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REVIEW ARTICLE

Eruptive Melanocytic Nevi: A Review

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Abstract
Eruptive melanocytic nevi (EMN) is a phenomenon characterized by the sudden onset of nevi. Our objective was to compile all published reports of EMN to identify possible precipitating factors and to evaluate the clinical appearance and course. We conducted a systematic bibliographic search and selected 93 articles, representing 179 patients with EMN. The suspected causes were skin and other diseases (50%); immunosuppressive agents, chemotherapy or melanotan (41%); and miscellaneous, including idiopathic (9%). The clinical manifestations could largely be divided into two categories: EMN associated with skin diseases were frequently few in number (fewer than ten nevi), large, and localized to the site of previous skin disease, whereas those due to other causes presented most often with multiple small widespread nevi. In general, EMN seem to persist unchanged after their appearance, but development over several years or fading has also been reported. Overall, 16% of the cases had at least one histologically confirmed dysplastic nevus. Five cases of associated melanoma were reported. We conclude that the clinical appearance of EMN may differ according to the suggested triggering factor. Based on the clinical distinction, we propose a new subclassification of EMN: (1) widespread eruptive nevi (WEN), with numerous small nevi, triggered by, for example, drugs and internal diseases, and (2) Köbner-like eruptive nevi, often with big and few nevi, associated with skin diseases and most often localized at the site of previous skin disease/trauma. The nature of the data precluded assessment of risk of malignant transformation.

1 Introduction

The first description of an "outbreak of pigmented moles" was by Hutchinson [1] in 1868, and several reports have since been published. The term eruptive nevi was first used in the 1970s [2]. Dermatologists have used the term in a variety of ways [3–6], but it is commonly used to describe the phenomenon of a sudden occurrence of multiple new moles. In the general population, the number of nevi gradually increase through childhood, with particularly rapid growth during puberty. The maximum number of moles occur around the age of 30 years, with a subsequent regression through life. However, longitudinal studies have shown the evolution of nevi to be a more dynamic process than previously thought, with nevi appearing and disappearing at all ages [7–9]. Therefore, the slow appearance of moles, especially in youths, does not usually attract attention. In contrast, the development of eruptive melanocytic nevi (EMN) is more dramatic and may provide insight into nevogenesis. The aim of this systematic review was to

Key Points

Although a rare phenomenon, eruptive melanocytic nevi (EMN) may provide interesting insights into nevogenesis.

Different precipitating factors may influence the clinical appearance, localization and course of EMN, suggesting different pathophysiological mechanisms.

We propose a new subclassification of EMN: Widespread eruptive nevi (WEN) and Köbner-like eruptive-nevi (KEN).

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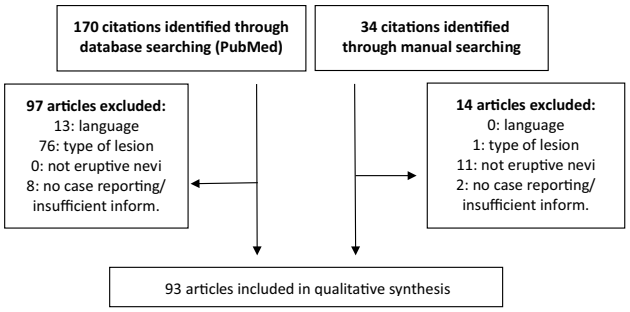

Fig. 1 Search strategy

provide a quantitative and qualitative analysis of the reported clinical manifestations and course of EMN in the published literature.

2 Methods

Bibliographic searches were conducted in PubMed in February 2018, with no date limits and using the keywords "eruptive nevi". Additional searching with the keywords "sudden nevi" or "new nevi" did not result in relevant articles and therefore is not included in the searching tree seen in Fig. 1. Reference lists were manually searched, and additional unpublished data were occasionally requested from authors via email. One author (EB) initially screened all titles and abstracts and excluded articles that were clearly ineligible (e.g., eruption of the wrong type of lesion, e.g., collagenoma). When eligibility was in doubt, another author (GJ) was involved. Articles were limited to those in English and Scandinavian languages. Abstracts were not included. Each report was screened for suggested precipitating factor, age, sex, ethnicity/skin type/history of sun exposure, dermatoscopy findings, localization of nevi, estimated number of new nevi, clinical course, histopathology, concomitant diseases and, lastly, follow-up and were documented in a standardized scheme. The data were subsequently qualitatively and quantitatively analyzed. Primarily, case reports and case series were included. Reports and cases were excluded if clinical details were lacking. We included only eruption of new common acquired melanocytic nevi and excluded cases with, for example, eruptive lentigines, Spitz nevi or blue nevi or cases only demonstrating changes in preexisting nevi. As no agreement and consensus of the definition of EMN exists, we chose to include almost all case reports using this term to review its usage. However, single articles were excluded based on quality assessment, mainly because of strong doubts about the usage of the term EMN, for example, cases only developing two to three small widespread new nevi. Reports describing a phenomenon indistinguishable from EMN but not specified as EMN were included. SPSS (Statistical Package for the Social Sciences; IBM, Armonk, NY, USA) was used for statistical analyses.

