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Case Report

Development of Dysplastic Nevi in a Child with *LEPR* Deficiency Treated with Setmelanotide

Nursoy H et al. Skin Changes with Setmelanotide Treatment

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What is already known on this topic?
Setmelanotide may induce hyperpigmentation through stimulation of melanocortin-1 receptors. Regular dermatological monitoring is recommended for patients receiving this treatment.

What does this study add?
Dysplasia may develop in pre-existing nevi during setmelanotide treatment. Our case is the first reported in the literature with this finding in a pediatric patient with *LEPR* deficiency.

Abstract
Setmelanotide is a recently approved medication for patients over two years of age with monogenic obesity that emerges from *POMC, LEPR*, *PCSK1* mutations, or Bardet-Biedl syndrome. While primarily targeting melanocortin-4 receptors (MC4R), setmelanotide also weakly stimulates melanocortin-1 receptors (MC1R), which may affect pigmentation. Clinical outcomes of this treatment modality remain limited due to the rarity of disorders mentioned above. We present a 12-year-old boy with a homozygous *LEPR* mutation who experienced skin hyperpigmentation shortly after the initiation of setmelanotide treatment. By the third month of treatment, gradual darkening of nevi was noted. At six-month follow-up, two nevi were excised due to pigmentation changes, and histopathology revealed dysplastic features in both. This case raises concerns about potential MC1R-mediated melanocytic activity during setmelanotide treatment. Therapy was temporarily discontinued. To our knowledge, this is the first reported pediatric case with *LEPR*-related monogenic obesity developing dysplastic nevi during setmelanotide use.
Keywords: Monogenic obesity, LEPR, setmelanotide, melanoma, dysplastic nevi

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Introduction

Setmelanotide is a melanocortin-4 receptor (MC4R) agonist approved for the treatment of monogenic obesity in patients with genetic variants involving the *POMC, LEPR,* and *PCSK1* genes, as well as in individuals diagnosed with Bardet-Biedl syndrome (1, 2). Setmelanotide primarily activates the melanocortin-4 receptor (MC4R), but it also weakly stimulates the melanocortin-1 receptor (MC1R), which may lead to changes in skin, hair, and nevus pigmentation (3). While it effectively achieves weight loss and improves metabolic parameters, it is also associated with various side effects. The most common side effects include skin hyperpigmentation, nausea, and injection site reactions (2, 4). Some patients may report darkening in the color of pre-existing nevi and hair (5). Malignant melanoma or its precursor lesions may rarely develop; however, the number of reported cases remains limited (3). Most side effects are tolerable and tend to improve with continued use. However, the occurrence and severity of side effects may vary among individuals (6).

Here, we present a 12-year-old boy with monogenic obesity due to a homozygous c.2929G>T variant in the *LEPR* gene, who developed dysplastic nevi during the sixth month of setmelanotide treatment.

Case Report

The patient was born at term via spontaneous vaginal delivery, weighing 3700 grams. His first clinical evaluation was at 7 months of age, at which time his weight was 19 kg (+7.4 SD), his height was 75 cm (1.7 SD), and his BMI was 33.2 kg/m² (+7.2 SD). At the age of 2 years, a homozygous variant (c.2929G>T, NM_002303.3) was identified in the *LEPR* gene. Both parents, who are consanguineous, were found to be heterozygous carriers of this variant. The LEPR c.2929G>T (p.Glu977) variant results in a premature stop codon, which is expected to cause loss of function in a gene where this is a known disease mechanism. Additionally, the variant is not reported in major population databases such as gnomAD, supporting its rarity and potential clinical significance in the context of a recessive disorder. Based on these findings, the variant has been classified as likely pathogenic according to ACMG guidelines.

