Abstract. A 59-year-old woman, undergoing treatment with encorafenib for metastatic BRAF mutated colorectal cancer, developed during the first two months of therapy multiple eruptive nevi and changes in pre-existing nevi. Development of eruptive nevi has increasingly been reported in association with medications, most frequently conventional immunosuppressants and biologics. Some drugs are associated with eruptive nevi through an indirect effect of their mechanism of action, whereas other drugs are directly implicated in melanocyte proliferation. In this regard, BRAF inhibitors have been demonstrated to activate the MAPK pathway, and to promote cellular proliferation and survival, therefore leading to the development of new melanocytic nevi and to an increase in the size and hyperpigmentation of pre-existing nevi. A dermatological assessment and follow-up should be recommended in all patients presenting with eruptive nevi, regardless of the pathogenesis, because a high number of acquired melanocytic nevi may represent an adjunctive risk factor for melanoma.

Currently, eruptive nevi (EN) are not precisely defined in the literature. This term describes the sudden onset of multiple melanocytic lesions, usually over weeks to a month, associated with severe blistering skin diseases, conditions leading to compromised immunity, and the administration of medications including immunosuppressants (1-3). In particular, EN associated with medications (ENAMs) can be categorised into three distinct types, according to the classification proposed by Benjiamin et al. (2): Type I) eruptive nevi associated with immunosuppressants; Type II) eruptive nevi associated with chemotherapeutics; Type III) eruptive nevi associated with direct melanocyte stimulators.

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Correspondence to: Mauro Alaibac, Unit of Dermatology, University of Padua, via Gallucci 4, 35128 Padua, Italy. Tel: +39 0498212901, e-mail: mauro.alaibac@unipd.it

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utilization of a combination therapy, with agents directed against EGFR and BRAF.

Encorafenib (LGX818) is a highly selective ATP-competitive small molecule RAF kinase inhibitor, which suppresses the RAS-RAF-MEK-ERK pathway in tumor cells expressing the p.V600E BRAF mutation. It is being investigated in phase III clinical trials for BRAF mutant metastatic melanoma (17, 18) and in p.V600E BRAF mutant metastatic colorectal cancers (19), particularly in combination with MEK inhibitors. Patients undergoing BRAFi treatments without an association with an anti-MEK agent have been reported to develop new nevi or primary melanomas (20, 21).

In this article, we report the first case of eruptive nevi in a patient treated with encorafenib for p.V600E BRAF mutant colorectal cancer.

Case presentation. A 59-year-old woman was referred to our Dermatologic Unit for recent development of multiple eruptive new nevi; she also noted that the pre-existing nevi had changed both in size and in colour.

Figure 1. Eruptive melanocytic nevi of the back.
The patient had been diagnosed approximately one year before our visit with advanced stage, BRAF mutated colorectal cancer, and metastasis to abdominal lymph nodes and liver, and was not considered as a candidate for surgery. She had been treated with seven cycles of FOLFOXIRI protocol plus bevacizumab (a humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A) between February and September 2017. Few months later, this therapy was judged ineffective and was changed to encorafenib associated with cetuximab (a chimeric monoclonal antibody which binds to and inhibits EGFR) (22).

After two months in this therapeutic protocol, the patient begun to note the development of several new pigmented lesions throughout her body (Figure 1), including palms (Figure 2) and soles.

A complete dermatological assessment was performed, with full-body photography and dermoscopy, and the nevi were diagnosed clinically and dermoscopically as benign; consequently, the patient was followed up for 8-weeks. Two months later, the patient returned for follow-up dermatological assessment and was noted to have developed a few isolated new lesions, but the previous ones were stable.

**Discussion**

BRAF is a key enzyme in the MAPK signalling pathway (RAS-RAF-MEK-ERK), which regulates cellular proliferation, differentiation, survival and angiogenesis.

BRAF inhibitors’ cutaneous toxicity is common, due to paradoxical activation of the MAPK pathway in wild type BRAF cells. It has been reported that treatment for 2-5 months resulted in different types of cutaneous toxicities, such as cutaneous squamous cell carcinoma, verrucal keratosis and plantar hyperkeratosis, Grover disease, hair follicle changes, panniculitis, photosensitivity, and eruptive nevi (23, 24).

Recent studies (25) have demonstrated that treatment with BRAFi induces proliferation of wild type (wt) BRAF cells in vivo, because of the activation of the RAS-RAF-MEK-ERK pathway, which promotes cell proliferation and survival. As a result, nevi increase in size and pigmentation, as we have described in our patient. **Vice versa**, the nevi that regressed during follow-up, were positive for the p.V600E BRAF mutation.

Cutaneous toxicities are a well-known side effect of BRAFi; however, little is known about the specific cutaneous side-effect profile of LGX818. We presented a
Conclusion

Many questions remain to be answered regarding the clinical significance of EN, a fascinating phenomenon that occasionally occurs in association with several conditions, and after several treatments. In particular, some medications seem to be associated with eruptive nevi through an indirect effect of their mechanism of action, such as immunosuppression; instead, other drugs seem to be directly implicated in the proliferation and growth of melanocytes. The mechanisms involved are still partially unknown, but current research is focused on the BRAF gene and the effects that anti-BRAF chemotherapeutics have on the RAS-RAF-MEK-ERK pathway and its relations with melanocyte tropism. Further research is necessary before conclusions can be made.

Moreover, little is known about the risk of melanoma in patients who are administered drugs that can directly stimulate the development of new nevi. Therefore, it is important to instruct patients to report new skin lesions and to recommend regular dermatological assessment, in order to identify and remove any new nevus presenting clinical and/or dermoscopic atypia, or changing pigmented lesions of concern.

Regardless of the pathogenesis, a strict dermatological follow-up for the melanocytic lesions should be recommended in all patients presenting with EN, because a high number of acquired melanocytic nevi represents itself a certain risk factor for melanoma skin cancer (25).

Considering this emerging association between anti-BRAF chemotherapeutics and EN, and the increasing use of this class of therapeutic agents, complete dermatological assessment and follow-up could reasonably be applied for all patients who begin treatment with a BRAFi.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors’ Contributions

AM, AL and MA have made substantial contributions to acquisition of clinical data, have been involved in drafting the manuscript and have given final approval of the submitted manuscript.

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