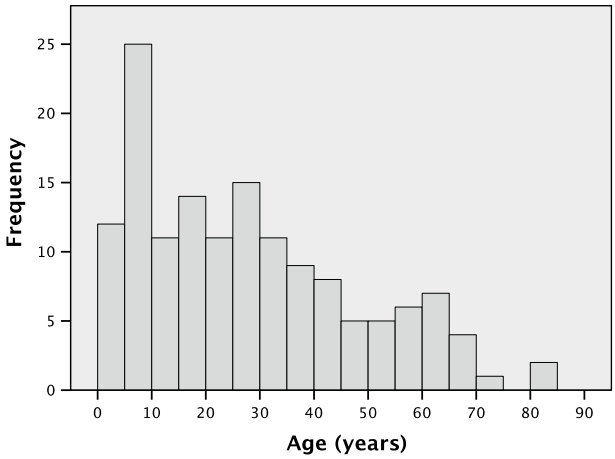

Fig. 2 Age at initiation of eruptive melanocytic nevi (presentation in dermatological department). Mean age 27.6 years; median age 24.5 years, range 0.5–84 years, standard deviation 19.9. $N = 146$

3 Results

3.1 General

In total, 93 articles about EMN, involving 179 patients, were included. EMNs were reported in most age groups (Fig. 2), with a higher frequency those aged 0–39 years. The median age of presentation with EMN was 24.5 years (range 0.5 days to 84 years), and 54% of the cases were male[1] (Fig. 2). A minority of patients had a history of sunbed use, excessive sun exposure, personal or family history of excessive nevi, atypical nevi or malignant melanoma. EMN were described in Fitzpatrick skin types I–IV and in a Black patient, but most reports were seen in patients with skin type II–III. EMN were reported in people of different heritages: Austrian, Scandinavian, Greek, Turkish, Hispanic, Korean, Chinese and Japanese.

3.2 Precipitating Factors

EMN were suggested to be triggered by diseases in 50% of cases or by drugs in 41% (immunosuppressive agents, chemotherapy, melanotan) and were either idiopathic or miscellaneous in 9%. The precipitating factors are further outlined in Fig. 3 and specified in Table 1. Most cases were associated with skin diseases (75/179 [42%]), particularly

[1] 21 cases of EMN after exposure to sulfur gas were excluded because of selection bias; all cases were male soldiers.

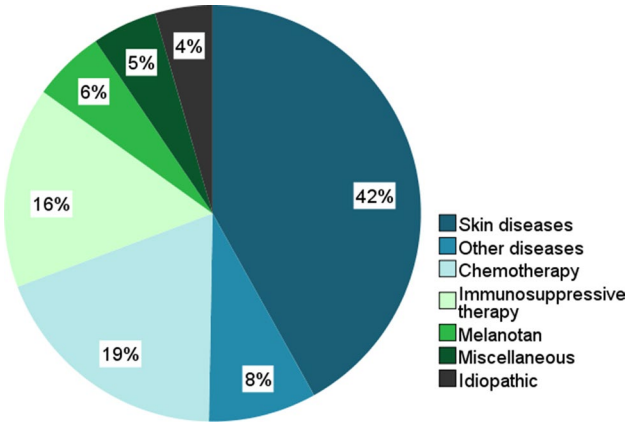

Fig. 3 Suggested precipitating factors of eruptive melanocytic nevi

with blistering diseases (67/75 [89%]), for example, epidermolysis bullosa. Furthermore, 77 of 179 (43%) patients were in an immunosuppressive/altered state:

1. Immunosuppressive therapy: Both traditional nonbiologic and biologic therapy was reported as monotherapy, but the majority of patients were receiving polypharmaceutical treatment (16/28 [57%]). Treatment was initiated for renal transplantation ($n=11$), inflammatory bowel disease ($n=11$), psoriasis ($n=2$) and other diseases ($n=4$).
2. Chemotherapy: The majority of these patients developed nevi with monotherapy (31/34 [91%]), primarily after biologic therapy (27/34 [79%]). Treatment was initiated for chronic myeloid leukemia ($n=11$), melanoma ($n=9$), acute lymphatic leukemia ($n=4$), renal cell carcinoma ($n=4$), colorectal carcinoma ($n=2$), breast cancer (2) and other cancers ($n=2$).
3. Other diseases (e.g. HIV).

3.3 Clinical Manifestations

The clinical manifestations of EMN are presented and stratified by the suggested causative factors in Table 2.