Setmelanotide was initiated at a dose of 1 mg/day when the patient was 12 years and 1 month old. At treatment initiation, his weight was 94.8 kg (+3.34 SD), his height was 155,6 cm (+0.53 SD), and his BMI was 39.16 kg/m² (+3.37 SD). As skin hyperpigmentation is an expected side effect, a dermatological evaluation was performed prior to treatment, and the patient's nevi were mapped. There was no family history of melanoma or dysplastic nevi. The first follow-up was conducted two weeks after treatment initiation, at which point increased skin pigmentation was noted. The patient also reported abdominal pain and nausea, which subsided over the following weeks. Due to issues with drug availability, a one-month interruption occurred after the second month of treatment. By the third month, the dose was titrated to the full therapeutic dose of 3 mg per day.

At the third month of treatment, darkening was observed in previously identified and monitored nevi. As a result, the dermatology follow-up interval, initially scheduled every 6 months, was shortened to every 3 months. In the sixth month of treatment, excision was recommended for two nevi, one on the right side of the umbilicus (Figures 1 and 2) and the other on the right axilla, due to progressive pigmentation and structural changes observed on dermoscopy. Punch biopsies were performed on both lesions. Histopathological assessment of the excised lesions revealed

a dysplastic compound nevus characterized by elongation and bridging of the rete ridges, consistent with architectural disorder (Figure 1). At higher magnification, nests of nevoid melanocytes were observed at the tips of the rete ridges (Figure 2). The presence of architectural irregularity and mild cytologic atypia is consistent with low-grade dysplasia. Immunohistochemical analysis of the axillary lesion showed PRAME negativity, no pagetoid spread in MART-1 staining, superficial HMB-45 positivity, and diffuse p16 expression—findings consistent with a dysplastic nevus rather than melanoma (Figure 3). No immunohistochemical staining was performed for the lesion on the right side of the umbilicus due to less suspicious histopathological features.

As of the latest evaluation, the patient had received setmelanotide for 7 months, resulting in an average weight loss of approximately 0.5 kg per week, corresponding to a 13.7% reduction from baseline (Figures 6 and 7). His most recent weight was 81.8 kg (+2.49 SD), his height was 158.9 cm (+0.34 SD), and his BMI was 32.4 kg/m² (+2.63 SD). A multidisciplinary evaluation involving pediatric endocrinology, dermatology, and pathology was conducted. Following a detailed discussion with the family regarding available options, it was decided to temporarily discontinue the treatment due to the presence of dysplastic nevi. Since the initial biopsies were performed using the punch technique, complementary excision of the dysplastic nevi has been planned to ensure complete removal.

Discussion

Here, we present a case report of a patient with a *LEPR* gene variant, in whom a dysplastic nevus was detected in the 7th month of setmelanotide treatment, leading to discontinuation of therapy. The patient had been receiving the medication at the maximum dose of 3 mg/day for the past 4 months. Before treatment initiation, nevus mapping had been performed, and the patient was under close dermatological surveillance.

Under normal conditions, activation of the MC1R is essential for regulating melanocyte proliferation and melanin synthesis, which together help protect the skin against ultraviolet (UV) radiation. MC1R signaling promotes the production of two types of melanin: eumelanin, a dark brown/black pigment that blocks UV radiation, and pheomelanin, a yellow/red pigment. Upon UV exposure, melanocytes shift melanin synthesis in favor of eumelanin. Increased eumelanin production leads to darkening of the skin and of pre-existing nevi—benign lesions composed of melanocyte clusters. This mechanism also provides a rationale for the close dermatologic monitoring of patients receiving setmelanotide, which has been shown to exert mild off-target activation of MC1R (3, 7). In phase 3 clinical trials, melanocytic nevi were reported in 17 out of 92 patients (18.4%) who received setmelanotide. However, the development of melanoma or dysplastic nevi was not reported (8-10).

Melanoma has been reported in two male patients with Bardet-Biedl syndrome receiving setmelanotide treatment. Both had fair skin and a history of high UV exposure, placing them at an already elevated risk for melanoma. One was diagnosed in the third year of treatment, and the other in the sixth month (3). Our patient also has fair skin (Fitzpatrick Skin Type III); however, he had no history of significant UV exposure, and the dysplastic nevi were located in areas of the body not typically exposed to sunlight.

