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CASE REPORT OPEN ACCESS

Cutaneous Pigmentary Changes During Setmelanotide Therapy: Dermoscopic and Confocal Findings in Two Patients

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ABSTRACT

Setmelanotide is a melanocortin-4 receptor agonist approved for the treatment of rare forms of genetic obesity. Through off-target activation of the melanocortin-1 receptor, it may induce cutaneous pigmentation changes; however, data regarding its effects on melanocytic nevi remain limited. We report two young patients with different skin phototypes who developed distinct pigmentary patterns during setmelanotide therapy. The first case involved a Caucasian girl (Fitzpatrick phototype III) who experienced rapid-onset pigmentary and architectural changes in multiple melanocytic nevi, clinically and dermoscopically mimicking melanoma. Reflectance confocal microscopy was performed, and two nevi were excised, with histopathology excluding malignancy; the lesions progressively regressed after treatment discontinuation. The second case involved a patient with Fitzpatrick skin phototype V who developed diffuse skin, nail, and mucosal hyperpigmentation, resulting in generalised darkening of the entire skin surface consistent with Fitzpatrick phototype VI, without any clinical or dermoscopic changes in pre-existing nevi. These cases highlight the heterogeneity of cutaneous pigmentary responses to setmelanotide and underscore the importance of close dermatologic monitoring, including dermoscopy and reflectance confocal microscopy (RCM), to accurately interpret therapy-induced changes.

Setmelanotide, a melanocortin-4 receptor agonist approved for rare genetic obesity, may induce pigmentation through off-target melanocortin-1 receptor activation. We describe two patients who developed distinct pigmentary changes during therapy: melanoma-like darkening and architectural changes of multiple melanocytic nevi in one patient, and diffuse skin, nail, and mucosal hyperpigmentation in the second. These cases underscore the heterogeneity of setmelanotide-induced pigmentation and the importance of dermatologic monitoring, including dermoscopy and reflectance confocal microscopy.

1 | Introduction

Setmelanotide is a selective melanocortin-4 receptor (MC4R) agonist approved for the treatment of rare forms of monogenic and syndromic obesity associated with impaired leptin–melanocortin signalling. In this pathway, proopiomelanocortin (POMC)-derived peptides activate several melanocortin receptors, including MC4R in the hypothalamus, which regulates appetite, and melanocortin-1 receptor (MC1R) in melanocytes, which controls skin pigmentation.

Although setmelanotide selectively targets MC4R, it may also activate the closely related MC1R as an off-target effect. This interaction has been proposed as a mechanism underlying treatment-related pigmentary changes, typically described as

generalised skin darkening or localised hyperpigmentation at injection sites.

However, the impact of setmelanotide on melanocytic nevi remains poorly characterised, and only isolated reports have described nevus darkening or atypical clinical features during therapy [1]. In this context, distinguishing benign, drug-induced pigmentary changes from true melanocytic dysplasia or melanoma may represent a relevant diagnostic challenge.

We report two cases of setmelanotide-induced pigmentary changes showing distinct clinical patterns in patients with different skin phototypes, highlighting the variability of cutaneous responses and the role of dermoscopy and RCM in clinical management.

1.1 | Case Reports

Case 1: A 20-year-old Caucasian woman (Fitzpatrick type III) with severe hypothalamic obesity (BMI 33,83) following craniopharyngioma resection was initiated on setmelanotide in April 2025, achieving early appetite reduction and weight loss. Dermatologic follow-up at 3 months, however, revealed a rapid increase in the number of melanocytic nevi and new pigmentary and architectural changes in pre-existing ones (Figure 1C) along with pigmentation of the dorsal hands and lower eyelids (Figure 1A,E). Several nevi appeared irregular, and dermoscopy showed increased pigmentation with atypical network, radial streaks and white–blue veil, raising suspicion for melanoma with spitzoid appearance (Figure 2A,C,E,G). RCM revealed hyper-reflective basal keratinocytes, scattered spindle cells at the epidermis and dermo-epidermal junction with Spitz-like appearance, but an otherwise regular junctional architecture and few dendritic cells on the epidermis (Figure 2B). Two clinically and dermoscopically suspicious lesions were excised, and histopathology confirmed compound melanocytic nevi. Thus, treatment was initially continued under close dermatologic follow-up. However, considering the persistence and further darkening of the lesions, the patient discontinued setmelanotide in July 2025. At the follow-up visit in August 2025 and November 2025, a progressive fading of the nevi was observed (Figure 1D), together with decreased pigmentation of the eyelids and dorsal hands (Figure 1B,F) and regression of atypical dermoscopic structures (Figure 2D,F,H).