3.3.1 Localization

EMN were often reported as widespread (80/161 [50%]), frequently involving intermittently sun-exposed areas such as the trunk (116/161 [72%]) and extremities (104/161 [65%]). Overall, involvement of chronically sun-exposed skin such as the face was observed to a lesser degree (57/161 [35%]), but stratification by causative agents might indicate a higher frequency after chemotherapy (14/24 [58%]), in melanotan users (4/8 [50%]) and by cutaneous diseases (31/69 [45%]). EMN on sun-protected areas such as the buttocks (palmoplantar nevi were regarded as a separate entity) were rarely reported (20/161 [12%]). Interestingly, EMN on the palms/soles were very frequent after immunosuppressive therapy (13/29 [45%]) and after chemotherapy (7/24 [29%]) but surprisingly low in association with other causes (5/108 [5%]). Clearly distinguished from other precipitating factors, EMN after skin diseases were predominantly localized at the site of previous bullae, blisters or skin damage (57/69 [83%]), often taking the outlines of previous blisters.

3.3.2 Morphology and Dermoscopy

The morphology of the EMN differed notably according to the precipitating factor and can be divided in two groups:

1. EMN from causes other than skin diseases (so-called widespread eruptive nevi [WEN]; see Sect. 4): These moles were small, asymptomatic monomorphous brown macules, most often ranging between 1 and 4 mm. A few cases involved the development of pigmented papules. The number of new nevi ranged between 10 and 2500, frequently reported as development of > 100 nevi or "multiple". The moles generally showed no signs of atypia on clinical evaluation and/or dermoscopy [10–20]. However, peripheral globules, regular reticular, globular or reticularglobular patterns were also demonstrated in single cases. A fibrillar pattern was often described in palmoplantar nevi. The morphology of EMN in melanotan users and those associated with "other diseases" were described as intensely pigmented, almost black. Signs of atypia were not infrequently reported in melanotan-associated nevi, often described as well-defined but with irregular globules and streaks at periphery.
2. EMN associated with skin diseases/trauma (so-called Köbner-like eruptive nevi [KEN]; see Sect. 4): These nevi were often reported as polymorphic, single or few in number, and very large, frequently measuring a few centimeters in diameter. The biggest lesion described measured 14 × 11 cm [21]. EMN triggered by skin diseases were often described as atypical with either asymmetry, irregular borders, bizarre configuration or irregular dark pigmentation. In some cases, satellite lesions were demonstrated. Fulfilling most ABCDE[2] criteria, EMN associated with skin diseases were highly suspicious of melanoma (81 biopsies among 75 patients). Although the majority of cases were described as large and few, widespread and clusters of small macular nevi were also described.

[2] ABCDE: asymmetry, border irregularity, color that is not uniform, diameter > 6 mm, evolving size, shape or color.

Table 1 Suggested precipitating factors of eruptive melanocytic nevi

Precipitating factor	*N*	References
Drugs	**72**	
Immunosuppression	**28**	
Biologic immunosuppression Alefacept[a] (*n* = 1) Etanercept[a] (*n* = 1) Adalimumab (*n* = 1) Tocilizumab (*n* = 1)	3	[20, 79, 80]
Nonbiologic immunosuppression Azathioprine (*n* = 5) 6-Mercaptopurine (*n* = 3) Cyclosporine (*n* = 1)	9	[5, 10, 11, 13, 14, 20, 81–83]
Polypharmacy Combinations of azathioprine, cyclosporine, prednisolone, methylprednisolone, infliximab, prednisolone, mesalazine, 6-mercaptopurine, rituximab; 14/16 cases treated with azathioprine; 13/16 treated with prednisolone	16	[12, 15, 19, 20, 35, 51, 58, 84]
Chemotherapy	**34**	
Biologic chemotherapy Radotinib (*n* = 10) Vemurafenib (*n* = 8) Sorafenib (*n* = 3) Sunitinib (*n* = 1) Erlotinib (*n* = 1) Nilotinib (*n* = 1) Regorafenib (*n* = 1) Encorafenib (*n* = 1) Interferon-α2b (*n* = 1)	27	[4, 16, 17, 29, 31, 33, 36, 43, 85–90]
Nonbiologic chemotherapy Capecitabine (*n* = 3) Cyclophosphamide (*n* = 1)	4	[18, 28, 91, 92]
Polypharmacy/post-chemotherapy	3	[27, 30, 93]
Melanotan	**10**	
Melanotan II	9	[24, 37–39, 94–96]
Melanotan unspecified	1	[97]
Diseases	**90**	
Skin diseases	**75**	
Blistering diseases	(67)	
Epidermolysis bullosa	(37)	[21, 41, 42, 47–49, 54, 56, 98–102]
Dystrophic epidermolysis bullosa	23	
Junctional epidermolysis bullosa	7	
EBS	6	
Unspecified	1	
SJS	4	[42, 45, 50]
TEN	3	[44, 46, 50]
TEN-like cutaneous lupus	1	[103]
Vulval pemphigoid	1	[40]
Blisters after sulfur mustard gas exposure	21	[104]
Other inflammatory skin diseases	(4)	
Erythema multiforme	1	[105]
Eczematous dermatitis	1	[22]
Cutaneous mastocytosis	1	[25]
Pyoderma gangrenosum	1	[106]
Local skin trauma	(4)	
Surgical suture	2	[107]
Trauma	1	[108]

