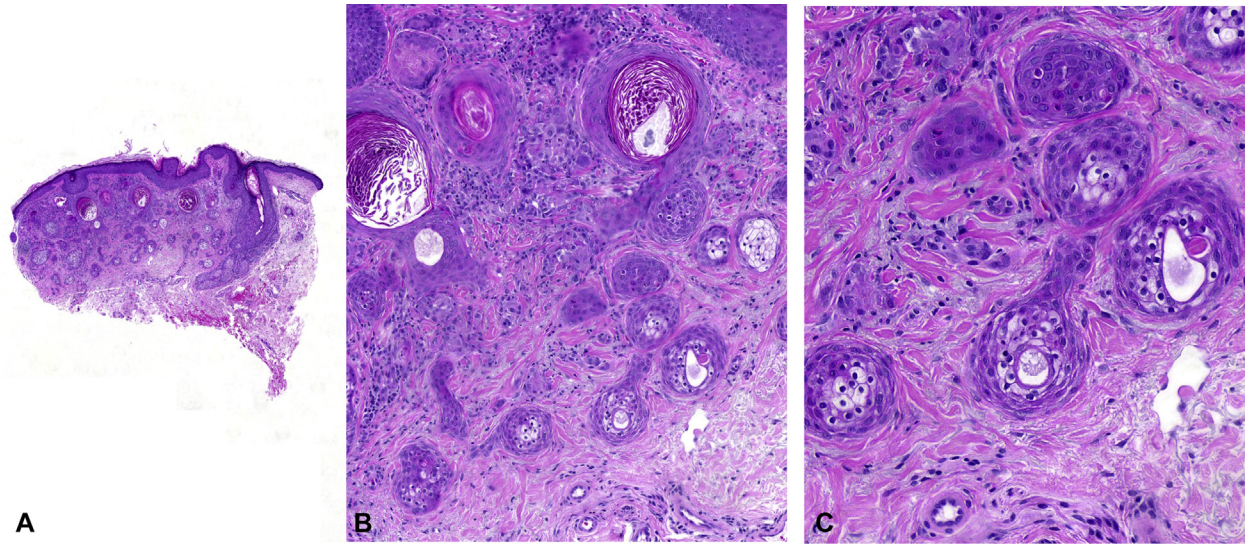

Fig 2. Dermal cystic epithelial proliferation with tadpole appearance and clear cytoplasm. (Hematoxylin-eosin stain; original magnification: **A**, ×1; **B**, ×10; **C**, ×20.)

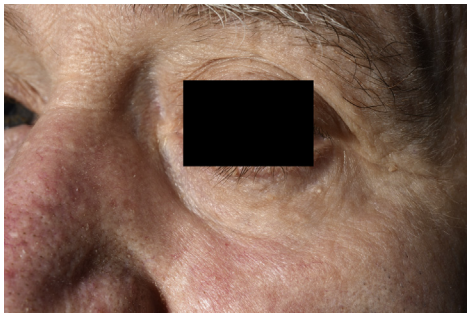

Fig 3. Disappearance of syringomas after 3 months of combined dabrafenib/trametinib therapy.

described as eccrine syringometaplasia have also been reported.[5]

Here we report a previously undescribed cutaneous side effect of BRAF inhibition therapy involving eccrine glands. The BRAF inhibitor–induced palpebral syringomatous eruption was completely and sequentially reversible under MEK inhibition therapy. The sequential appearance under BRAF inhibition therapy and disappearance under combined BRAF and MEK inhibition argues in favor of the commonly accepted hypothesis that the induced epithelial proliferation, in this case within eccrine glands, results from the paradoxical activation of the MAPK pathway. This paradoxical effect is less likely to occur in epithelial tissues carrying wild-type BRAF under combined therapy.[6]

Interestingly, multiple syringomas have been reported in the congenital Costello syndrome, which is caused by mutations in the *HRAS* gene resulting in dysregulated MAPK signaling and developmental disorders.[7] As already discussed in many reports, BRAF inhibitor–induced skin changes such as verrucal keratosis, keratosis pilaris, palmoplantar hyperkeratosis, and syringomas (from this report), can mimic to some extent the skin phenotypic changes observed in some congenital RASopathies.

REFERENCES

1. Boussemart L, Routier E, Mateus C, et al. Prospective study of cutaneous side-effects associated with the BRAF inhibitor vemurafenib: a study of 42 patients. *Ann Oncol*. 2013;24:1691-1697.
2. Boyd KP, Vincent B, Andea A, Conry RM. Nonmalignant cutaneous findings associated with vemurafenib use in patients with metastatic melanoma. *J Am Acad Dermatol*. 2012;67:1375-1379.
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.
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.
5. Lescoat A, Droitcourt C, Stock N, Le Gall F, Dupuy A. Vemurafenib-induced eccrine squamous syringometaplasia. *Dermatology*. 2013;226:362-364.
6. Huang V, Hepper D, Anadkat M, Lynn C. Cuaneous toxic effects associated with vemurafenib and inhibition of the BRAF pathway. *Arch Dermatol*. 2012;148:628-633.
7. Nguyen V, Buka RL, Roberts BJ, Eichenfield LF. Cutaneous manifestations of Costello syndrome. *Int J Dermatol*. 2007;46: 72-76.