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LETTER TO THE EDITOR

Radotinib-induced eruptive melanocytic nevi in patient with chronic myeloid leukemia: a case report and literature review

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Dear Editor,

Eruptive melanocytic nevi (EMN) were first described by Hutchinson in 1868 [1]. Since then, the sudden eruption of benign melanocytic nevi has been associated with severe bullous diseases, renal transplantation, human immunodeficiency virus, and medications including immunosuppressant, chemotherapy, and biologics [2–8].

A 71-year-old man presented with a 6-month history of multiple small brownish macules on whole body. Pigmented macules abruptly grew in numbers and size for 6 months. He had a 19-year history of chronic myeloid leukemia (CML). He had previously been treated with imatinib, nilotinib, and dasatinib for 15 years, and is now being treated with a 400-mg once-daily dose of radotinib for 2 years in the hemato-oncology department. Physical examination revealed 295, 1–2-mm-sized brownish macules on whole body, especially in the forearm, elbows, neck, and dorsa of hands (Fig. 1a–c), and the distribution of EMN is showed on schematical drawing (Fig. 1d). The skin biopsies from his left forearm and neck showed benign junctional lentiginous nevi. The laboratory findings, including a blood chemistry and urinalysis, were normal. Thus, we came to the conclusion of EMN caused by radotinib. We provided reassurance without any treatment for EMN and continued to closely monitor the nevi for changes of numbers and size at every follow-up.

Common acquired melanocytic nevi typically begin after birth, peaks to the median number of 16 to 24 nevi during third decades, and then the number of nevi slowly declines until the ninth decade. EMN are rare phenomenon characterized by sudden eruption of multiple melanocytic nevi over weeks to months often in the setting of immunosuppression or chemotherapy. Although the etiologies of the eruptive nevi are not completely understood, immunosuppression clearly plays a significant role. Furthermore, activation of biologic-specific mechanisms may cause the development of biologic-related EMN. Adverse cutaneous reactions secondary to tyrosine kinase inhibitors (TKIs) had been previously reported [2–5, 7, 8], most were TKI-induced hypopigmentation, and hyperpigmentation or EMN were rarely reported [5, 7, 8]. TKI targets the ATP binding site of BCR-ABL, platelet-derived growth factor, and c-Kit [2]. c-Kit and its ligand stem-cell factor have a major role in melanogenesis, melanocyte homeostasis, and UVB-induced pigmentation. So, it is considered that TKI-associated pigmentary changes are likely to be due to the effect of TKI on c-Kit. Radotinib is a novel and selective second-generation BCR-ABL1 TKI, which is currently approved in Korea for the treatment of patients with CML [9]. Recent data shows that radotinib selectively acts on BCR-ABL1, but has little effect on c-Kit compared to other TKIs [10]. Radotinib-induced pigmentary changes, including dysplastic nevi, EMN, and lentiginosis, have been reported previously in three English literatures (Table 1) [6, 8, 9]. The authors hypothesized that reduced c-Kit suppression by selective inhibition of BCR-ABL1 may develop paradoxical c-Kit activation, subsequently promoting hyperpigmentation. Furthermore, immunosuppressed state promotes the melanocytic proliferation, and cytotoxic effects in epidermal melanocytes of radotinib itself may contribute to the induction of nevi. Kim et al. reported ten patients with radotinib-induced EMN. Among them, one patient has decreased in number of nevi 2 weeks after stopping radotinib and four patients were treated with an alexandrite laser for cosmetic reasons, but two patients developed local recurrence due to continuous administration of radotinib [8]. We monitored the patient closely during every visit without the discontinuation of radotinib, which serves as a critical therapy for the patients with CML. During 1 year of follow-up, there has been no evidence of change in numbers and size suggesting malignant transformation. With the increasing use of biologic immunosuppressants

