Case report

**Eruptive Nevi Associated with Estrogen-Progestin Therapy: A Unique Case Report**

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ABSTRACT

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| **Background:** Eruptive nevi represents a quite rare dermatological phenomenon with a sudden onset of multiple melanocytic nevi over a short period of time. **Objective:** To describe a unique case of eruptive nevi developed along with estrogen-progestin therapy; and to consider the clinical significance of this case and possible hormonal aetiology. **Methods:** This is a single case report detailing the rapid development of around fifty new melanocytic nevi during the course of three months in an 18-year-old girl, concurrent with the commencement of estrogen-progestin therapy. The nevi were evaluated clinically and dermoscopically, and laboratory investigations were undertaken to rule out systemic illness or malignancy. **Results:** The nevi had symmetrical distribution, uniform pigmentation, and benign dermatoscopic features. There were no other signs of either systemic illness or malignancy. It became noticeable after discontinuation of estrogen-progestin therapy that no new moles appeared within the six-month follow-up period. **Limitations:** This is a single-case study; therefore, generalizability is limited. There remain some speculative issues in the pathophysiological connection between estrogen-progestin treatment and nevogenesis. **Conclusion:** This case report highlights the potentiality of estrogen-progestin treatment to cause eruptive nevi and urges consideration of all such hormonal factors by clinicians in similar cases. |

***Keywords:*** *Eruptive nevi, Estrogen-progestin therapy, Melanocytic proliferation, Hormonal factors, Cutaneous manifestations*

1. INTRODUCTION

Eruptive nevi represents an unusual dermatological occurrence marked by the sudden development of multiple melanocytic nevi in a fairly short time. These eruptions are generally induced by triggers such as immunosuppression, chemotherapy, or hormonal changes; however, the exact underlying mechanisms are not entirely understood. Hormonal factors, with particular emphasis on the estrogen and progesterone connection, were implicated in selected cases and, thus, might have a part to play in the stimulation of melanocytic proliferation[1]. Melanocytic nevi are benign proliferations of melanocytic cells said to be arranged in nests in the epidermis, dermis or other tissues of the body [9]. The lesions are usually dark brown to black in colour. Eruptive melanocytic nevi resulting in hundreds of nevi is a rare phenomenon with largely unclear pathogenesis. Mutations in NRAS, HRAS, and BRAF have been identified in activating the mitogen-activated protein kinase pathway, resulting in the development of benign nevi[6-8]. Here, a unique case of eruptive nevi associated with the use of estrogen-progestin therapy is reported highlighting the importance of recognizing this rare adverse effect in clinical practice.

2. Presentation of case

An 18-year-old girl, with no history of medical illness, presented to us with complaints of multiple dermal nevi that had formed over three months. She was put on estrogen-progestin therapy for the treatment of a menstrual cycle-related problem. The nevi started to appear concurrently with this treatment. The patient denied earlier incidents of any similar lesions and stated that she had normal skin with a few nevi before treatment prior to initiation of therapy.

About 50 melanocytic nevi distributed over the face, trunk, limbs and Palmoplantar region were revealed in clinical examination. The lesions were symmetric, uniformly pigmented, and ranged from 3 to 7 mm. Dermoscopic examination showed features described as typical for benign lesions, including a homogenous brown pigmentation and regular borders. Features of atypical lesions or malignancy were not observed.

The patient denied fever, weight loss, fatigue, or systemic sickness. Blood lab tests such as the complete blood count, liver function tests, and thyroid profile were within the norm. The HIV test was negative. Beta-hCG was also performed and found to be negative. No family history of melanoma or any previous skin ailment. Because of the close time between the first incidence of nevi and the beginning of treatment, a diagnosis of estrogen-progestin-induced eruptive nevi was made. The patient was counselled on the benign nature of the condition, with regular dermatological follow-ups.

In consultation with gynaecologists, the treatment was discontinued. At the six-month follow-up, no new nevi were observed.

To distinguish eruptive nevi associated with medications (ENAM) from acquired melanocytic nevi, the authors suggest the following set of criteria:[4]

-Development of more than 5 palmoplantar melanocytic nevi at any age.

-Development of more than 10 melanocytic nevi bodywide outside of puberty or pregnancy.

