

## Eruptive Melanocytic Naevi Caused by Radotinib Therapy in Patients with Chronic Myeloid Leukaemia: 10 Cases and a Literature Review

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Development of eruptive melanocytic naevi (EMN) is an uncommon phenomenon characterized by the sudden onset of hundreds of melanocytic naevi. EMN have been described after severe bullous diseases and administration of immunosuppressive drugs (1–5). The mechanism leading to EMN is unclear, but it is thought that an immunosuppressed state may play an important role (6). We describe here 10 cases of EMN in patients with chronic myeloid leukaemia (CML), all of which developed while receiving radotinib. Radotinib is a novel selective BCR/ABL tyrosine kinase inhibitor (TKI) for the treatment of CML with intolerance of other TKIs. To our knowledge, this is the first report of an association between radotinib therapy in patients with CML and the development of EMN.

### MATERIALS AND METHODS

Ten patients with CML in the Department of Hematology who developed multiple eruptive pigmented lesions during oral administration of radotinib were referred to our clinic between January 2012 and May 2015. Past medical history and clinical examination was documented for all patients. Each participant was given written information regarding the aim of the study. The study was approved by the ethics committee of the Catholic University of Korea.

### RESULTS

The characteristics of the 10 patients with CML (5 males and 5 females, mean age 43.4 years, age range 24–74 years) are summarized in Table S1<sup>1</sup>. The mean duration of radotinib therapy was 16.7 (range 7–48) months, and the mean number of naevi was 549.7 (range 212–1,756) (Fig. S1<sup>1</sup>).

Skin samples were taken from 2 enrolled patients who consented to skin biopsies. Histopathological examination of the pigmented lesions demonstrated discrete melanocytes or nests at the dermoepidermal junction with slightly elongated and clubbed rete ridges (Fig. S2<sup>1</sup>). Based on the clinical and histopathological findings, we diagnosed melanocytic naevi with EMN that developed during radotinib therapy. We treated 4 patients who wanted to remove multiple naevi for cosmetic reasons

with a long-pulse 755-nm alexandrite laser (GentleMax<sup>®</sup>, Syroner Candela, East Coast) with settings of 300 J/cm<sup>2</sup>, using a 1.5-mm spot size, and a 10-ms pulse width. Among the 4 patients treated with laser therapy, 2 (cases 2 and 7) developed local recurrence due to continuous administration of radotinib. In our case series, a 32-year-old man (case 1) was diagnosed with CML and started on 800 mg radotinib twice a day in 2013. After several months, he developed multiple pigmented macules and papules on his face and extremities. Over the next year, the number of pigmented macules and papules increased and spread across his entire body, including areas not exposed to the sun. On physical examination, we found more than 500 naevi with diameters of 2–5 mm (Fig. 1). Interestingly, after the patient had stopped radotinib for 2 weeks due to elevated liver enzymes, the number of EMN decreased to approximately 300 and their colour was reduced (Fig. 1). He did not receive any treatment for many pigmented macules.

### DISCUSSION

In this report, we present 10 cases of EMN occurring in CML patients treated with radotinib. There have been only a few reports of cutaneous adverse events caused by radotinib in CML patients. To the best of our knowledge, no report has been published about radotinib-induced EMN in patients with CML.



**Fig. 1. Case 1. Multiple pigmented macules on the face and neck during treatment with radotinib (left) and after stopping radotinib for 2 weeks (right).** The number of eruptive melanocytic naevi decreased and the colour of the macules faded.

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Multikinase inhibitor-induced EMN have already been reported (7–9). Kong et al. (7) reported 2 cases of EMN associated with sorafenib, a FDA-approved multikinase inhibitor for renal cell carcinoma and hepatocellular carcinoma. Bennani-Lahlou et al. (8) reported 5 cases of eruptive naevi in patients treated with sorafenib. Sunitinib, a multikinase inhibitor with a mechanism of action similar to that of sorafenib also caused EMN in a 53-year-old man with metastatic renal cell carcinoma; the authors hypothesized that the development of EMN was probably due to exceptional inhibition of the BRAF/MAP/ERK pathway by sorafenib and sunitinib, and this triggered the proliferation of melanocytes due to loss of senescence induced by BRAF (10). It is unclear whether the proliferation of melanocytes is a direct effect of drugs or an effect of immunosuppressive action. One study reported that a CML-related immune status was associated with widespread melanocytic naevi before treatment for CML (11). However, in the present study, the multiplicity and the abrupt onset of appearance after starting radotinib, as well as the regression after stopping the treatment lead us to speculate that these multiple naevi may have resulted from effects of radotinib. The pathogenesis of radotinib-induced EMN has not been elucidated. Won et al. (12) reported one case of lentiginosis after radotinib treatment. An increased number of basal melanocytes was observed in their patient, and this suggested that melanocyte proliferation had been stimulated. The authors suggested that the activation of melanocytes was caused by selectively inhibiting only BCR-ABL1, not c-KIT (12). Perhaps radotinib has a similar potential to paradoxically up-regulate MAPK or other enzymes in the pathway, thus stimulating melanocyte proliferation and survival. In addition, although we could not determine the factors that triggered EMN in our patients, it is likely that various cytokines and iatrogenic immune suppression produced by radotinib are responsible for the abrupt appearance of multiple melanocytic naevi.

In conclusion, we suggest that radotinib can be considered as a potential secondary cause of EMN. Because of the increasing use of multi-TKIs, clinicians should be aware of this potential association and make recommendations for the proper management of multiple naevi. It is important to consider that EMN can adversely affect the patient's appearance and create significant psychological

problems. Therefore, we propose that clinicians should carefully evaluate CML patients' cutaneous adverse reactions caused by selective BCR/ABL TKIs and treat appropriately.

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