Similarly, in a female patient in her twenties with hypothalamic obesity and hypopituitarism secondary to craniopharyngioma, eruptive dysplastic melanocytic nevi were detected at the 14th week of setmelanotide treatment. The therapy was continued under close dermatologic surveillance. Long-term follow-up data for this patient are not yet available (11). In our patient, a dysplastic nevus was also identified; however, due to the lack of sufficient evidence and established guidelines, treatment was temporarily discontinued following a multidisciplinary discussion involving dermatology, pathology, and the patient's family. Table 1 summarizes reported cases of patients who developed dysplastic nevi or melanoma while receiving setmelanotide therapy.

Real-world data on the development of dysplastic nevi and melanoma in patients receiving setmelanotide are quite limited. Therefore, identifying individual risk factors—such as UV exposure, geographic location, skin type, medication dose, baseline weight, and duration of treatment—is essential for establishing an appropriate monitoring plan.

Conclusion

Skin hyperpigmentation is the most common side effect of setmelanotide, but there is limited information on how to manage it especially when dysplastic lesions are found. Therefore, standard protocols are needed. Regardless, all patients receiving setmelanotide should undergo regular dermatological evaluations, including baseline nevus mapping before treatment initiation. As a final remark, since our study is observational in nature, further research is required to clarify the causal relationship between setmelanotide use and the development of dysplastic nevi.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Author Contributions

Hatice Nursoy: Conceptualization, Investigation, Writing – Original Draft
Yasemin Denkboy Öngen: Writing – Original Draft, Review & Editing
Ferdi Öztürk: Resources, Visualization (dermatoscopic images), Review & Editing
Şaduman Balaban Adım: Resources, Visualization (pathology images), Review & Editing
Erdal Eren: Supervision, Writing – Review & Editing

Ethical Approval

Written informed consent was obtained from the patient and the parents.

AI Assistance Disclosure

During the preparation of this case report, the authors used OpenAI's ChatGPT to support the drafting and editing of certain sections, including language refinement and summarization of related literature. The content generated by the AI was critically reviewed, edited, and verified by the authors to ensure accuracy, clinical relevance, and scientific integrity. Full responsibility for the final content of the manuscript rests solely with the authors. The use of this tool contributed to improving the clarity of expression and the efficiency of the writing process.

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Table 1: Patients reported to have developed dysplastic nevi or melanoma while receiving setmelanotide treatment (3, 10).

	Age/Gender	Primary diseases	Diagnosis	Fitzpatrick skin type	UV/Sun Exposure	Duration of setmelanotide treatment	Discontinuation of treatment
Case 1	N/A	Bardet-Biedl Syndrome	Stage pT1a melanoma	Type II	Yes	3 years	N/A
Case 2	N/A	Bardet-Biedl Syndrome	Stage pT1a melanoma	Type II	Yes	6 months	N/A
Case 3	20s/Female	Hypothalamic obesity and panhypopituitarism due to craniopharyngioma	Eruptive melanocytic dysplastic nevi	N/A	N/A	14 weeks	No

Figure 1. Dermoscopic image of the nevus on the right side of the umbilicus before treatment

