Eruptive melanocytic nevi associated with ponatinib

Inès Devred, MD,[a] Jean-Philippe Arnault, MD,[a] Alanoud Adas, MD,[a] Delphine Rea, MD,[b] Florian Lombart, MD,[a] Henri Sevestre, MD, PhD,[c] Stèphanie Trudel, MD,[d] Catherine Lok, MD, PhD,[a] and Guillaume Chaby, MD[a]
Amiens and Paris, France

Key words: adverse effects; chronic myeloid leukemia; drugs; eruptive melanocytic nevi; ponatinib.

INTRODUCTION

Ponatinib (ICLUSIG, Takeda; Osaka, Japan) is an oral third-generation tyrosine kinase inhibitor (TKI) approved by US Food and Drug Administration in 2012 used to treat chronic myeloid leukemia (CML) and Philadelphia chromosome−positive (Ph^+) acute lymphoblastic leukemia (ALL), for whom no other tyrosine kinase inhibitor therapy is indicated, and for patients with $T3151^+$ CML or $T315I$ Ph^+ ALL.[1]

Skin rash and dry skin are the most frequent dermatologic adverse effects, reported as high as 34% and 32%, respectively.[1] Recently, pityriasiform and ichthyosiform cutaneous toxicities were also reported, sometimes associated with eyebrow alopecia.[2] Here, we report the first case, to our knowledge, of eruptive melanocytic nevi (EMN) induced by ponatinib, an adverse effect previously reported with a few other TKI.

Abbreviations used:

ALL:	acute lymphoblastic leukemia
CML:	chronic myeloid leukemia
EMN:	eruptive melanocytic nevi
Ph^+:	Philadelphia chromosome−positive
TKI:	tyrosine kinase inhibitor

CASE REPORT

A 64-year-old woman was started on ponatinib (45 mg/d) as a sixth-line therapy for Ph^+ CML evolving for 20 years, which was further reduced down to 30 mg/d after 24 months of therapy because of arterial hypertension. Her previous therapy regimens included hydroxycarbamide, interferon-α, imatinib, dasatinib, and nilotinib. All these treatments failed to induce any cytogenetic response. No *BCR-ABL1* was identified.

The patient also had a regular follow-up examination in the dermatology department after a 1-mm-thick melanoma with axillary lymph node metastasis developed, for which she had local resection, lymph node dissection (8N+/10), and adjuvant chemotherapy with temozolomide during 6 months, without recurrence of melanoma after more than 10 years of follow-up.

After 3 months of treatment by ponatinib, physical examination found more than 500 small uniform dark brown nevi, which appeared on the entire body including non−photo-exposed areas. The eruption did not include palmar and plantar surfaces nor mucosal areas (Fig 1).

The dermoscopic examination of the lesions showed monomorphous melanocytic macules with lentiginous growth pattern, measuring a few millimeters with homogenous-pigmented networks with ring-shaped structures (Fig 2). Histologic evaluation found melanocytic proliferation at the basal layer of the epidermis of lentiginous type, occasionally forming small nests. The proliferation was more prominent at the level of the epidermal ridges, corresponding to the dermoscopic ring-shaped structures (Fig 3).

Molecular analysis of the nevi did not find any mutation in *BRAF* (exons 11, 15), *NRAS* (exons 2, 3,

From the Service de Dermatologie,[a] Laboratoires d'Anatomie et Cytologie Pathologiques,[c] and Laboratoire d'Oncobiologie moléculaire, Centre de Biologie Humaine,[d] CHU Amiens Picardie and the Service d'Hématologie Adulte, Hôpital Saint-Louis, Paris.[b]

Funding sources: None.
Conflicts of interest: None disclosed.

Correspondence to: Inès Devred, MD, Service de dermatologie, CHU Amiens Picardie, 80054 Amiens. E-mail: inesdevred@hotmail.com.

