Eruptive melanocytic nevi in a patient with Parkinson disease treated by carbidopa-levodopa

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Key words: carbidopa-levodopa; eruptive melanocytic nevi; eruptive nevi associated with medications; melanoma; Parkinson disease.

INTRODUCTION

Eruptive melanocytic nevi (EMN) is a rare phenomenon characterized by the rapid development of multiple melanocytic nevi on the skin. Although the exact mechanism is unknown, EMN has been associated with immunosuppression, bullous skin disease, severe sunburn, and Crohn's disease.[1,2] The literature regarding the development of eruptive nevi in association with different medications is relatively low and tends to be associated with immunosuppressive therapies; however, the prevalence of this phenomenon is likely underestimated.[2] It is currently unknown if there is an association between EMN and the development of melanoma; however, the association between Parkinson disease (PD) and melanoma is well established.[3,4] Here we report a case of eruptive melanocytic nevi on the palms that developed in a patient with PD while being treated with carbidopa-levodopa.

Abbreviations used:

6-MP:	6-mercaptupurine
CMM:	cutaneous malignant melanoma
ENM:	eruptive melanocytic nevi
ENAMS:	eruptive nevi associated with medications
L-DOPA:	levodopa
PD:	Parkinson disease

CASE REPORT

An 86-year old man with a medical history significant for hypertension, coronary artery disease, chronic renal insufficiency, myelodysplastic syndrome, and recently diagnosed Parkinson disease (PD) presented with a 5-month history of black spots on the bilateral palmar surface of his hands. Notably, 6 months before presentation when his PD was diagnosed, he was started on 0.5 mg carbidopa-levodopa 3 times daily. Recently, 2 months before presentation, his dose was increased to 1 mg 3 times daily, and the patient noted that the spots were more numerous and darker. Physical examination found numerous dark brown macules with regular reticulated pigmented networks under dermoscopy (Fig 1). There was no difference in the number of nevi between left and right palms, and there were no nevi on the dorsal surface of both left and right hands and feet. Additionally, there was no involvement of the plantar feet and no other suspicious lesions on the rest of the body. Specifically, before starting carbidopa-levodopa, the patient did not have any nevi on his palms. After doubling his does, the number of nevi increased from approximately 25 to 40 discrete lesions per palm. Biopsy was recommended for confirmation of the diagnosis; however, because of patient's declining health, he refused.

DISCUSSION

EMN is a relatively uncommon phenomenon and typically develops over weeks to months in association with an underlying trigger. There is a strong predilection for the palmoplantar locations, especially when EMN is associated with medication use.[5] The predisposition for the palms and soles may be

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Funding sources: None.
Conflicts of interest: None disclosed.
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JAAD Case Reports 2019;5:21-3.
2352-5126

https://doi.org/10.1016/j.jdcr.2018.10.005

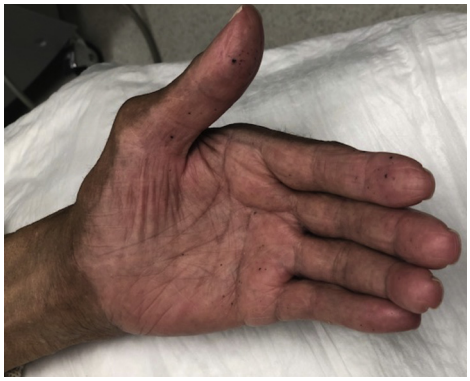

Fig 1. Numerous dark brown macules with regular reticulated pigmented networks under dermoscopy.

because of the high density of eccrine glands found in these regions.[5] Eccrine glands carry the melanocortin-5 receptor, which is one of the receptors in which α-melanocyte–stimulating hormone (α-MSH), a hormone involved in the melanin synthesis pathway, binds.[5] There is support for the role of medications that stimulate melanocytes via α-MSH leading to the development of EMN.[5] In 1 case report, EMN occurred after subcutaneous insulin injections in a pediatric patient with type 1 diabetes mellitus thought to be induced by stimulating α -MSH.[3]