Table 1 (continued)

Precipitating factor	*N*	References
Burn injury	1	[109]
Other diseases	**15**	
HIV	8	[34, 110]
Primary adrenocortical insufficiency	2	[111, 112]
Langerhans cell histiocytosis	2	[113]
Prostate cancer/paraneoplastic phenomenon	1	[52]
Chronic myelocytic leukemia	1	[114]
Melanoma	1	[115]
Miscellaneous	**9**	
Common genetic background (freckles, fair skin color)	7	[32]
Insulin	1	[116]
Natalizumab/melanoma	1	[26]
Idiopathic	**8**	[2, 55, 117–119]
Total	**179**	

EBS epidermolysis bullosa simplex, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

[a]The same patient developed eruptive melanocytic nevi by each drug separately

3.3.3 Time to Onset

Time to onset refers to the latent period from exposure of the suggested precipitating factor to the first appearance of EMN. Time to onset ranged from 24 h to several years but was most frequently reported as weeks (47/110 [43%]), a few months (21/110 [19%]) and several months[3] (28/110 [25%]). Interestingly, it appears that EMN after melanotan develops quickly, most often within days or weeks (6/8 [75%]); in skin diseases, EMN were primarily described within weeks (25/38 [66%]) after the debut of a skin lesion. Nevi after immunosuppressive treatment or chemotherapy might have developed more slowly: within days or weeks in 24% (13/55), within a few months in 25% (14/55) and after several months in 40% (22/55).

3.3.4 Histopathology

Histology specimens confirmed the development of compound, junctional and intradermal nevi. Compound nevi were most common (63/109 [58%]). EMN after skin diseases seemed to have a greater likelihood of being junctional nevi (28/50 [56%]). Of all the patients in this report, 16% (29/179) had at least one nevus with histopathologically confirmed dysplasia/atypia, ranging from mild to severe atypia. Data stratification revealed more dysplastic nevus (DN) in EMN after "other diseases" (8/15 [53%]) and in the melanotan group (4/10 [40%]) but a lower frequency in skin diseases (9/75 [12%]). Of a total of 200 biopsied lesions, 31% had atypia or other "non-benign pathology". Melanoma was reported in five cases. One patient developed melanoma in relation to eczematous dermatitis [22], whereas two cases developed melanoma in correlation with usage of melanotan (however, the two latter cases had melanoma in preexisting nevi) [23, 24]. A fourth case was seen in association with cutaneous mastocytosis, but the timeframe/correlation to the development of EMN was very uncertain [25]. The fifth case developed melanoma in correlation with natalizumab initiated 6 years earlier, 2 months before the EMN [26]. Melanoma in situ was reported in two cases [27], and lentigo-maligna-like lesions [28] were reported in another case.

3.3.5 Other Cutaneous Manifestations

In general, EMN presented on seemingly normal and otherwise unaffected skin with no other cutaneous manifestations, except in patients with EMN thought to be caused by skin diseases. However, patients receiving antineoplastic treatment were not infrequently reported to have cutaneous side effects, such as photosensitivity, hand-foot-skin reactions, erythema and papulopustular eruptions. In addition, the majority of cases with EMN after melanotan usage reported darkening of preexisting nevi (8/10 [80%]) nevi and/or general tanning (8/10 [80%]).

[3] Days includes ≤ 14 days and "a few days" and "several days". Weeks includes > 14 days to ≤ 8 weeks and "a few weeks" and "several weeks". A few months includes > 8 weeks to ≤ 4 months and "a few months". Several months includes > 4 months to ≤ 1 year and "several months". "Years" includes > 1 year.

