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Nevus-associated Lentigo Maligna and Lentigo Maligna Melanoma, Clinicopathological Features

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Nevus-associated lentigo maligna and lentigo maligna melanoma (NALMM) are rarely described in the literature and are considered an incidental finding. This study aimed to evaluate the frequency of NALMM and its clinicopathological features. A total of 201 histopathology reports were reviewed and among them 20% of the samples corresponded to NALMM, with females overrepresented in this group ($p = 0.02$). A significant association was also observed between NALMM with the presence of multiple nevi ($p = 0.01$), and dysplastic nevi ($p = 0.04$). Moreover, the risk of developing a second melanoma of nevus-associated type was 4.3 times higher in patients with NALMM. These results indicate that NALMM is more frequent than previously reported, suggesting that the associated nevus could interact or even act as a precursor for LM/LMM. Future studies with larger samples allied to techniques like confocal microscopy and molecular analysis are essential to determine this biological link between nevus and LM/LMM.

Key words: de novo melanoma; lentigo maligna; lentigo maligna melanoma; nevus; nevus-associated melanoma.

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SIGNIFICANCE

To our knowledge, we conducted the first Swedish study focusing on nevus-associated lentigo maligna and lentigo maligna melanoma (NALMM) in adults, and its clinical and histological aspects. We are concluding that NALMMs are more frequent than previously reported, that NALMM patients have a high number of nevi, are associated in higher degree with the presence of atypical nevus, and have a higher risk that the second melanoma is also nevus associated. Our results suggest that LM/LMM could also interact with or even originate from a nevus.

Lentigo maligna and lentigo maligna melanoma (LM and LMM) are types of melanomas that affect mainly chronically sun-exposed skin, predominantly the head and neck of elderly patients, with slow radial growth, and high local recurrence (1–3). LM and LMM are considered to be *de novo* melanomas, originating from sun-damaged epidermal melanocytes rather than associated with a melanocytic nevus, a well-known direct precursor for cutaneous melanomas (CM) (1–8). According to previous studies, LM and LMM are less likely to have evidence of nevus remnants compared with other melanomas, and this association is usually considered a coincidental finding (4–8).

The frequency of nevus-associated melanoma (NAM) in a meta-analysis including 38 studies, with a total of 20,126 melanomas was estimated to be 29.1%, with the NAM mostly linked to thinner superficial spreading melanoma (SSM), occurring on the trunk of younger adults with multiple nevi (6).

Numerous melanocytic nevi and the presence of atypical nevi are considered risk factors for developing CM with the estimated annual risk of a nevus transforming into melanoma, before the age of 40 years, being approximately 0.0005% (1 in 200,000), increasing to 0.003% (1 in 30,000) for males older than 60 years (9–11). However, no correlation between LM and LMM and the presence of multiple nevi was found, supporting previous evidence that the total number of nevi decreases with age (12, 13).

Regarding the frequency of this coincidental occurrence between nevi and other skin tumours, a large study with 2,482 cutaneous excisions of non-melanocytic lesions from the face and neck of elderly individuals (mean age 65 years), found the presence of incidental microscopic foci of nevic aggregates (micronevi) in only 0.8% of the samples, showing that this collision phenomenon is low despite the high frequency of intradermal facial nevi of Miescher type, especially in adults (14, 15).

The purpose of this study is to evaluate the frequency of nevus-associated LM/LMM (NALMM) and its relationship with clinical and pathological aspects.

MATERIALS AND METHODS

We conducted a retrospective observational study from consecutive histopathology reports from patients who attended the dermatology department (Skin Cancer Center), Karolinska University Hospital, Sweden, between 1 January 2013 and 31 December 2018, for Grenz rays (GR) treatment for lentigo maligna (LM) and early lentigo maligna melanoma (LMM). The selection criteria for GR treatment were the same as used and described by Hedblad and Mallbris (3). A total of 348 histopathology reports collected before

GR treatment were reviewed for the presence of benign focus of intradermal melanocytic nevus in association with the LM/LMM. The reports from tangential (shave) excisions and punch biopsies, a total of 147, were excluded as the complete examination of the tumour was not possible. Demographic and clinical data were collected from the patient's medical records such as age and gender, tumour size, anatomical location, tumour stage (in situ or invasive), total number of melanocytic nevi, history of removal of dysplastic nevus and other melanoma (histologically confirmed), the presence of other nevus-associated melanoma (NAM), and family history of melanoma.