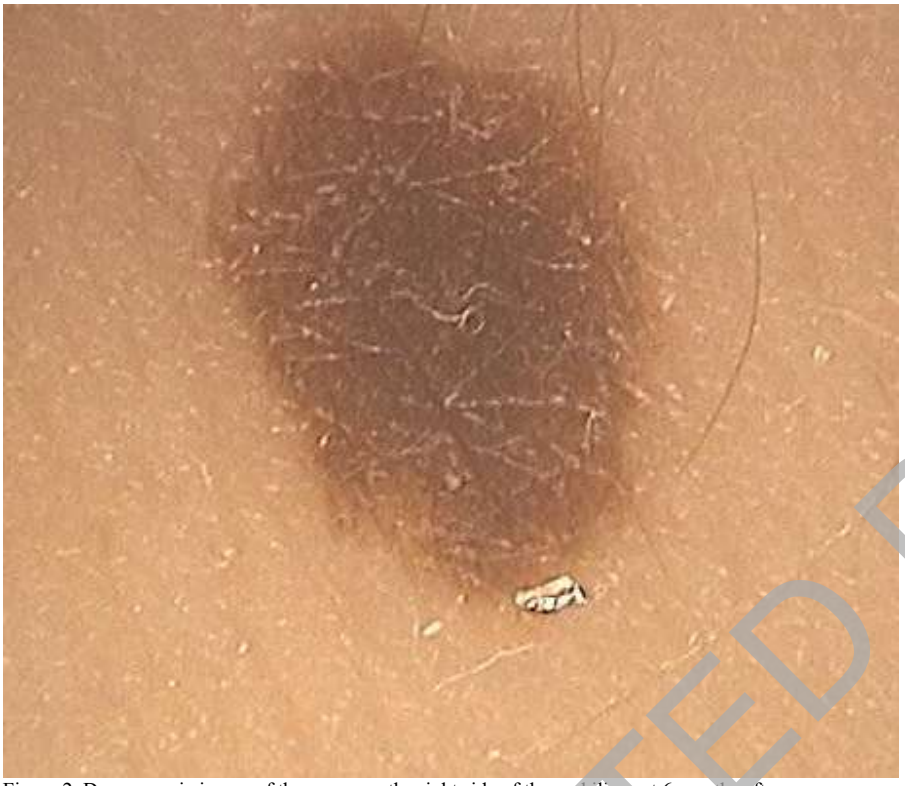

Figure 2. Dermoscopic image of the nevus on the right side of the umbilicus at 6 months after treatment