Table 2 Clinical manifestations of eruptive melanocytic nevi, categorized by suggested causative agents[a]

Suggested precipitating factors	Age, y[b]	Male (%)	Cases with multiple nevi, *n* (%)	Localization: no of cases (%)	Time-to-onset of new nevi[c] (no. of cases)	Histology[d]	Type of nevus: no. of lesions	Conclusion/comment
Drugs								
Immunosuppressive therapy ($n=28$)	24 (8–64)	48	28/29 (97)	Diffuse 15/29 (52) Trunk 23/29 (79) Ext 12/29 (41) Palm/plant 13/29 (45) SPA 2/29 (7) SEA 2/29 (7)	Days (1) Weeks (3) Few months (5) Several months (13) Years (2)	a. 5/28 (18%) b. None c. 10/37 (27%)	C: 26 J: 4 IND: 1	Small and multiple nevi Development of palm/plant nevi frequently reported (45%) C nevi most often reported Most cases were under polypharmaceutical treatment (57%)
Chemotherapy ($n=34$)	51 (8–74)	53	32/33 (97)	Diffuse 15/24 (63) Trunk 17/24 (71) Ext 15/24 (63) Palm/plant 7/24 (29) SPA 4/24 (17) SEA 14/24 (58)	Days (0) Weeks (9) Few months (9) Several months (9) Years (4)	a. 3/34 (9%) b. 1 pt: lentigo maligna-like lesion (6) 1 pt: melanoma in situ (3) c. 5/27 (19%)	C: 5	Small and multiple nevi Age of onset of nevi higher than by other precipitating factors Involvement of sun-exposed areas as the face commonly reported (58%) Palm/plant nevi frequent (29%) Most cases were under monotherapeutic treatment (91%)
Melanotan ($n=10$)	27 (19–42)	50	8/8 (100)	Diffuse 5/8 (63) Trunk 8/8 (100) Ext 5/8 (63) Palm/plant 0/8 (0) SPA 1/8 (13) SEA 4/8 (50)	Days (4) Weeks (2) Few months (2) Several months (0) Years (0)	a. 4/10 (40%) b. 2 pt: melanoma c. 16/18 (89%)	C: 2 J: 1 IND: 1	Small and multiple nevi, often darkly pigmented Very fast development of nevi: most often within days/weeks after initiation of melanotan usage Involvement of sun-exposed areas as the face commonly reported (50%) Darkening of preexisting nevi: 9/10 (90%). Generalized tanning: 8/10 (80%) of total no pt. History of sun tanning/sunbed use: 8/10 (80%) Several cases with DN and/or melanoma Removal of melanotan often leads to fading of nevi

Table 2 (continued)

Suggested precipitating factors	Age, y[b]	Male (%)	Cases with multiple nevi, *n* (%)	Localization: no of cases (%)	Time-to-onset of new nevi[c] (no. of cases)	Histology[d]	Type of nevus: no. of lesions	Conclusion/comment
Diseases								
Skin diseases ($n=75$)	9[e] (0.5–84)	45[e]	33/62 (53) No. of nevi specified: 1: 13/61 (21); 2–10: 15/61 (25); > 100: 3/61 (5)	EMN localized to site of injury: 57/69 (83) Diffuse 25/69 (36) Trunk 42/69 (61) Ext 51/69 (74) Palm/plant 4/69 (6) SPA 8/69 (12) SEA 31/69 (45)	Days (0) Weeks (25) Few months (5) Several months (5) Years (3)	a. 9/75 (12%) b. 2 pt: melanoma 1 pt: melanoma in situ c. 22/81 (27%)	C: 19 J: 28 IND: 3 Persisting nevus: 4	Few and big nevi (1–10 seen in 28/61 [46%]), often cm in diameter. Localization at the site of previous skin disease in most pts (83%). But small widespread nevi/clusters of small nevi also reported Atypical bizarre morphology of nevi, fulfilling the ABCDE criteria, but mostly benign on clinical follow-up and pathology Most often caused by blistering skin diseases, e.g., epidermolysis bullosa, often taking the outlines of bullae. Nevi most often development within weeks after the skin trauma (25/38 [66%]) Primarily children An overabundance of junctional nevi
Other diseases ($n=15$)	30 (9–80)	100	15/15 (100)	Diffuse 13/15 (87) Trunk 12/15 (80) Ext 12/15 (80) Palm/plant 1/15 (7) SPA 3/15 (20) SEA 2/15 (13)	Before initiation of therapy and in close relation to debut of disease (13/15 = 87%)	a. 8/15 (53%) b. None c. 8/18 (44%)	C: 5 J: 1 IND: 1	Small and multiple nevi Only men, 53% had HIV Many reports of DN
Miscellaneous/idiopathic ($n=17$)	21 (5–48)	53	17/17 (100)	Diffuse 7/16 (44) Trunk 14/16 (88) Ext 9/16 (56) Palm/plant 0/16 (0) SPA 2/16 (13) SEA 4/16 (25)	Miscellaneous: Days (0) Weeks (8) Few months (0) Several months (1) Years (0) Idiopathic: not applicable	a. 0/17 (0%) b. 1 pt: melanoma c. 1/19 (5%)	C: 6 J: 4 IND: 2	Small and multiple nevi

Table 2 (continued)

