Looking beyond the Hutchinson's sign: a retrospective study of clinical factors indicating the presence and invasiveness of nail unit melanoma in patients with longitudinal melanonychia

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ABSTRACT

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Longitudinal melanonychia (LM) presents a challenge since nail unit melanoma (NUM) must be considered as a differential diagnosis. As nail matrix biopsy may result in nail dystrophy, it is important to distinguish NUM from LM. Thus, we aimed to provide evidence of previously reported clinical factors indicative of NUM in patients with LM.

This was a retrospective study of patients who presented with LM and had biopsy-confirmed NUM from 2005 to 2021. Benign LM was either confirmed by biopsy or considered benign if followed without the need for biopsy. Clinical factors associated with LM and NUM were compared by multivariate regression.

A total of 177 patients (97 LM and 80 NUM) were included. Multivariate regression showed that high band color intensity ($p = 0.0031$), variegation ($p = 0.0005$), nail plate splitting ($p = 0.0017$), Hutchinson's sign ($p = 0.0027$), and band change ($p = 0.001$) correlated with malignancy. Nail plate splitting was associated with Breslow thickness. The limitations of this study was that it was retrospective in nature, and not all benign cases were biopsy-confirmed.

Malignancy should be suspected and biopsy performed in patients with LM and high band color intensity, variegation, nail plate splitting, Hutchinson's sign, and band change.

Key words : longitudinal melanonychia; nail unit melanoma; subungual melanoma; retrospective study; Hutchinson's sign

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I. INTRODUCTION

Longitudinal melanonychia (LM) is a tan, brown, grey, or black longitudinal streak in the nail plate that extends from the proximal nail matrix or cuticle to the distal free edge of the nail plate.[1-3] LM has multiple etiologies, which can be classified into the following three categories: exogenous pigmentation, melanocyte activation, and melanocyte proliferation.[3,4] Exogenous pigmentation includes nonmelanocytic causes such as bacterial, mycotic, and blood pigmentation.[4] Melanocyte activation refers to normal number of melanocytes with increased melanin production due to systemic causes such as infection and chemotherapeutic agents.[4] Lastly, melanocyte proliferation represents increased pigmentation due to increased number of melanocytes in the nail matrix. The causes can be benign, such as nail matrix nevus or lentigo, or malignant, specifically nail unit melanoma (NUM).[5]

NUM is considered a variant of acral lentiginous melanoma that arises from the nail matrix. It is relatively rare worldwide, accounting for 0.7% to 3.5% of all melanomas.[6] NUM is more common among dark-skinned individuals, accounting for 20% of all melanomas in African-Americans and 18.2% in Koreans.[7,8] NUM is associated with late diagnosis, leading to poor prognosis, with a 5-year survival rate of 30%, compared to 70-

90% in all cutaneous melanomas.[2,9] The reasons for diagnostic delay include lack of recognition of this clinical entity, difficulties in performing satisfactory biopsies, and occasional pathologic misinterpretation of early lesions.[10,11] Performing nail matrix biopsy is especially difficult since wide excisional biopsies may result in permanent nail dystrophy, malalignment, or postoperative cyst or spicule formation, while smaller punch biopsies may not yield enough specimen.[12] As nail matrix biopsy is not an easily approachable option for both clinicians and patients, the clinical distinction between NUM and benign LM is crucial for early recognition of NUM in patients with LM.

Levit et al. proposed the ABCDEF of subungual melanoma, a screening system aimed at aiding in the early detection of melanoma.[13] *A* stands for age (peak incidence in the fifth to seventh decades of life) and African-Americans, Asians, and native Americans; *B* stands for brown to black band color, with a breadth of 3 mm or more and variegated borders; *C* stands for change in nail band; *D* stands for digit most commonly involved (thumb); *E* stands for extension of the pigment (Hutchinson's sign); and *F* stands for family history of melanoma.[13] Although this rule facilitated the clinical evaluation of LM, studies verifying its validity resulted in conflicting findings. Ko et al. reported that the number of ABCDEF criteria met was not significantly different between benign LM and NUM groups, suggesting that the ABCDEF criteria should be re-examined.[2] Lee et al., on the other hand, found the sensitivity and specificity of the ABCDEF rule to be 100% and 96.6%, respectively, concluding it to be a simple and sensitive clinical strategy for early detection of NUM in situ.[14] Yim et al. also tried to verify some of the factors mentioned in the ABCDEF rule, and they found width to be a significant factor.[15]