Case 2: A 17-year-old African girl (Fitzpatrick type V), treated with setmelanotide for post-craniopharyngioma hypothalamic obesity (BMI 54,90), developed severe pigmentation of the entire skin surface, consistent with the Fitzpatrick VI phenotype (Figure 3A,B). Hyperpigmentation also involved nails, with diffuse darkening of the nail folds, and oral mucosa, where multiple punctate pigmented macules were evident, especially on the tongue (Figure 2C–E). Despite these widespread pigmentary changes, all pre-existing nevi exhibited neither dermoscopic alterations nor an increase in number. At the 6-month follow-up visit, the patient was still on setmelanotide therapy, although administered discontinuously because she experienced difficulty with the injections. The hyperpigmentation persisted without significant changes.

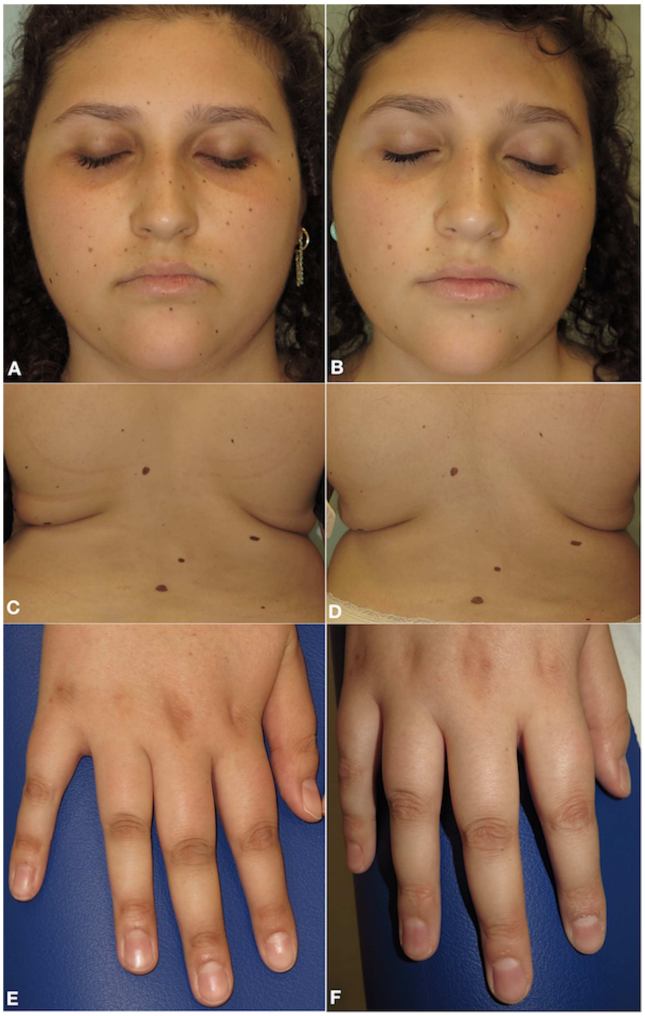

FIGURE 1 | Clinical images showing hyperpigmentation during setmelanotide therapy of the eyelids (A), nevi (C), and dorsal hands (E). Reduction in pigmentation after discontinuation of setmelanotide is observed in the eyelids (B), nevi (D), and dorsal hands (F).

2 | Discussion

Setmelanotide has been associated with cutaneous pigmentary changes in clinical trials and safety reports, most frequently described as generalised darkening or localised pigmentation at injection sites. [1–3] Given that the melanocortin-1 receptor (MC1R) plays a central role in the regulation of melanogenesis and melanocyte biology, its off-target activation by setmelanotide may enhance eumelanin production and potentially influence melanocytic activity, leading to clinically apparent darkening of pre-existing nevi. Evidence regarding its effects on melanocytic nevi remains extremely limited, with only a few isolated reports describing nevus darkening or atypical-appearing lesions during therapy [2, 4]. It remains unclear whether these findings represent true dysplasia or increased melanin in otherwise benign structures.