Suggested precipitating factors	Age, y[b]	Male (%)	Cases with multiple nevi, *n* (%)	Localization: no of cases (%)	Time-to-onset of new nevi[c] (no. of cases)	Histology[d]	Type of nevus: no. of lesions	Conclusion/comment
Total, excluding skin diseases ($n=104$)	31 (5–80); mean 34	58	100/102 (98)	Diffuse 55/92 (60) Trunk 74/92 (80) Ext 53/92 (58) Palm/plant 21/92 (23) SPA 12/92 (13) SEA 26/92 (28)	Days (5) Weeks (22) Few months (16) Several months (23) Years (6)	a. 20/104 (19%) b. See above c. 40/119 (34%)	C: 44 J: 10 IND: 5	
Total ($n=179$)	24.5[e] (0.5–84); mean 27.6	54[e]	133/164 (81)	Diffuse 80/161 (50) Trunk 116/161 (72) Ext 104/161 (65) Palm/plant 25/161 (16) SPA 20/161 (12) SEA 57/161 (35)	Days (5) Weeks (47) Few months (21) Several months (28) Years (9)	a. 29/179 (16%) b. See above c. 62/200 (31%)	C: 63 J: 38 IND: 8	

Diffuse is used as a synonym for widespread

C compound nevus, *DN* dysplastic nevus, *Ext* extremities, *IND* intradermal nevus, *J* junction nevus, *Palm/plant* palmar/plantar, *pt* patient, *SEA* chronically sun-exposed area, e.g., face and dorsum of hands, *SPA* chronically sun-protected area, e.g., buttocks (excluding palmar/plantar nevi)

[a]See the main text for a discussion of histology

[b]Age is presented as median (range) unless otherwise indicated

[c]Refers to lag time between exposure of suggested precipitating factor and first signs of eruptive melanocytic nevi

[d]Histology is presented as follows: a. Cases with ≥ 1 DN/total no. cases; b. Other pathology of importance (no. of lesions); c. DN + melanoma + melanoma in situ/total no. biopsies

[e]Excluding 21 cases (male soldiers) with eruptive melanocytic nevi after exposure of sulfur gas

3.3.6 Follow-Up

Follow-up data were generally missing, especially long-term follow-up. The available reports indicated that EMN either (1) remained stable, (2) disappeared/faded or (3) continued developing over years in number and/or morphology, as follows.

1. EMN were most often reported clinically stable over time in terms of number and/or color after their first appearance [4, 12–14, 16, 17, 19, 26, 27, 29–32][4]. EMN precipitated by drugs were reported as stable under different clinical scenarios – under continuous treatment [19, 33] (see Footnote 4) and after treatment discontinuation [4, 26, 30, 31] (see Footnote 4), dosage reduction [29] or replacement with another therapy [13, 14]. In patients with EMN after HIV, nevi did not regress with treatment [34].
2. Fading of nevi after treatment discontinuation was less frequently reported [18, 19, 28, 35, 36] (see Footnote 4). Interestingly, this was particularly seen in melanotan users [37–39], often within some months after termination of treatment. EMN in skin diseases, not uncommonly suspicious of melanoma, were also occasionally seen to fade away [40–43].
3. Although most cases showed a sudden outburst of nevi with subsequent clinical stabilization/cessation of nevi development, some cases did demonstrate development of new nevi over much longer times, for example, 20 months [13] and over a period of 4 years [20].

With EMN in skin diseases, nevi were frequently described with an initially dynamic growth pattern within weeks, months and sometimes up to 1–2 years after the first appearance. This included changes in color and growth, development of protrusions and/or an increase in the number of nevi [6, 21, 40, 44–49]. However, these nevi were often reported as unchanged on subsequent follow-up [6, 21, 44–46, 50]. Gelfer and Rivers [6] presented the longest follow-up time, reporting no appreciable changes over 38 years in the hundreds of nevi developed after Stevens–Johnson syndrome [6, 44].

3.3.7 Treatment

In general, a 'wait-and-see' treatment strategy was selected in most cases, with a long period of surveillance generally advocated [2, 11, 14, 15, 47, 51–54] rather than potentially unnecessary surgery. Removal of nevi for cosmetic reasons was occasionally reported, with long-pulsed diode laser [13] and chemosurgery with 65% trichloroacetic acid [55] both used successfully. However, in one case, laser therapy resulted in temporary fading but subsequent recurrence after 3 months [56].