JAAD Case Reports 2018;4:1052-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2018.07.010

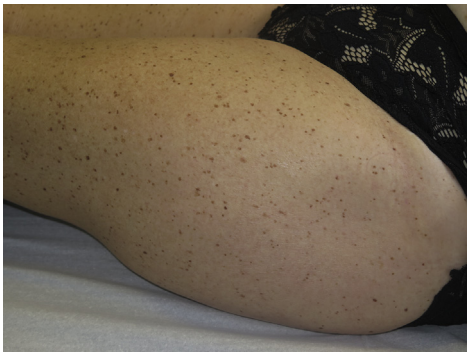

Fig 1. Small uniform brown nevi on the thigh.

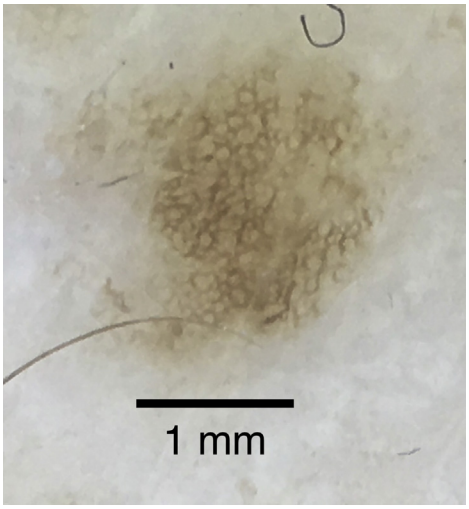

Fig 2. Dermatoscopic view of nevi shows regular ring-shaped structure.

4), or *C-KIT* (exons 8, 9, 11, 13, 14, 17, 18) genes, using panel-based next-generation sequencing.

In addition to ponatinib, she was taking lercanidipine and enalapril for a ponatinib-induced arterial hypertension. The Naranjo scale was 6, meaning EMN is a probable adverse effect owing to ponatinib. The benefit-risk balance was in favor of continuing the ponatinib. The nevi remained stable, and the patient had no melanoma recurrence with 4-year hindsight.

DISCUSSION

EMN is an abrupt development of multiple melanocytic nevi in previously unaffected skin associated with an underlying trigger, first described by Hutchinson in 1868.[3] It is commonly reported in association with severe blistering diseases, after renal transplantations, malignancies, AIDS, and medications. The mechanism of the eruption of melanocytic nevi remains unknown.

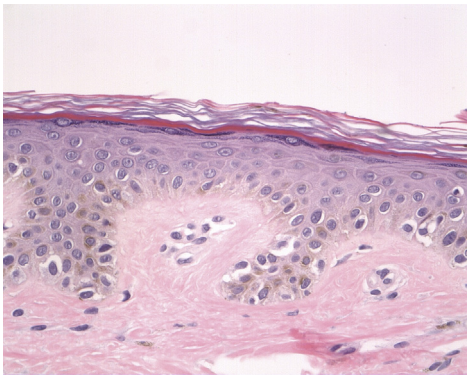

Fig 3. Histologic evaluation of the lesions found melanocytic proliferation at the basal layer of the epidermis, sometimes forming a small nest. (Hematoxylin-eosin-safran stain; original magnification: ×400.)

Eruptive nevi associated with medications have been reported with increasing frequency. Perry et al[4] defined eruptive nevi associated with medications as development of one or more of the following during the first 6 months of a newly started medication:

1. Greater than 5 palmoplantar melanocytic nevi at any age
2. Greater than 10 melanocytic nevi outside the period of puberty and pregnancy
3. Greater than 20 melanocytic nevi during puberty of pregnancy

To our knowledge, the development of eruptive nevi has never been reported with ponatinib. However, EMN occurrence is well known with other kinase inhibitors, particularly with RAF inhibitors vemurafenib and dabrafenib.[5] Some observations of EMN were also reported with other TKIs like sorafenib,[6] and regorafenib.[7] These kinase inhibitors are well-known nonselective RAF inhibitors.

The emergence of these lesions may be related to a paradoxical activation of the MAP (mitogen activated protein) kinase in the *BRAF* wild-type melanocytes.[8] In *BRAF* wild-type cells, inhibitors trigger heterodimerization of BRAF-CRAF, which can lead to MEK/ERK phosphorylation and in some cases to enhanced proliferation. The high frequency of EMN under vemurafenib is associated with a specific affinity between the TKI and RAF pathway, whereas the low frequency of EMN with other TKI suggests a weaker affinity.