In our first case, the sudden clinical evolution together with several atypical dermoscopic features raised concern for melanoma. RCM, however, did not reveal significant cytologic or architectural atypia. Histopathology confirmed the absence of melanocytic dysplasia, supporting the hypothesis that setmelanotide may accentuate pigmentation without “inducing” melanoma.

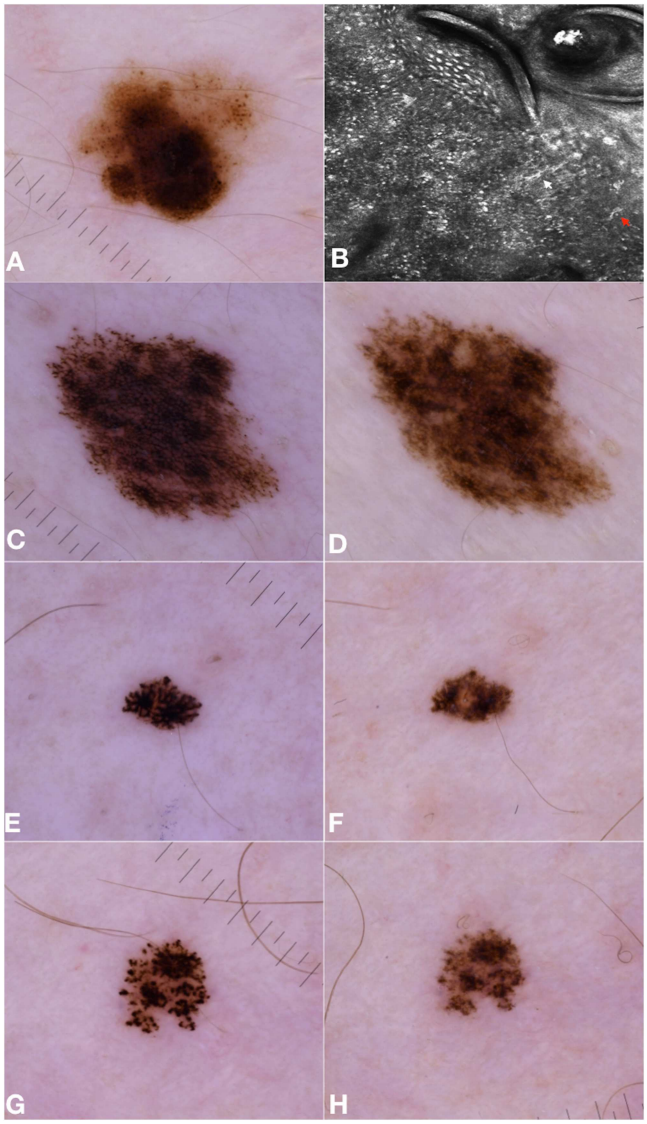

FIGURE 2 | Dermoscopic and reflectance confocal microscopy features of nevi during setmelanotide therapy. (A) Dermoscopy of a nevus showing hyperpigmentation and asymmetry, including asymmetrically distributed peripheral globules. (C, E, G) Dermoscopy of nevi showing hyperpigmentation, atypical pigment network, radial streaks, and a white–blue veil. (B) Reflectance confocal microscopy of nevus in (E), revealing hyper-reflective basal keratinocytes, scattered spindle-shaped cells (red arrow), and few dendritic cells (white arrow) within the epidermis. (D, F, H) Progressive fading of the nevi is observed after discontinuation of setmelanotide therapy, together with regression of atypical dermoscopic structures.