In addition to the factors mentioned in the ABCDEF rule, other significant predictors, as reported in the literature, are multicolor pigmentation, blurred lateral borders, triangular shape of the band, and nail plate splitting.[16] To this date, there have only been a few studies validating significant clinical factors suggestive of NUM in patients with LM, and they include only a small population of patients with NUM. Therefore, in our study,

we aimed to provide evidence for clinical factors indicating NUM in patients with LM in a large population of NUM and patients with LM. Furthermore, since the survival rate in NUM is associated with the presence of invasion in the hyponychium and nail bed[17] and tumor thickness,[18] we sought to discover which clinical factors were significantly related to invasiveness and invasion depth in NUM.

II. MATERIALS AND METHODS

1. Patient population and data collection

After approval from the institutional review board at Gangnam Severance Hospital (IRB approval number 3-2022-0042), we retrospectively reviewed patients who visited Gangnam Severance Hospital or Severance Hospital for LM from January 2005 to February 2021.

Benign LM was either diagnosed by nail biopsy or considered benign if followed passively without the need for biopsy. In order to ensure a long enough follow-up period for those who did not undergo biopsy, data ranging from January 2010 to December 2016 were included for benign LM in this study. NUM was diagnosed by biopsy; among these patients, those presenting with nodular melanoma were excluded as it was not difficult to assume malignancy in these patients.

Patients with NUM were further classified into melanoma in situ (MIS) and invasive melanoma (IM), according to their histopathology reports. Patients with NUM whose pathology reports did not specify presence or the depth (in millimeters or micrometers) of invasion were excluded from analysis.

Electronic medical records, clinical photographs, and histopathology reports were retrospectively reviewed. The electronic medical records included sex, age at time of diagnosis, number and location of digit(s) involved, and band changes. For patients with

single digit involvement, clinical photographs were analyzed for band color, color intensity, presence of variegation (Figure 1A), band width as a third of the nail plate width (less than 1/3, 1/3 to 2/3, greater than 2/3), triangular shape of the band (Figure 1B), nail plate splitting (Figure 1C), blurred lateral borders (Figure 1D), and presence of the Hutchinson's sign. In this study, Hutchinson's sign was defined as the extension of pigmentation from the longitudinal melanonychia into the adjacent proximal or lateral nailfolds or hyponychium.[13] We differentiated true Hutchinson's sign from pseudo-Hutchinson's sign, which we defined as pigmentation of the nail matrix observed through the transparent cuticle at the proximal nailfold.[19] The intensity of the band color was scored on a subjective scale of 1 to 10 by a dermatology physician, with 1 representing "least intense" and 10 representing "most intense". For patients with NUM and multiple digit involvement, the digit diagnosed with NUM was examined for photographic analysis.

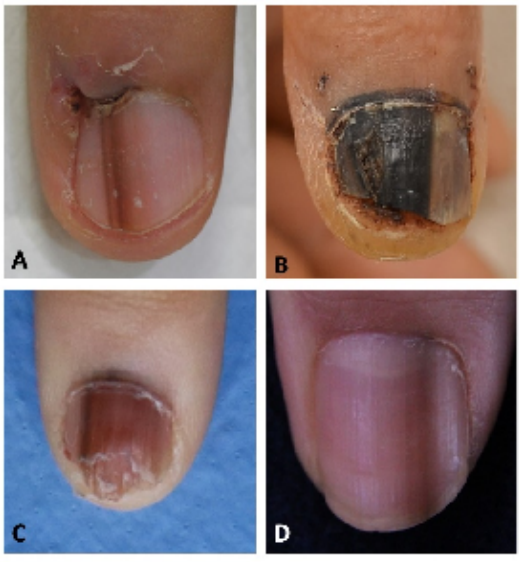

Figure 1. Examples of factors. **A**, variegation; **B**, triangular shape of the band; **C**, nail plate splitting; **D**, blurred lateral border.