4 Discussion

The word eruptive derives from the French *éruptif* [57], meaning to start suddenly and violently. This review reveals a lack of consensus over what constitutes eruptive nevi, with a wide diversity in the number of newly acquired nevi in each patient and the time to onset. The number of new moles referred to as EMN ranged between 1 and 2500, with development within 24 h up to several years. However, most authors reported "multiple nevi" with development within several months. In 2016, Perry et al. [58] introduced the criteria "eruptive nevi associated with medications" (ENAM), defined as the development of at least one of the following over a 6-month period associated with the use of medications: (1) more than five melanocytic nevi on palmoplantar surfaces at any age, (2) more than ten melanocytic nevi body-wide outside of puberty and pregnancy, (3) more than 20 nevi during puberty or pregnancy [58]. Although these criteria are a pragmatic approach and not evidence based, they seem useful. It would also be a useful definition for other causes of EMN, except in association to skin diseases. Given the clinical differences between EMN related to skin diseases and those with other precipitating factors, we suggest the following subcategories for eruptive nevi.

1. WEN: Characterized by the sudden appearance of numerous small, often benign-looking nevi. This particularly includes ENAMs and eruptive nevi in association with internal diseases such as HIV. These nevi are often widespread, but exclusive involvement of specific sites such as the palmoplantar area is also seen.
2. KEN: Characterized by the sudden appearance of nevi on the site of previous skin disease or trauma, for example, at the site of a preceding bulla. These nevi are usually few in number (one to ten nevi) and very large and are not infrequently clinical mimickers of melanoma. However, widespread small nevi/clusters of small nevi are also seen. Histopathology and follow-up most often reveals a benign course. KENs are seen in different skin diseases, particularly in patients with blistering diseases such as epidermolysis bullosa (epidermolysis bullosa nevi) and inflammatory skin diseases and after physical trauma.

The prevalence of EMN in the general population is unknown, but it is thought to be rare [3, 6]. However,

[4] References include unpublished data obtained via correspondence with authors.

patients undergoing immunosuppressive or chemotherapy may develop more nevi than immunocompetent controls. Routine dermatological examination of 420 patients who were immunosuppressed after renal transplantation revealed EMN in ten (2.4%) patients [19]. Several other studies have provided evidence that chemotherapy [59–61] and immunosuppressive treatment [62–65] increased the nevi count in both children and adults. Smith et al. [62] demonstrated a difference in the nevi count between pediatric renal transplant patients and a control group of 71 ± 55 and 46 ± 32, respectively [62]. Another study in renal transplant patients described an excessive number of nevi: 93.6 ± 52.2 versus 36.1 ± 29.9 in the control group [64]. Similar results were also seen in adults receiving different immunosuppressive drugs, with a nevus count after immunosuppression of 266 versus 180 in the control group [65]. The number of nevi in these cohorts receiving immunosuppressive therapy or chemotherapy appears to be twice that found in controls. However, whether the development of excessive nevi in patients receiving immunosuppressive therapy or chemotherapy should be defined as EMN is debatable.

Our material suggests that EMN appear to occur predominantly in intermittently sun-exposed skin such as the trunk (72%) and extremities (65%), whereas chronically sun-exposed (35%) and sun-protected (12%) skin (excluding palmoplantar nevi) was less commonly involved. As we could not assess the nevus density count, we are unable to say whether this only reflected the bigger surface areas or whether these sites might be more susceptible. The overall frequency of palmoplantar nevi in our material was 16% (25/161) but as high as 38% (20/53) in cases receiving either immunosuppression or chemotherapy. Nevi development in these sun-protected and anatomically small areas is noteworthy. Similar results have been reported in several case–control studies in renal transplants and after chemotherapy, with the majority showing the biggest increase in nevi count on the palms and/or soles [59, 62, 64, 66] and/or the back [62–64]. The prevalence of one or more nevi on the palm and soles in children with renal transplants has been reported to be as high as 42.8% compared with 3% in the healthy population [62]. A combination of altered immune surveillance and anatomic factors of the palmoplantar skin may be at play. The increased density of eccrine sweat glands and Pacinian corpuscles has also been speculated to play a role [12].

The pathophysiology of EMN remains largely unknown, but a role for several clinical scenarios has been implied (Table 1), most frequently, an immunologically altered state and skin diseases, especially blistering skin diseases. The development of EMN in correlation with immunosuppressive drugs is, in our opinion, more likely related to the general immunosuppression than the specific drug, as evidenced by the wide variety of immunosuppressants targeting different sites of the immune system. It has also been suggested that mast cells can contribute to the proliferation of melanocytes. This is suggested by higher levels of serum tryptase in patients with more melanocytic nevi than in those with few nevi [67]. This could be supported by one case in our material, where EMN developed in association with cutaneous mastocytosis [25]. However, the role of mast cells in EMN remains speculative, and serum tryptase levels have not been routinely measured in patients with EMN. Considering EMN in association with skin diseases, it is tempting to speculate on possible local factors impacting the development of nevi rather than systemic immunosuppression, as many of the EMN developed at the sites of previous bullae. Interestingly, Lanschuetzer et al. [47] detected individual melanocytes/nevus cells in blister fluid from a blister over an epidermolysis bullosa nevus and proposed that the cytokines or growth factors detected in the blister fluid might increase the rapid proliferation of free-floating melanocytes/nevus cells to form the blister-shaped nevi [47]. Although medical treatment was not reported in most cases of EMN in skin diseases, the majority of reported cases had epidermolysis bullosa with limited medical therapies. Immunosuppression of autoimmune cases is a relevant confounder but is thought to be less important.