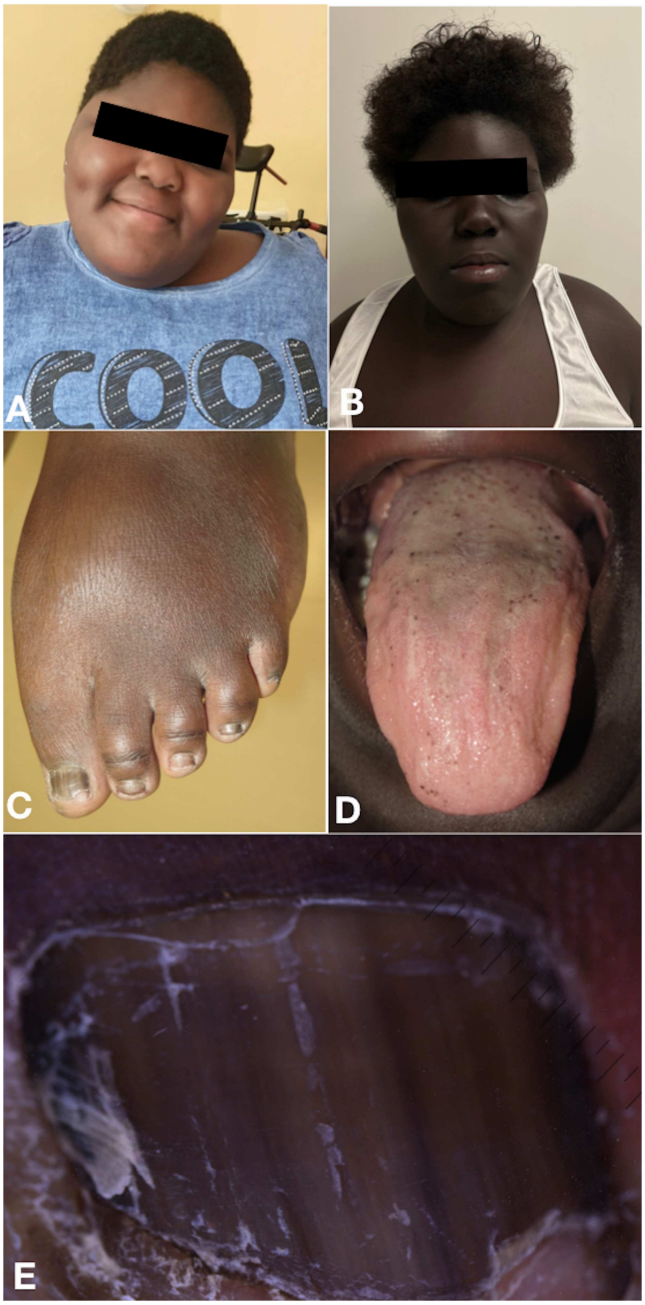

FIGURE 3 | Clinical appearance of the patient before (A) and during (B) setmelanotide therapy, showing diffuse darkening of the entire skin surface, consistent with a Fitzpatrick skin phototype VI. Hyperpigmentation of the nail folds (C) and punctate macules on the tongue and oral mucosa (D) are also observed. Onychoscopy of the nail fold showing hyperpigmentation (E).

Conversely, the second patient exhibited a different pattern, with diffuse and homogeneous darkening of the entire skin surface, including mucosae and nails, without clinical or dermoscopic changes in nevi. These contrasting phenotypes highlight the heterogeneity of pigmentary responses to setmelanotide and their variability across patients and phototypes.

A recent review discussing chronic MC1R activation reported two cases of melanoma in patients treated with setmelanotide [5]. However, both patients carried multiple melanoma risk factors—such as fair phototype and significant cumulative UV exposure—making a causal relationship with the drug highly uncertain. Currently, there is no evidence that setmelanotide promotes melanoma, and current observations—including ours—indicate that its effect appears limited to pigmentary changes, reversible after discontinuation. Although larger clinical datasets and longer follow-up are needed to clarify the cutaneous safety profile of setmelanotide, close dermatologic monitoring with baseline and serial dermoscopy—and confocal microscopy when available—remains essential.

Author Contributions

Martina Cavicchi, Claudia Lasagni, and Caterina Longo contributed to the conception and design of the study. Martina Cavicchi, Claudia Lasagni, and Francesca Giusti were responsible for clinical data acquisition. Silvana Ciardo and Martina Cavicchi performed dermoscopic and reflectance confocal microscopy analyses. Albino Eccher carried out the histopathological evaluation. Martina Cavicchi drafted the manuscript. All authors contributed to data analysis and interpretation, critically revised the manuscript for important intellectual content, and approved the final version.

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The authors have nothing to report.

Ethics Statement

The parents/guardians of minor patients have given written informed consent for their child's participation in the study, as well as for the use of their child's case details (including photographs) for publication. Adult patients in this manuscript have given written informed consent for participation in the study and the use of their case details (including photographs) for publication. Ethical Approval: not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Supporting File: jvc270366-sup-0001-Short_Abstract_Setmelanotide.docx.