The use of biologics has become increasingly common in recent years and as a result is a frequent cause of eruptive nevi associated with medications (ENAMS).[5] Melanocytic nevi eruptions are most commonly associated with the thiopurines, azathioprine and 6-mercaptupurine (6-MP).[5] Many additional classes of medications may lead to the development of EMN; however, for simplicity, the classification of ENAMs has been divided into 3 distinct types and additional subtypes (Table I).[5] Some patients may be genetically predisposed to EMN, and the impairment of an intact immune system by use of any of these agents may allow for the proliferation of melanocytes.[3,5]

Levodopa (L-DOPA) is a metabolic precursor in both dopamine and melanin synthesis. In Parkinson disease, there is a relative loss of dopamine, and the cornerstone of treatment is dopamine replacement therapy, most commonly with carbidopa-levodopa. This combination helps to increase the relative concentration of L-DOPA delivery into the central nervous system, where it is then converted to dopamine.[6] In addition to dopamine synthesis, L-DOPA also serves as an important intermediate in melanogenesis, where increased levels of L-DOPA favor further melanin production.[7] Dysregulation of the molecular pathways within melanocytes can lead to the formation of lesions such as nevi and melanoma, where there is an increase density of melanin pigment.[7] We hypothesize that the relative increase in L-DOPA during treatment with carbidopa-levodopa may stimulate the development of melanocytic nevi production leading to the development of EMN (Fig 2).

Table I. Classification of ENAMs

ENAM classification	Example medications
Type Ia: Nonbiologic immunosuppressants	Azathioprine, 6-mercaptopurine, corticosteroids, cyclosporine, methotrexate
Type Ib: Biologic immunosuppressants	Etanercept, alefacept, infliximab, rituximab
Type IIa: Nonbiologic chemotherapeutics	Combination chemotherapy, capecitabine, interferon alfa-2b, cyclophosphamide, octreotide
Type IIb: Biologic chemotherapeutics	BRAF inhibitors (vemurafenib, encorafenib), sorafenib, sunitinib, erlotinib, regorafenib, rituximab
Type III: Direct melanocyte stimulators	Melanotan I and II (synthetic alpha melanocyte-stimulating hormone analogs), corticotrophin

Melanoma is the most lethal form of skin cancer. A predictive factor for the development of melanoma is the presence of large numbers of nevi, and individuals harboring greater than 120 nevi have a 20-fold increased risk of melanoma.[8] Another well-established risk factor for cutaneous malignant melanoma (CMM) is Parkinson disease. CMM rates are 1.5 to 3.5 times higher in Parkinson patients when compared with the general population.[4] Although the exact mechanism underlying the association between PD and CMM is unknown, it is thought that the dysfunction of melanin-related enzymes and genetic predisposition play a role.[4]

The limited literature on EMN has made it difficult to assess whether EMN constitutes an increased risk for melanoma.[8] There is, however, growing interest in the pathogenesis of EMN and the *BRAF* gene—a gene commonly associated with melanoma.[5,8] The role of mutated *BRAF* drives melanoma progression, and it is thought that the overexpression of *BRAF V600E* in melanocytes may lead to an initial burst of