Melanotan has been linked to EMN. It is an analog to alpha-melanocyte-stimulating hormone (α-MSH) and stimulates the eumelanin production of melanocytes, causing increased pigmentation [68]. It is suggested that melanotan stimulates the development of EMN via direct stimulation of the melanocortin receptor on the melanocytes rather than by immunosuppression.

In general, the development of EMN may be due to either de novo development of nevus cells or activation of preexisting inactive and invisible nevus cells. The existence of a susceptible nevus progenitor cell is supported by the fact that not all individuals exposed to these stimuli develop EMN and that patients who do undergo this phenomenon develop isolated lesions as opposed to general hyperpigmentation [69] (except from melanotan-associated EMN, often also resulting in general tanning).

The overall frequency of patients with at least one histopathologically confirmed DN in our material was 16% (29/179). Interestingly, even though EMN in association with skin diseases (KENs) were highly suggestive of melanoma on clinical examination, histopathologically confirmed DN were reported in 12% when associated with a skin disease. The prevalence of histopathologically confirmed DN in the background population ranges between 2.4 and 8% [70–72]. Clinically, DN are reported in as many as 7–19% [72–74] of the general population. The nature of this review precludes direct comparisons, although an association may be hypothesized. Of the 179 patients identified in the literature, five melanoma cases were identified. Four of these

associations were regarded as weak (see Sect. 3.3.4), but the long-term risk of melanoma development is uncertain, as long-term follow-up studies are lacking. However, it is well-established that increased numbers of nevi [75] and the presence of DN [76, 77] are themselves known risk factors for melanoma. An Australian study found an increased risk of melanoma, raised to 12 times the risk in cases with > 100 nevi compared with those with fewer than ten [78]. Another study estimated that the presence of DN incurred a tenfold increased risk for melanoma [77].

Evidence-based management of EMN is limited because of the rarity of the disease and lack of sufficient long-term follow-up studies. However, it would appear prudent to suggest a whole-body analysis of the nevi, usage of dermoscopy (video dermoscopy or teledermoscopy could be considered) and periodic follow-ups. Discontinuation of the illegal tanning product melanotan is also encouraged when it is suspected to be the cause of EMN. Increased sun protection should be recommended to all patients.

4.1 Strengths and Limitations

As we used no retrospective time limit in our search, we suggest that we found the majority of the published case reports using the term "eruptive nevi" in the English literature. However, we excluded bigger cohort studies describing generally excessive nevi from the analysis because of the lack of sufficient individual case reporting, which means the phenomenon of EMN is likely underestimated in this report. As there is no established consensus of the definition, a debate concerning the inclusion or exclusion of cases is also inevitable, with the risk of selection bias. We therefore deliberately omitted objective criteria in this review to increase the sensitivity of the search. Finally, it should be mentioned that a causative link between the suggested precipitating factors and the development of nevi is suggested only by correlation and is not proof of causation.

5 Conclusion

EMN is a rare phenomenon, usually reported as the sudden development of new nevi over a few weeks or months. EMN has been described in all age groups but is most commonly seen in young adults aged < 40 years. EMN are associated with several clinical scenarios, but a large proportion (43%) of cases occurred in immunosuppressed patients.

Interestingly, EMN precipitated by immunosuppressive agents or antineoplastic agents were more frequently reported on the palmoplantar skin rather EMN from other causes. Also noteworthy, EMN after melanotan usage were often associated with general skin hyperpigmentation, and the nevi frequently showed a greater tendency to fade after discontinuation of treatment than those related to other agents. In general, EMN were often unchanged after their first appearance, but fading and continuous development have also been reported. The clinical appearance and course of EMN may thus differ according to the triggering factor. Based on the clinical distinction, we therefore propose two new subclassifications of EMN: (1) WEN – numerous small, often benign-looking, nevi associated with immunosuppressive therapy, chemotherapy, melanotan, and several internal diseases and (2) KEN – often few in number (fewer than ten nevi) and big in size, developing in skin diseases, especially bullous diseases. KENs are often located at the site of a previous bulla/trauma.

Treatment usually involved a "wait-and-see" strategy with long-term surveillance. Overall, 16% of cases had at least one histologically confirmed DN, and five cases of associated melanoma were reported. However, the nature of the data precluded assessment of the risk of malignant transformation, especially as follow-up data were generally missing.

Compliance with Ethical Standards

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