2. Statistical analysis

The demographic and clinical factors were analyzed to discover differences between benign LM and NUM. The independent two-sample t-test was used for continuous variables, and chi-squared or Fisher's exact tests were used for categorical variables. To identify factors indicating NUM rather than benign LM, multivariate logistic regression analysis by stepwise selection was performed.

The same factors were analyzed by univariate and multivariate logistic regression analysis to identify factors distinguishing MIS and IM or affecting invasiveness. Furthermore, to identify factors affecting depth of invasion in patients with IM, univariate and multivariate linear regression analyses were performed.

P values < 0.05 was considered statistically significant. All data were analyzed using Statistical Analysis Software (SAS) version 9.4 (SAS Inc., Cary, NC).

III. RESULTS

1. Baseline demographic and clinical characteristics of benign LM and NUM

A total of 177 patients, comprising 97 patients with benign LM and 80 biopsy-proven patients with NUM, were included in the analysis. Demographics of the 177 patients are described in Table 1. The mean age of all patients was 46.8 years, with 107 (60.4%) male and 70 (39.6%) female patients. The mean age of patients with NUM was 53.5 years, which was statistically significantly higher than that of benign LM (41.3 years, $p < 0.0001$). The NUM group also had a statistically higher proportion of female patients (n=38, 47.5%), than the benign LM group (n=32, 32.9%) ($p = 0.0494$).

Among the 177 patients, 140 (79.1%) had single digit involvement. The NUM group had a significantly higher proportion of single digit involvement (n=78, 97.5%) than the

benign LM group (n=62, 63.9%) ($p < 0.0001$). For these 140 patients with single digit involvement and the two patients with NUM and multiple digit involvement, location of the melanonychia was noted and photographs were analyzed. Of these 142 patients, 71 patients (50.0%) had melanonychia on the right side and 103 (72.5%) patients had it on the hand, with the first digit being the most common site, with 92 (64.8%) patients. The NUM group had a statistically higher proportion of hand involvement (n=64, 80.0%) than the benign LM group (n=39, 62.9%) ($p = 0.0236$). There was no significant difference in the proportion of the affected side or digit number (first to fifth).

Table 1. Baseline demographic and clinical characteristics by malignancy status

Characteristic	Total LM (N=177 or 142*) Mean±SD or N (%)	Benign LM (n=97 or 62**) Mean±SD or n (%)	NUM (n=80) Mean±SD or n (%)	*P* value
Age	46.831±18.577	41.320±19.741	53.513±14.585	<.0001***
Sex				0.0494***
Male	107 (60.45)	65 (67.01)	42 (52.50)	
Female	70 (39.55)	32 (32.99)	38 (47.50)	
Number of digits involved				<.0001***
Single	140 (79.10)	62 (63.92)	78 (97.50)	
Multiple	37 (20.90)	35 (36.08)	2 (2.50)	
Side				0.0906
Right	71 (50.00)	26 (41.94)	45 (56.25)	
Left	71 (50.00)	36 (58.06)	35 (43.75)	
Extremity				0.0236***
Hand	103 (72.54)	39 (62.90)	64 (80.00)	
Foot	39 (27.46)	23 (37.10)	16 (20.00)	
Digit				0.0668

First	92 (64.79)	46 (74.19)	46 (57.50)
Second	19 (13.38)	9 (14.52)	10 (12.50)
Third	10 (7.04)	3 (4.84)	7 (8.75)
Fourth	11 (7.75)	1 (1.61)	10 (12.50)
Fifth	10 (7.04)	3 (4.84)	7 (8.75)

LM, Longitudinal melanonychia; *NUM*, Nail unit melanoma; *SD*, standard deviation.
*N=177 for Age, Sex, Number of digits involved. N=142 for Side, extremity, digit. The 35 excluded are those with multiple digit involvement in benign LM.
** N=97 for Age, Sex, Number of digits involved. N=62 for Side, extremity, digit. The 35 excluded are those with multiple digit involvement in benign LM.
****P* values less than .05 are significant