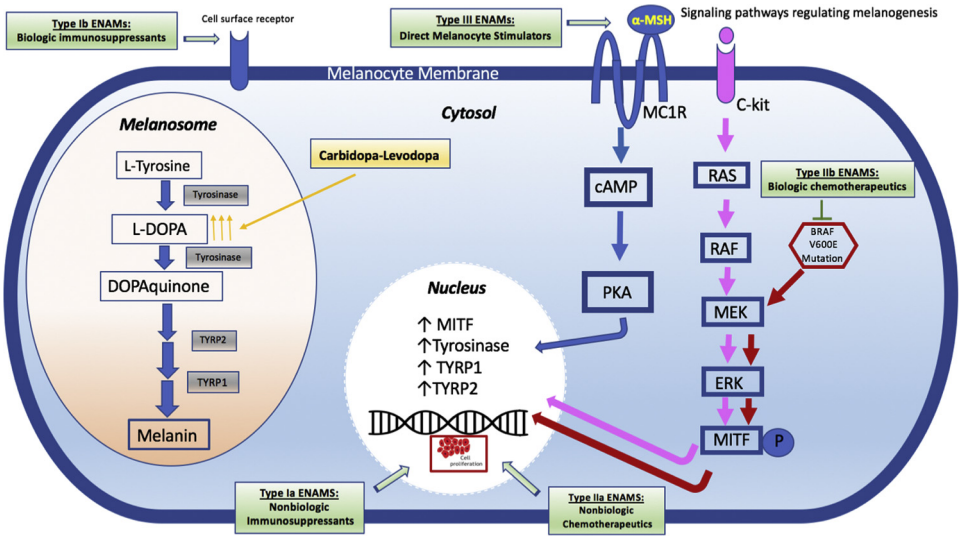

Fig 2. Schematic representation of the melanogenesis pathway shows where common ENAMs affect the pathway. *PAH,* phenylalanine hydroxylase; *TYRP1,* tyrosinase-related protein 1; *TYRP2,* tyrosinase-related protein 2; *MITF-P,* microphthalmia associated transcription factor-phosphorylated; *cAMP,* cyclic adenosine monophosphate.

cell proliferation followed by growth arrest and the adoption of a senescence-like phenotype.[8] The senescence status and level of growth arrest observed in the nevi of patients with EMN may provide additional insight into the potential for future melanoma development.[8]

We cannot say with certainty whether the increase of L-DOPA attributes to the development of EMN by stimulating the melanin synthesis pathway. To the best of our knowledge, there have not been any other reported cases of EMN associated with levodopa-carbidopa treatment for PD. However, this may be because of the absence of close dermatologic monitoring and relatively presumed benign course of the disease.[5] The development of EMN is likely multifactorial in which a combination of genetics, immunosuppression, and hormone dysregulation play a role in its progression. Current understanding suggests that immunosuppression, *BRAF V600E* mutations, and increased nevi are all risk factors for melanoma.[5] Until there is a better understanding of the pathogenesis of EMN, closer surveillance of patients starting immunosuppressive therapies should be considered. Patients who have EMN should have nevi assessed for senescence status and level of growth arrest, which may lead to a better understanding of the association, if any, between EMN and melanoma.

REFERENCES

1. Binder B, Ahlgrimm Siess V, Hoffman-Wellenhof R. Eruptive melanocytic nevi of the palms and soles in a patient with Crohn disease. *J German Soc Dermatol*. 2006;4(6):486-488.
2. Vena G, Fargonoli C, Cassano N, Argenziano G. Drug-induced eruptive melanocytic nevi. *Exp Opin Drug Metab Toxicol*. 2016; 13(3):293-300.
3. Kim D, Lee J, Koo D, Jung K. Eruptive melanocytic nevi with satellite lesions following insulin treatment in a girl with type 1 diabetes mellitus. *J Dermatol*. 2015;42:547-548.
4. Inzelberg R, Flash S, Friedman E, Azizi E. Cutaneous malignant melanoma and Parkinson disease: common pathways? *Ann Neurol*. 2016;80:811-820.
5. Perry B, Nguyen A, Desmond B, Blattner C, Thomas S, Young J. Eruptive nevi associated with medications (ENAMs). *J Am Acad Dermatol*. 2016;75(5):1045-1052.
6. Margolesky J, Singer C. Extended-release oral capsule of carbidopa-levodopa in Parkinson disease. *Ther Adv Neurol Disord*. 2018;11:1756285617737728.
7. D'Mello S, Finlay G, Baguley B, Askarian-Amiri M. Signaling pathways in melanogenesis. *Int J Mol Sci*. 2016;17(7):1144.
8. John J, Smalley K. Identification of BRAF mutations in eruptive melanocytic nevi: new insights into melanomagenesis? *Expert Rev Anticancer Ther*. 2011;11(5):711-714.