# ERUPTIVE MELANOCYTIC NEVI

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**Summary**

*Eruptive melanocytic nevi (EMN) is defined as the sudden development of multiple nevi during a variable time period associated with different conditions. Most cases have been reported in the last 10 years, probably due to increased use of biological therapies and other immunosuppressants for the treatment of psoriasis, intestinal bowel disease, rheumatoid arthritis and hematologic malignancies and due to a rise in organ transplantation. Other associated conditions were also reported such as blistering diseases, solid organ malignancies, insulin therapy, use of α-MSH synthetic analogues, AIDS. The pathogenesis of eruptive melanocytic nevi is not completely understood. Several theories try to explain the mechanism that lead to the development of this condition: altered immune surveillance, genetic factors and a direct effect of medications. The evolution of EMN is mainly determined by the course of the underlying associated condition. Reports show that reverse of immunosuppression leads to a decrease in size and colour fading of the existing nevi. Lesions may also have the potential to evolve into dysplastic nevi, therefore long-term follow-up is recommended. Additional studies are required on this matter to better understand the prognosis and to develop a management strategy.*

***Key words:*** *eruptive melanocytic nevi, immuno-suppression, melanoma, biologic therapies.*

*Received: 29.11.2017* *Accepted: 16.01.2018*

## Introduction

Eruptive melanocytic nevi (EMN) is defined as the sudden development of multiple nevi during a variable time period associated with different conditions. Currently there is no consensus regarding the definition of this pathology. This term was first introduced by Sir Hutchinson in 1868 [1].

For EMN related to medication use Perry et al proposed a set of diagnostic criteria. The development of at least 1 of the following features during a 6-month period is considered to define the association between eruptive nevi and drug use:

1) more than 5 melanocytic nevi on acral surfaces at any age

2) more than 10 melanocytic nevi outside pregnancy or puberty

3) more than 20 melanocytic nevi in the course of pregnancy or puberty [2].

## Epidemiology

Several medical conditions have been reported in association with EMN, most common in transplant recipients undergoing immunosuppressive therapy (Table 1). It can occur at any age and gender does not seem to play an important role. Higher incidence was observed in lighter skin phototypes and the race predilection is comparable with that of typical acquired benign melanocytic nevi.

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**Table 1. Conditions associated with eruptive melanocytic nevi**

| | |
|---|---|
| Immunosuppression | Transplantation<br>- renal<br>- bone-marrow<br>Malignancy<br>- solid organ malignancy (prostatic cancer)<br>- hematologic malignancy<br>AIDS |
| Blistering diseases | Erythema multiforme<br>Stevens-Johnson syndrome<br>Toxic epidermal necrolysis<br>Pemphigoid epidermolysis bullosa<br>Suflur mustard gas |
| Medications | Immunosuppressive agents<br>- biologic agents<br>- nonbiologic agents<br>Melanocyte stimulators<br>Insulin therapy |
| Other medical conditions | Trauma<br>Addison disease<br>Langerhans cell histiocytosis<br>PUVA therapy |
| Idiopathic | |

Most cases have been reported in the last 10 years, probably due to an increased use of biological therapies for the treatment of psoriasis, intestinal bowel disease, rheumatoid arthritis and hematologic malignancies such as lymphomas and leukaemia and due to a rise in organ transplantation. A study which followed 420 renal transplant recipients undergoing post-operative immunosuppression showed that 10 of them (2,4%) developed eruptive melanocytic nevi [3].

## Clinical and dermoscopic features

The melanocytic nevi present clinically as well-circumscribed, light- to dark-brown pin-point lesions, generally measuring 1-3 mm in diameter, with regular borders. Unlike the common acquired melanocytic nevi which usually spare the acral sites, EMN often develop on palms and soles. They can also show a diffuse pattern or they can be confined to the proximal extremities and the trunk.