2. Comparison of factors associated with benign LM and NUM

The comparison of factors associated with benign LM and NUM is shown in Table 2. Factors that showed significant difference between benign LM and patients with NUM were as follows: the NUM group had higher band color intensity (7.78 vs 3.85, $p < 0.0001$); higher proportion of black (34 (42.5%) vs 24 (38.7%)) and multicolor (25 (31.2%) vs 0 (0.0%), $p < 0.0001$) bands; higher proportion of variegation (46 (57.5%) vs 8 (12.9%), $p < 0.0001$); higher proportion of width involving 1/3 – 2/3 of the whole nail (24 (30.0%) vs 10 (16.1%)) and greater than 2/3 (45 (56.2%) vs 1 (1.6%), $p < 0.0001$); higher proportion of nail plate splitting (42 (52.5%) vs 1 (1.6%), $p < 0.0001$); higher proportion of Hutchinson's sign (59 (73.7%) vs 5 (8.06%), $p < 0.0001$); and higher proportion of recent band change (48 (60.0%) vs 9 (14.5%), $p < 0.0001$). Triangular band shape and blurred lateral borders did not show significantly different proportions between benign LM cases and patients with NUM.

Table 2. Comparison of factors between benign LM and NUM

Characteristic	Total LM (N=142)	Benign LM (n=62)	NUM (n=80)	*P* value

	Mean±SD or N (%)	Mean±SD or n (%)	Mean±SD or n (%)	
Intensity	6.070±3.036	3.855±2.462	7.788±2.220	<.0001*
Color				<.0001*
Brown	59 (41.55)	38 (61.29)	21 (26.25)	
Black	58 (40.85)	24 (38.71)	34 (42.50)	
Multicolor	25 (17.61)	0 (0.00)	25 (31.25)	
Variegation				<.0001*
Homogeneous	88 (61.97)	54 (87.10)	34 (42.50)	
Variegated	54 (38.03)	8 (12.90)	46 (57.50)	
Width (proportion of nail width)				<.0001*
<1/3	62 (43.66)	51 (82.26)	11 (13.75)	
1/3~2/3	34 (23.94)	10 (16.13)	24 (30.00)	
>2/3	46 (32.39)	1 (1.61)	45 (56.25)	
Triangular shape of the band				0.1318
No	138 (97.18)	62 (100.00)	76 (95.00)	
Yes	4 (2.82)	0 (0.00)	4 (5.00)	
Nail plate splitting				<.0001*
No	96 (67.61)	58 (93.55)	38 (47.50)	
Yes	46 (32.39)	4 (6.45)	42 (52.50)	
Blurred lateral borders				0.1444
No	74 (52.11)	28 (45.16)	46 (57.50)	
Yes	68 (47.89)	34 (54.84)	34 (42.50)	
Hutchinson's sign				<.0001*
No	78 (54.93)	57 (91.94)	21 (26.25)	
Yes	64 (45.07)	5 (8.06)	59 (73.75)	
Band change				<.0001*

No	85 (59.86)	53 (85.48)	32 (40.00)
Yes	57 (40.14)	9 (14.52)	48 (60.00)

LM, Longitudinal melanonychia; *NUM*, Nail unit melanoma; *SD*, standard deviation.
**P* values less than .05 are significant

3. Factors indicating malignancy in patients with LM

Factors indicating malignancy in patients with LM were estimated using multivariate logistic regression analysis by stepwise selection (Table 3). High band color intensity (p = 0.0031), presence of variegation (p = 0.0005), nail plate splitting (p = 0.0017), Hutchinson's sign (p = 0.0027), and band change (p = 0.001) showed significant correlations with malignancy.

Table 3. Multivariate logistic regression analysis for factors indicating NUM in LM

	Multivariate model	
Characteristic	OR (95% CI)	*P* value*
Intensity	2.342 (1.333-4.115)	0.0031
Variegation		
Homogeneous	ref	
Variegated	280.503 (11.917-6602.597)	0.0005
Nail plate splitting		
No	ref	
Yes	102.599 (5.722-1839.634)	0.0017
Hutchinson's sign		
No	ref	
Yes	95.154 (4.839-1871.159)	0.0027

Band change		
No	ref	
Yes	306.564 (10.100-9305.052)	0.001

NUM, Nail unit melanoma; *LM*, Longitudinal melanonychia; *OR*, Odds ratio; *CI*, Confidence interval.
**P* values less than .05 are significant