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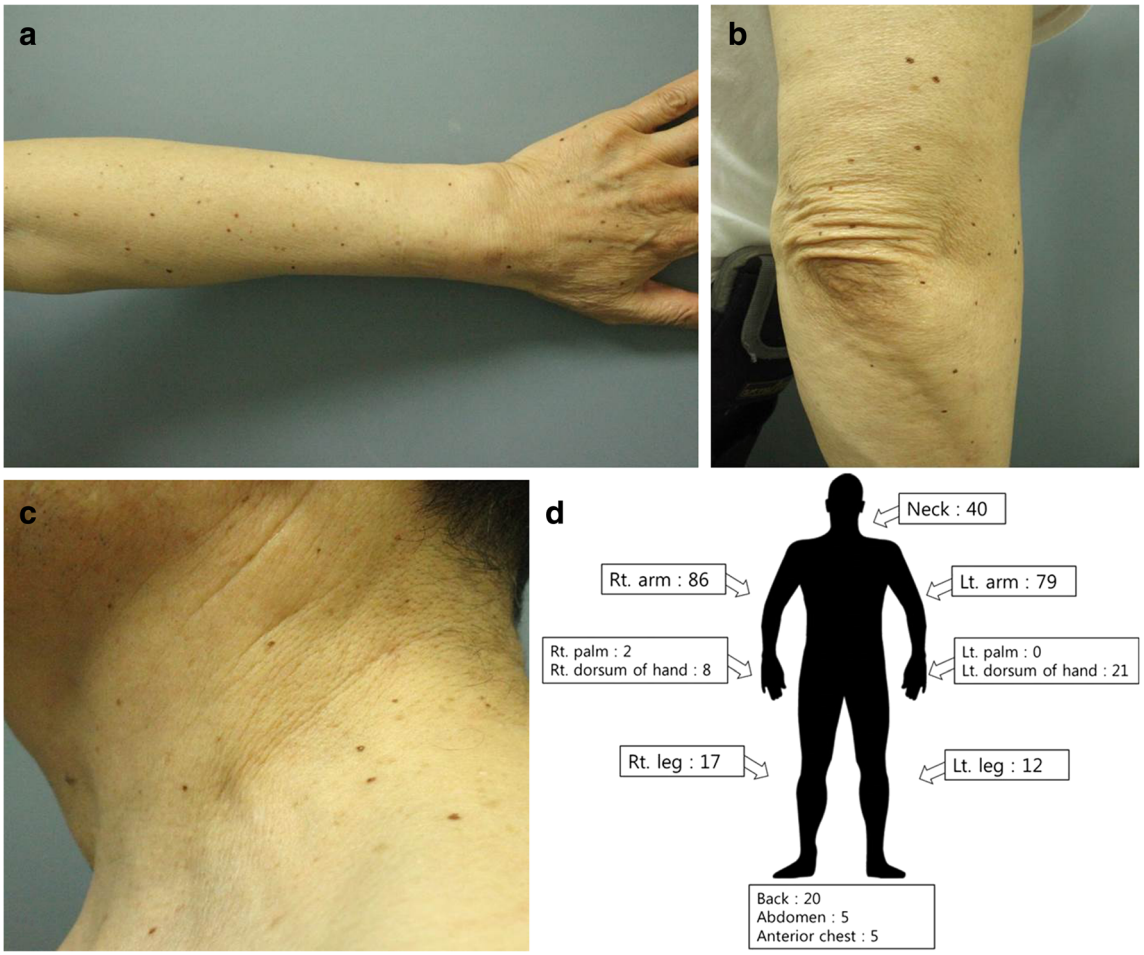

Fig. 1 Multiple 1–2-mm-sized brownish macules on left forearm (**a**), right elbow (**b**), and left side of neck (**c**). **d** Distribution of EMN is showed on schematical drawing

Table 1 Summary of reported cases of radotinib-induced pigmentary changes

Authors	No.	Type of pigmentary change	Age (years)/ sex	Duration of radotinib therapy (months)	Onset of pigmentary lesions from radotinib therapy (months)	Number of lesions	Site of lesions
Kim et al. [5]	1	EMN	32/M	12	Several months	523	Entire body
	2		32/F	7	x	212	x
	3		31/F	12	x	230	x
	4		52/F	11	x	415	x
	5		51/M	23	x	1756	x
	6		42/M	24	x	455	x
	7		24/F	12	x	220	x
	8		74/F	9	x	312	x
	9		27/M	48	x	1023	x
	10		69/M	9	x	351	x
Won et al. [7]	11	Lentiginosis	69/M	6	6	Numerous	Face, both forearms
Woo et al. [8]	12	EMN with	35/M	48	12	Numerous	Face
	13	dysplastic	59/M	24	1	Numerous	Face
	14	change	25/M	48	6	Numerous	Face, arms
Our case		EMN	71/M	48	45	295	Entire body, especially both forearms, neck, dorsa of hands

EMN, eruptive melanocytic nevi; *M*, male; *F*, female; *x*, not mentioned

and chemotherapeutics in recent years, biologic-related EMN has been also increasingly reported [2–8]. We believe this case can help clinicians in making a diagnosis and differentiating from more worrisome neoplasm, and also help in educating patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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