-Development of more than 20 melanocytic nevi bodywide during puberty or pregnancy

The authors also suggest categorizing ENAMs based on the specific medications involved. Applying these criteria, they identified a total of 66 reported cases of ENAM. Thiopurines, including azathioprine and 6-mercaptopurine, were the most commonly associated drugs, accounting for 34.8% of cases. Notably, cases reported in the last decade represent 66.2% of all documented instances in the literature, with 44.2% of these linked to biological therapies.

Based on these criteria, combined estrogen-progestin therapy was identified as the likely primary cause of the eruption of nevi in our patient. To our knowledge, no similar cases have been reported in the literature, making this the first documented instance of nevi eruption associated with estrogen-progestin therapy.

3. discussion

Eruptive nevi constitutes a condition initially described by Hutchinson in 1868 as a shocking episode that results in the development of multiple melanocytic nevi over several weeks to months, usually provoked by an underlying factor[2]. It used to be spontaneously associated with severe blistering dermatoses (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, pemphigoid, or epidermolysis bullosa). Moreover, EMN has also been reported following exposure to toxic agents such as sulfur mustard gas.[3]

The links of EMN to certain conditions comprising immune system compromise have been published. These include a series of renal transplantations, bone marrow transplantations, malignancies, and HIV/AIDS. Rare instances of eruptive nevi have been described in the setting of primary adrenal insufficiency, injury, cutaneous mastocytosis, Langerhans cell histiocytosis, or by psoralen with concomitant ultraviolet therapy.

Eruptive nevi are an uncommon type of condition that can be found to pose a diagnostic challenge due to their sudden appearance and widespread distribution. Their development in the setting of estrogen-progestin therapy demonstrates the potential that hormonal factors may play in modulating the activity of melanocytes. Estrogen and progesterone, known to influence the biology of the melanocytes, exert their effects through interactions with certain hormonal receptors expressed on melanocytes. This may well lead to stimulation of melanin production and the proliferation of melanocytes, and thus the appearance of new nevi.[1]

Since this patient began estrogen-progestin therapy with an associated sudden appearance of multiple nevi, the possibility of causation might be entertained. Since there is substantial evidence for hormones being involved in melanocytic proliferation, there are estrogen and progesterone receptors in congenital melanocytic nevi, according to Ellis et al. These lesions could be subjected to hormonal influence. Also, in the skin, melanocytic nevi, and malignant melanomas, expression of progesterone receptor beta has indicated that estrogen receptors are found in these tissues, thus supporting estrogen's potential role in melanocytic biology. [1]

While the exact mechanism of estrogen and progesterone-inducing nevogenesis remains unclear, such hormones could promote the proliferation of affected melanocytes by receptor-mediated pathways. The sudden appearance of nevi after the institution of a hormonal regimen in this patient also has implications for the clinician and raises awareness about this possible complication.[5]

The differential diagnoses for eruptive nevi include dysplastic nevus syndromes, melanoma metastases, and certain genodermatoses like familial atypical multiple mole and melanoma syndrome (FAMMM), with the rapid appearance of numerous lesions also being an indicator that makes ENAM more likely. However, based on the absence of atypical features on dermoscopy and a benign clinical picture in our patient, these differential diagnoses can be ruled out. Also, the lack of systemic symptoms and laboratory abnormalities made systemic diseases unlikely.

Excision of eruptive nevi requires patient education and routine surveillance. Inasmuch as most are benign, periodic dermatological evaluations are essential to ascertain any changes presaging malignancy. In this particular case, responsibility for a decision regarding estro-progestin therapy, whether to continue or to discontinue, was left up to the patient after a discussion of the risks and benefits.

4. Conclusion

The case illustrates a rare but important cutaneous manifestation of estrogen-progestin therapy. Even though the precise pathophysiological mechanism is still unknown, this report emphasizes the necessity for clinicians to consider hormonal factors when patients present with eruptive nevi. Identification of this association is critical to appropriate counselling and regular monitoring, thus avoiding undue panic and intervention. Further studies shall be needed to elucidate the mechanisms by which hormones may induce melanocytic proliferation and better understand the history of eruptive nevi.

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