The size of the LM/LMM was divided into 4 groups according to the largest diameter: ≤10 mm, >10 ≤20 mm, >20 to ≤30 mm, and >30 mm. The amount of total body nevi in this study was determined based on clinical photographs. At the first visit, patients with more than 50 nevi were routinely photographed and were included in the group with high nevus count (≥ 50 nevi). Patients without clinical pictures were included in the less than 50 nevi group (<50 nevi). Family history of melanoma was considered positive if at least one consanguine developed melanoma.

Statistical analysis

The collected data were analysed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Odds ratios and corresponding 95% confidence intervals, and *p*-values were calculated using univariate logistic regression. Multivariable logistic regression calculated the adjusted odds ratios, corresponding 95% confidence intervals and *p*-values were calculated for the independent variables with significant *p*-value in the univariate logistic regression. For all the statistical tests, $p < 0.05$ was considered significant.

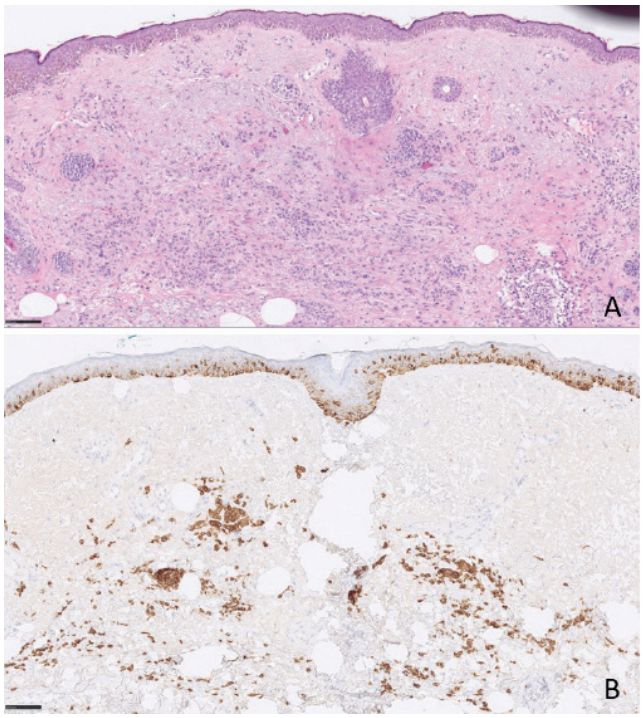

Fig. 1. Histological and immunohistochemical findings of early lentigo maligna associated with intradermal nevus. (A) Atypical melanocytes distributed in the dermal–epidermal junction with the presence of intradermal melanocytic nevus cells with signs of maturation and without atypia (haematoxylin-eosin, original magnification ×20). (B) Nevus nests are highlighted with Melan-A (original magnification ×20).

RESULTS

After applying exclusion criteria, a total of 201 LM/LMM histopathologic reports from skin excisions over a 6-year period were included in the analysis. In this cohort, 108 patients (53%) were females, and most of the tumours were in the head and neck region (183 [91%] of 201), mainly on the cheek (95 [46.7%] of 201) and small lesions ≤10 mm predominated (100 [49.7%] of 201). *In situ* tumours were most common and corresponded to 77% (156 of 201) of the tumours, and the mean age of the patients was 70.3 years (SD 11.17). Of the general LM/LMM samples, 42 (20%) of 201 corresponded to nevus-associated LM/LMM (NALMM) (**Fig. 1**). The clinical aspects of the cohort are described in **Table I**.

Table I. Summary of the demographics of the 201 cases of cutaneous excisions with lentigo maligna/lentigo maligna melanoma (LM/LMM)

Factor	Nevus absent LM/LMM (*N*=159) Cases, *n* (%)	NALMM (*N*=42) Cases, *n* (%)	*p*-value	OR (95% CI)	aOR and *p*-value
Mean age (years)	70.4	70.2	–	–	–
Gender			0.02	2.25 (1.09–4.66)	2.78 (1.28–6.70); *p*=0.01
Female	79 (49.7)	29 (69.0)			
Male	80 (50.3)	13 (31.0)			
Size (mm)			0.41	NS	–
≤10	81 (51.0)	19 (45.2)			
>10 ≤20	52 (32.7)	13 (31.0)			
>20 ≤30	19 (11.9)	5 (11.9)			
>30	7 (4.4)	5 (11.9)			
Location			0.27	NS	–
Cheek	69 (43.4)	26 (62.0)			
Forehead	24 (15.1)	5 (12.0)			
Nose	16 (10.1)	2 (4.7)			
Periorbital	15 (9.4)	2 (4.7)			
Over lip	2 (1.3)	1 (2.4)			
Scalp	4 (2.6)	1 (2.4)			
Chin	1 (0.6)	2 (4.7)			
Ear	5 (3.1)	2 (4.7)			
Neck	6 (3.8)	0 (0)			
Trunk	3 (1.8)	1 (2.4)			
Upper limbs	9 (5.7)	0 (0)			
Lower limbs	5 (3.1)	0 (0)			