Several dermoscopic aspects of EMN have been described. A study on 10 renal allograft patients found that the predominant pattern

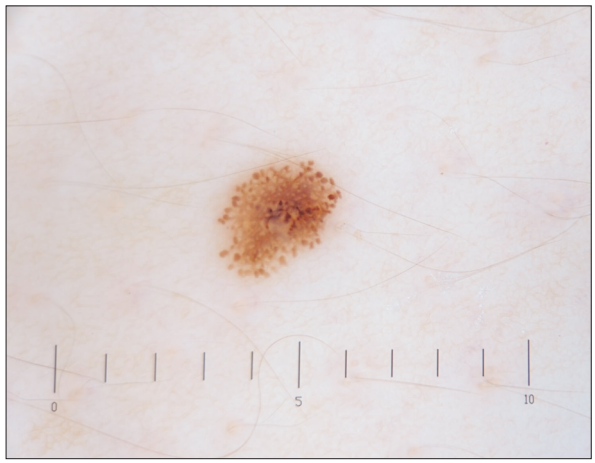


*Fig 1. Dermoscopic image showing brown globules arranged symmetrically at the periphery of the lesion*

consists of brown globules arranged symmetrically at the periphery of the lesion (Fig. 1) [3].

On histological examination, EMN most commonly are compound nevi but other histologic diagnosis have been reported such as dysplastic nevi [3].

## Pathogenesis

The pathogenesis of eruptive melanocytic nevi is not completely understood. Several theories try to explain the mechanism that lead to the development of this condition.

A normal immunological state inhibits melanocytic proliferative lesions. Since this phenomenon is observed especially in immuno-compromised patients it has been suggested that

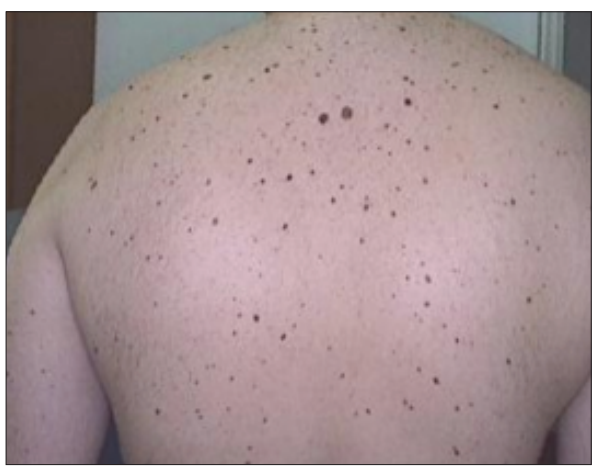

*Fig. 2. Eruptive nevi located on the posterior trunk*

an altered immune surveillance can lead to melanocyte proliferation by allowing growth factors such as melanocyte stimulating hormone (MSH) and melanoma growth stimulatory activity (MGSA) to enhance mitogenic activity [4]. A second theory suggests an important role of genetic factors like mutations in BRAF gene, MGSA or other pathways of cellular proliferation [5]. Thirdly, a direct effect of medications have been proposed to contribute to EMN development [6].

Cases of EMN have been reported 3 weeks to 3 months following the onset of severe bullous dermatoses (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigoid epidermolysis bullosa) [7,8]. The lesions can be localized or diffuse. The mechanism is unknown but some authors have suggested that dysregulation of local growth factors after damage of the epidermis could play a role in the pathogenesis. The blister fluid overlying the EMN lesions associated with epidermolysis contains high levels of various cytokines and other growth factors. Residual melanocytes stimulated by these factors during regeneration of the epidermis may lead to excessive proliferation and melanocytic nevus formation [9]. Also the level of epidermal cleavage may play an important role [7]. Nonetheless, this hypothesis does not explain the development of acral nevi in immunosuppressed patients.

Melanocyte-stimulating hormone (α-MSH) is a proopiomelanocortin-derived cytokine synthetized mainly in the pituitary gland but production can also occur locally in keratinocytes and melanocytes where it has a paracrine action. α-MSH is well known to play a role in skin pigmentation and innate immunity. Upon binding to melanocortin 1 receptor (MCR1) and melanocortin 5 receptor (MCR5) it stimulates melanin production and increases tyrosinase activity, therefore inducing melanocyte proliferation [10]. It has been postulated that α-MSH may be involved in the development of EMN. It has been reported in the literature the case of a 40-year-old Caucasian man with history of melanoma who developed EMN three weeks after initiating treatment with Melanotan II. Melanotan II along with Melanotan I are non FDA approved synthetic analogues of α-MSH used for their effects of producing tanning in order to prevent the deleterious effects of UVB [11,12]. There is a higher density of eccrine glands on the acral sites which could provide an explanation for the most common localization of melanocyte nevi in EMN given their important expression of MCR 5 [4].