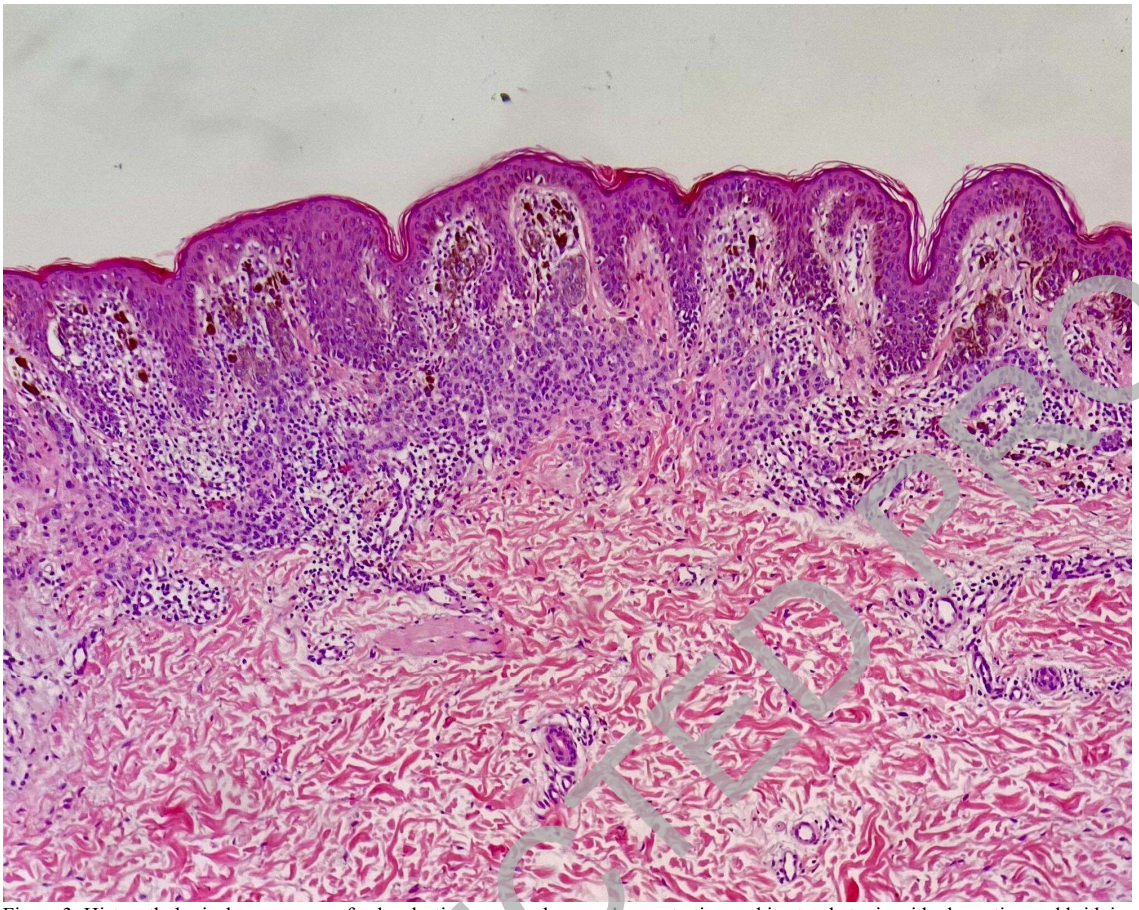

Figure 3: Histopathological appearance of a dysplastic compound nevus demonstrating architectural atypia with elongation and bridging of rete ridges, shown in Hematoxylin and Eosin staining at ×100 magnification.