NALMM: nevus-associated lentigo maligna/lentigo maligna melanoma; NS: nonsignificant; OR: odds ratio; CI: confidence interval; aOR: adjusted odds ratio.

Table II. Odds ratios for the association of clinical and histopathological variables for NALMM and control group

Factor	Nevus absent LM/LMM ($N=159$) Cases, n (%)	NALMM ($N=42$) Cases, n (%)	p-value	OR (95% CI)	aOR and p-value
Family history	6 (3.7)	3 (7.1)	0.35	1.96 (0.47–8.19)	–
≥ 50 nevi	13 (8.1)	9 (21.4)	0.01	3.06 (1.20–7.76)	2.28 (0.73–7.11) $p=0.15$
Dysplastic nevi	24 (15.0)	12 (28.5)	0.04	2.25 (1.01–4.99)	1.53 (0.59–3.99) $p=0.37$
Other melanoma(s)	29 (18.2)	13 (30)	0.07	2.01 (0.93–4.33)	–
Other NAM	7 (4.4)	7 (16.6)	0.01	4.25 (1.40–12.92)	2.81 (0.75–10.42) $p=0.12$

LM/LMM: lentigo maligna/lentigo maligna melanoma; NALMM: nevus-associated LM/LMM; NAM: nevus-associated melanoma; OR: odds ratio; CI: confidence interval; aOR: adjusted odds ratio.

The univariate logistic regression analysis between the NALMM and nevus-absent LM/LMM group showed a significant association between gender and NALMM, with most patients in this group (69%) corresponding to females (OR 2.25; 95% CI, 1.09–4.66, $p=0.02$). It was observed that 21.4% of NALMM patients presented with multiple nevi (≥ 50 nevi) (OR 3.06; 95% CI 1.20–7.76, $p=0.01$). In addition, 12 patients (28.5%) in the NALMM group (OR 2.25; 95% CI 1.01–4.99, $p=0.04$) have previously had at least one dysplastic nevus removed. About 30% of patients (13 of 42) in the NALMM group presented other cutaneous melanoma, of whom 7 patients (16.6%) (OR 4.25; 95% CI 1.40–12.92, $p=0.01$) had another nevus-associated melanoma (NAM) (**Tables II** and **III**). No significant relationship between variables (gender, multiple nevi, presence of DN, and other NAM) was found with multivariable analysis; however, all the adjusted ORs were higher than 1 (OR > 1), and this divergence is possibly related to the small sample size.

Notably, the only 2 patients who developed melanoma metastasis were from the NALMM group. Both were males, with facial *in situ* lesions that had deep follicular melanocytic distribution (1.6 mm and 1.7 mm) and none of them had another primary melanoma.

DISCUSSION

Two different biological pathways are described for cutaneous melanomas (CM)s, the first one, *de novo* type, corresponding to two-thirds of CMs, is related to chronic sun exposure and occurs preferably in elderly patients. LM and LMM are included in this category and are associated with *TERT* and *TP53* mutations (4, 16, 17). The other type, nevus-associated melanoma (NAM), is related to intermittent sun exposure and sunburn during childhood, and affects younger patients with high nevus count. According to the meta-analysis of Pampena et al. (6), 77.4% of NAMs grow in conjunction with acquired nevi, mainly of intradermal type. A large series, by Shitara et al., with 61 cases, showed a 66.7% concordance in the mutational status of six genes (BRAF, NRAS, KIT, PPP6C, STK19, and RAC1) in melanoma and its associated nevus indicating that both are clonally related (18). NALMM had been described in other studies with a lower frequency (7.7%) compared with our study with 20% (6). This large number in our cohort could be related to the fact that 91% of the LM/LMMs were located in the head and neck region, areas in which intradermal nevi are commonly found (14, 15, 19).