A case of a 31 year-old man suggested the association of EMN with human immunodeficiency virus infection. The patient without personal or family history of pigmented lesions, noticed the sudden development of multiple melanocytic nevi during the month preceding the diagnosis of acquired immunodeficiency syndrome. After initiation of antiretroviral therapy no new pigmented lesion were reported and the existing ones remained unchanged [13].

Eruptive melanocytic nevi can also be associated with the use of several drugs like TNF-α inhibitors (monoclonal antibodies - infliximab, circulating receptor fusion protein - etanercept), anti- CD20 monoclonal antibodies (rituximab), BRAF inhibitors (vemurafenib, LGX818), tyrosine kinase inhibitors (sorafenib, sunitinib), various non-biologic chemotherapeutics (5-fluorouracil, cyclophosphamide, interferon alfa-2b), somatostatin analogues (octreotide), other immunosuppressants (methotrexate, corticosteroids, azathioprine, cyclosporine), calcineurin inhibitors (tacrolimus), insulin, α-MSH synthetic analogues [14-18]. It has been hypothesized that these drugs contribute to proliferation of melanocytes by direct stimulation or as a consequence of immunosuppression.

Corticosteroids have an immunosuppressive effect induced by several mechanism: cell cycle arrest in G1, a reversible effect, inhibition of cytokine production (interleukin-1, interleukin-2, interleukin-6, TNF-α, interferon γ), acute peripheral lymphopenia, inhibition of antibody synthesis by plasmocytes, promotion of lymphocyte apoptosis. A direct effect on proliferation of the melanocytes has not been yet proven. Thus, it is believed that EMN development in these cases is a consequence of immunosuppression [19].

Inhibition of calcineurin with further effects on T-cell activation explains the immunosuppressive action of tacrolimus, which could be

responsible for the indirect effect of this drug that leads to development of EMN. Furthermore, tacrolimus could also act in a direct manner on melanocyte by promoting tyrosinase activation and cell migration and by creating a favourable environmental milieu for cell growth [20].

Another condition associated with the development of eruptive melanocytic nevi is the use of BRAF inhibitors (vemurafenib, dabrafenib, LGX818). Anforth et al described a case of EMN after the administration of a new-generation BRAF inhibitor (LGX818) for metastatic melanoma. This adverse event was reported after 2 months of therapy [15]. BRAF inhibitors are a relatively new drug class, only recently approved for the treatment of various neoplasms. The reason for this adverse event remains to be studied.

Insulin therapy in a patient with type I diabetes mellitus was believed to induce EMN. In this case insulin was considered to promote excessive α-MSH secretion which could lead to melanocyte proliferation.

## Evolution and prognosis

It is important to differentiate EMN from melanoma, melanoma metastases or other melanocytic tumours. Some EMN lesions can evolve into dysplastic nevi [11] such that routine follow-up is warranted for patients with eruptive nevi.

The evolution of EMN is mainly determined by the course of the underlying associated condition. Reports show that reverse of immunosuppression (i.e. discontinuation of immunosuppressive agents, start of antiretroviral therapy in AIDS patients) leads to a decrease in size and colour fading of the existing nevi [22]. Similar evolution was noticed after interrupting the administration of α-MSH synthetic analogues [11]. In a case of a patient diagnosed with prostatic cancer with associated EMN, 12 months after therapy completion, there were no new melanocytic lesion and the existing ones remained stable [23].

## Conclusions

EMN is a rare condition and most cases have been reported in recent years, probably due to an increased use of biological and other immunosuppressive therapies for the treatment of various diseases, hence clinicians must be aware of this adverse event. As far as we know, there are no long-term follow-up studies for malignant transformation of EMN. The lesions have the potential to evolve into dysplastic nevi, therefore long-term follow-up is recommended. Although there are several hypothesis, the pathogenesis of eruptive melanocytic nevi remains to be elucidated. Additional studies are required on this matter to gain a better understanding of the prognosis and to develop a management strategy.

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Conflict of interest
NONE DECLARED

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