More globally, some cardio-facio-cutaneous such as Noonan syndrome, gathered under the nomenclature *rasopathy*, could be also associated with the onset of multiple lentiginous nevi. The mechanism in these syndromes is explained by the mutation of

genes encoding proteins, regulating the MAP kinase signaling pathway, in which RAF inhibitors could be a therapeutic perspective.

Ponatinib, which was designed as a very potent inhibitor of native BCR-ABL, as well as the T315I mutant, also inhibits the in vitro kinase activity of other kinases (FLT3, RET, KIT, PDGFRα, PDGFRα, and FGFR1). Ponatinib is also a potent inhibitor of RAF, including ARAF, BRAF, and CRAF.[9] EMN induced by ponatinib could be explained by a paradoxical activation of MAP-kinase with a similar mechanism as vemurafenib and dabrafenib. Furthermore, under vemurafenib and dabrafenib, changes in pre-existing pigmented lesions were reported, such as regression or darkening of nevi, appearance of new nevi, or acquired atypical dermoscopic features. Perier-Muzet et al[10] also described the occurrence of new melanoma.

The possibility that the development of these melanocytic lesions is related to the underlying malignancy itself cannot be excluded, as paradoxical activation of the MAP-kinase pathway has been reported to be a mechanism of CML-TKI resistance.[11] However, the eruptive nevi appeared suddenly after the first 3 months of ponatinib treatment and she had CML for more than 20 years; so the occurrence of EMN is highly attributed to the use of ponatinib.

CONCLUSION

We speculate that ponatinib might have a potential to paradoxically up regulate MAPK, thus stimulating melanocyte proliferation. A more regular periodic dermatologic examination should be considered for patients taking ponatinib and other TKI with EMN. Furthermore, RAF inhibitors have shown their potential to unmask the expression of RAS mutant tumor proliferation, so EMN-associated TKI should be avoided in these RAS mutant tumors.

REFERENCES

1. Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369:1783-1796.
2. Alloo A, Sheu J, Butrynski JE, et al. Ponatinib-induced pityriasiform, folliculocentric and ichthyosiform cutaneous toxicities. *Br J Dermatol*. 2015;173:574-577.
3. Hutchinson J. Outbreak of a large crop of moles. Remarks as to possible connection with melanosis. *J Cutan Med Dis Skin*. 1868;1:170-171.
4. Perry BM, Nguyen A, Desmond BL, Blattner CM, Thomas RS, Young RJ. Eruptive nevi associated with medications (ENAMs). *J Am Acad Dermatol*. 2016;75:1045-1052.
5. 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 Off J Eur Soc Med Oncol*. 2013;24:1691-1697.
6. Bennani-Lahlou M, Mateus C, Escudier B, et al. Naevus éruptifs sous sorafenib. *Ann Dermatol Venereol*. 2008;135:672-674.
7. Sibaud V, Munsch C, Lamant L. Eruptive nevi and hair depigmentation related to regorafenib. *Eur J Dermatol EJD*. 2015;25:85-86.
8. Hatzivassiliou G, Song K, Yen I, et al. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature*. 2010;464:431-435.
9. Gozgit JM, Rivera VM, Shakespeare WC, Zhu X, Dalgarno DC. Methods and Compositions for RAF Kinase Mediated Diseases. Google Patents, 2015. Available from: https://www.google.com/patents/US20150105377.
10. Perier-Muzet M, Thomas L, Poulalhon N, et al. Melanoma patients under vemurafenib: prospective follow-up of melanocytic lesions by digital dermoscopy. *J Invest Dermatol*. 2014;134:1351-1358.
11. Schnetzke U, Fischer M, Frietsch JJ, et al. Paradoxical MAPK-activation in response to treatment with tyrosine kinase inhibitors in CML: flow cytometry loses track. *Cytometry B Clin Cytom*. 2013;17:601-603.