The relatively high number of NALMMs observed in our study, composed of elderly patients (mean age 70.2 years) diverges from the previous concept that NAM is more frequently found in younger adults (< 40 years old) because the number of commonly acquired nevi gradually involutes after the fifth decade (5–11). At the same time, the remaining nevi have an increased risk of becoming malignant, and this trend was especially observed in males (11). Controversially, in our study, females were overrepresented in the NALMM group ($p=0.02$).

Another relevant finding in the univariate logistic regression analysis is that NALMM showed a significant association with multiple nevi ($p=0.01$), likewise with the presence of dysplastic nevus DN ($p=0.04$), both well-known risk factors strongly related to NAM (6). Nevertheless, this aspect contradicts previous concepts that LM/LMM, a *de novo* melanoma (DNM), is rather associated with a low number of moles as it is alleged that intermittent exposure to ultraviolet light has a "naevogenic" effect while chronic exposure might be protective (12, 20, 21).

In our study, there were no differences between groups regarding the risk of developing multiple melanomas, although if another melanoma occurred, patients with NALMM had a 4.3 greater risk that the second melanoma was also of nevus-associated type. Similar findings were described by Echeverría et al. (22), for truncal superficial spreading melanomas (SSM) in younger patients (less than 40 years old). In that specific group of patients,

Table III. Subtypes of other melanomas diagnosed in lentigo maligna/lentigo maligna melanoma (LM/LMM) patients

Groups (n = number of patients)	SSM	LM/LMM	Melanoma *in situ*	Nodular melanoma	Unknown type	Total
NALMM ($n=13$)	4	6	10	2	1	23
Nevus absent LM/LMM ($n=29$)	6	19	20	1	7	53

SSM: superficial spreading melanoma; NALMM: nevus-associated lentigo maligna/lentigo maligna melanoma.

having a primary NAM would increase 9-fold the risk of developing a second NAM, implying a need for careful follow-up for this group.

In previous studies, NAMs were also correlated to a favourable prognosis due to significantly lower mean Breslow compared with *de novo* melanomas, because in thicker melanomas malignant cells can consume or obscure nevus remnants (6, 23–26). However, no differences in sentinel lymph node status and overall survival were described in a large retrospective analysis by Lin et al. (27). Interestingly, the only two melanoma metastases found in our study were from the NALMM group, and both from *in situ* lesions (LM). One of the patients was treated with cryotherapy before surgical excision and 10 years after the GR treatment developed a brain metastasis, which proved to have the same molecular signature as the initial LM (TERT and NF1 mutations). This is the second time that the authors (Drakensjö et al.) describe a metastasis from an *in situ* LM, which was previously abrasively treated before surgical excision (28). Metastasis from *in situ* melanomas are rare, though Bax et al. found an occult invasive component in 33% of previously diagnosed *in situ* melanomas only by taking deeper sections into tissue blocks. Interestingly, they also describe the presence of occult intradermal nevus in 12% of the samples (29). A plausible explanation for the aggressive behaviour of the LM is that previous local trauma, like cryotherapy, ablative, and abrasive treatments, would enhance tumour growth and enable invasion; also the fibrotic tissue after the procedure would render difficult for the identification of the invasive component (30). Lastly, another alternative would be an incorrect interpretation of the dermal component as an incidental nevus rather than an invasive part of the lentigo maligna with nevoid differentiation (31).

Limitations

This study was based on a review of histopathological reports and medical records from a cohort of patients with LM/LMM attending our department for Grenz-ray treatment. As we are looking at a selected subgroup of LM/LMM patients the characteristics might differ when compared with the total population of patients with LM/LMM. Furthermore, confocal microscopy and PRAME (Preferentially expressed Antigen in Melanoma) were not available at our department by the time the samples were collected and histologically analysed.

Conclusion

We conducted the first Swedish study focusing on nevus-associated lentigo maligna and lentigo maligna melanoma (NALMM) in adults and its clinical and histological aspects. We conclude that NALMMs are more frequent than previously reported in the literature, suggesting that the associated nevus could interact or even act as a precursor for LM/LMM through the induction of epidermal melanocytic proliferation, likewise in the recurrent nevus phenomenon.

Future studies including larger samples with multiple histological sections allied to techniques like reflectance confocal microscopy and molecular analysis are essential to determine this biological link between nevus and LM/LMM.

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IRB approval status: The study protocol was submitted and approved by the Regional Ethical Review Board of Stockholm (approval no.: 2017/1511-31/2) and was performed according to the principles of the Declaration of Helsinki.

The authors have no conflicts of interest to declare.

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