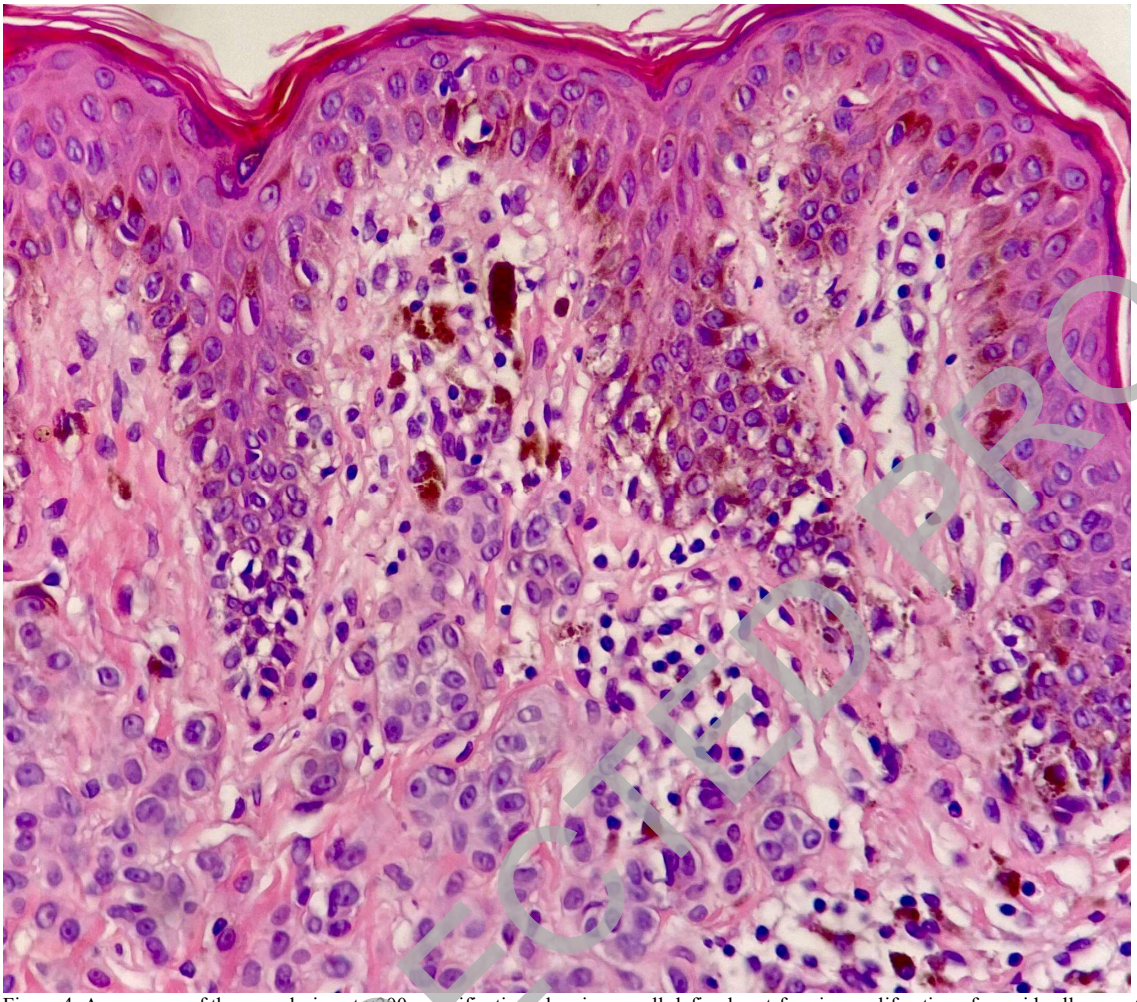

Figure 4: Appearance of the same lesion at ×200 magnification, showing a well-defined nest-forming proliferation of nevoid cells accentuated at the tips of the rete ridges.

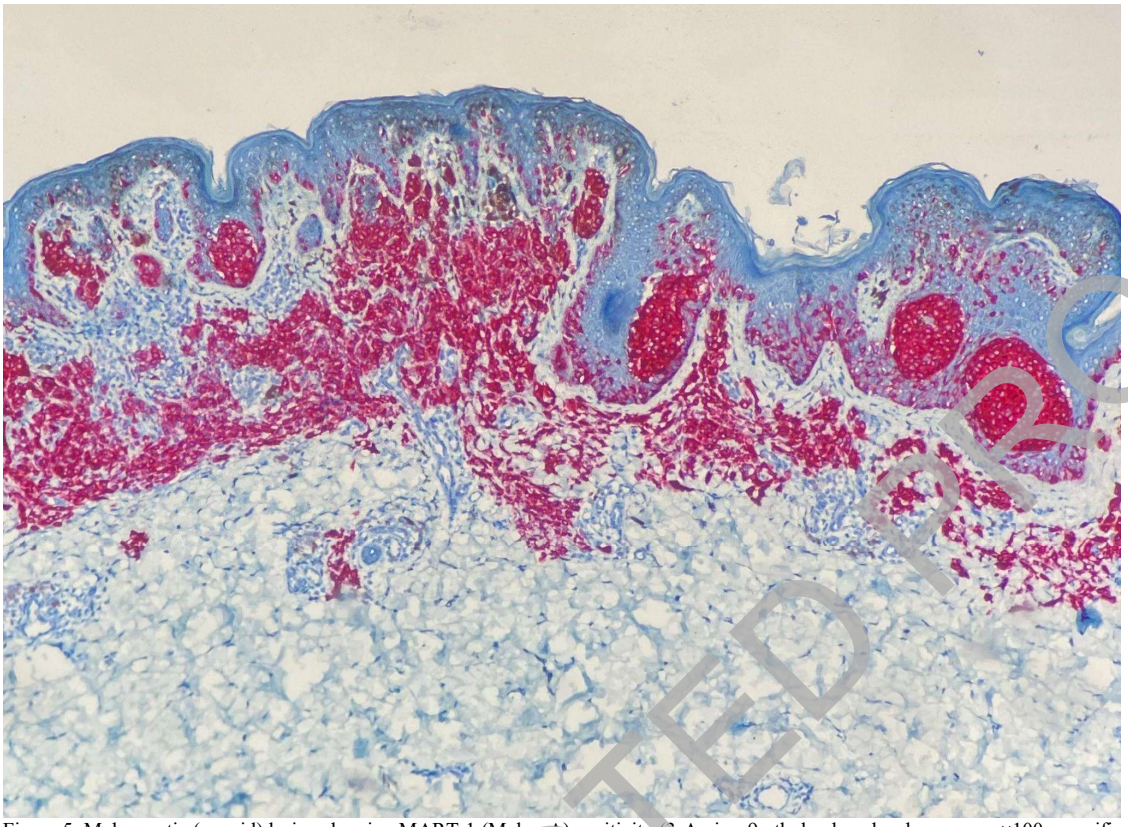

Figure 5: Melanocytic (nevoid) lesion showing MART-1 (Melan-A) positivity (3-Amino-9-ethylcarbazole chromogen, ×100 magnification)

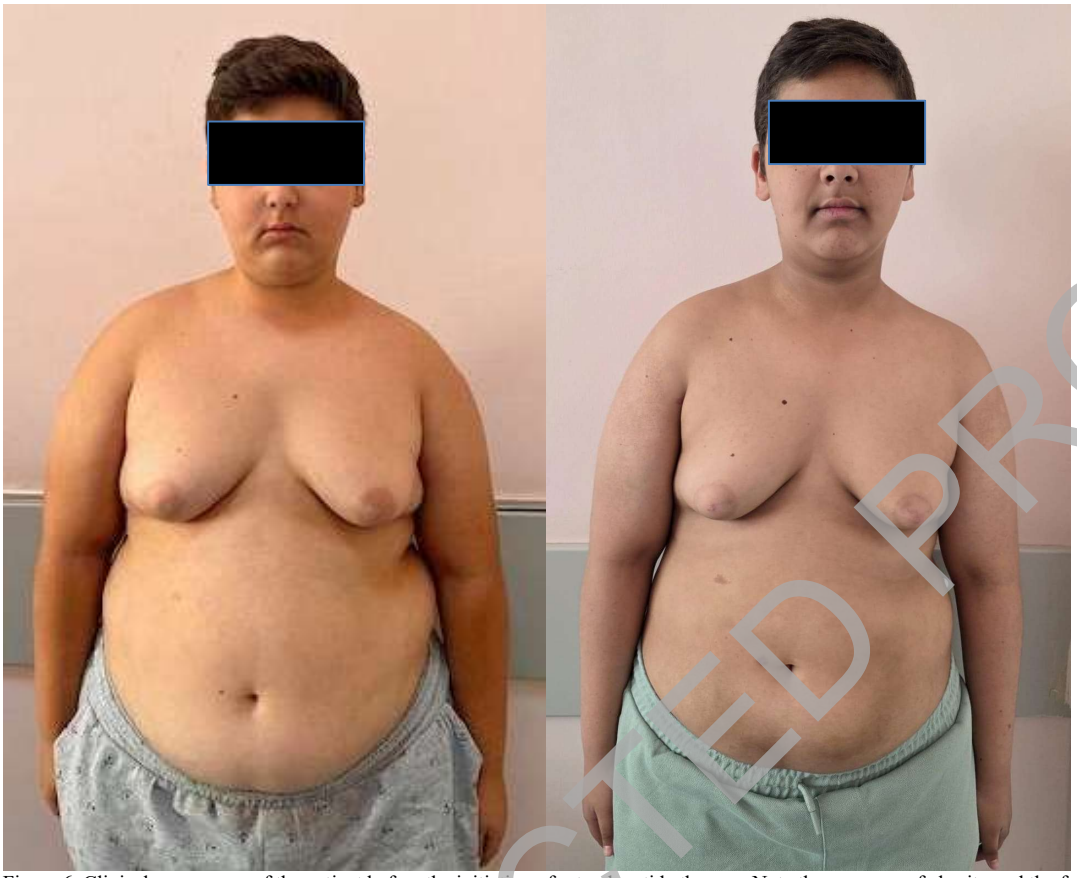

Figure 6. Clinical appearance of the patient before the initiation of setmelanotide therapy. Note the presence of obesity and the fair skin phenotype.

Figure 7. Clinical appearance at the 7th month of setmelanotide treatment. Approximately 13.7% weight loss is observed, along with increased skin pigmentation.