4. Factors indicating invasiveness in patients with NUM

Among the 80 biopsy-proven patients with NUM, histopathologic reports did not specify the presence of invasion in three patients. Therefore, a total of 77 patients, comprising 55 and 22 patients with MIS and IM, respectively, were included in the analysis. Baseline demographic and clinical characteristics are shown in table 4. All variates were subject to univariate logistic regression analysis, from which significant factors were selected by stepwise selection method to perform multivariate logistic regression (Table 5). Univariate analysis showed that nail plate splitting had a positive correlation (p = 0.002) with invasion, while blurred lateral borders had a negative correlation (p = 0.0392). Multivariate analysis corroborated these results.

Table 4. Baseline demographic and clinical characteristics by invasion status

Characteristic	Total (N=77) Mean±SD or N (%)	In situ (n=55) Mean±SD or n (%)	Invasive (n=22) Mean±SD or n (%)	p-value
Age	53.675±14.818	51.691±15.419	58.636±12.132	0.0627
Sex				0.3109
Male	42 (54.55)	28 (50.91)	14 (63.64)	
Female	35 (45.45)	27 (49.09)	8 (36.36)	
Intensity	7.740±2.233	7.436±2.291	8.500±1.921	0.0584
Number of digits involved				1
Single	75 (97.40)	53 (96.36)	22 (100.00)	

Multiple	2 (2.60)	2 (3.64)	0 (0.00)	
Side				0.8846
Right	43 (55.84)	31 (56.36)	12 (54.55)	
Left	34 (44.16)	24 (43.64)	10 (45.45)	
Extremity				0.2116
Hand	61 (79.22)	46 (83.64)	15 (68.18)	
Foot	16 (20.78)	9 (16.36)	7 (31.82)	
Digit				0.6467
First	45 (58.44)	34 (61.82)	11 (50.00)	
Second	10 (12.99)	6 (10.91)	4 (18.18)	
Third	7 (9.09)	5 (9.09)	2 (9.09)	
Fourth	9 (11.69)	5 (9.09)	4 (18.18)	
Fifth	6 (7.79)	5 (9.09)	1 (4.55)	
Color				0.9158
Brown	20 (25.97)	15 (27.27)	5 (22.73)	
Black	34 (44.16)	24 (43.64)	10 (45.45)	
Multicolor	23 (29.87)	16 (29.09)	7 (31.82)	
Variegation				0.0687
Homogeneous	33 (42.86)	20 (36.36)	13 (59.09)	
Variegated	44 (57.14)	35 (63.64)	9 (40.91)	
Width (proportion of nail width)				0.2146
<1/3	10 (12.99)	8 (14.55)	2 (9.09)	
1/3~2/3	23 (29.87)	19 (34.55)	4 (18.18)	
>2/3	44 (57.14)	28 (50.91)	16 (72.73)	
Triangular shape of the band				0.5735
No	73 (94.81)	53 (96.36)	20 (90.91)	
Yes	4 (5.19)	2 (3.64)	2 (9.09)	
Nail plate splitting				0.0009*
No	37 (48.05)	33 (60.00)	4 (18.18)	
Yes	40 (51.95)	22 (40.00)	18 (81.82)	
Blurred lateral borders				0.034*
No	45 (58.44)	28 (50.91)	17 (77.27)	
Yes	32 (41.56)	27 (49.09)	5 (22.73)	
Hutchinson's sign				0.324
No	20 (25.97)	16 (29.09)	4 (18.18)	
Yes	57 (74.03)	39 (70.91)	18 (81.82)	
Band change				0.4599

No	30 (38.96)	20 (36.36)	10 (45.45)
Yes	47 (61.04)	35 (63.64)	12 (54.55)

SD, standard deviation.
**P* values less than .05 are significant

Table 5. Univariate and multivariate logistic regression analysis for factors indicating IM in NUM

	Univariate model*		Multivariate model**	
Characteristic	OR (95% CI)	*P* value***	OR (95% CI)	*P* value***
Nail plate splitting				
No	ref		ref	
Yes	6.750 (2.012-22.643)	0.002	7.333 (2.098-25.627)	0.0018
Blurred lateral borders				
No	ref		ref	
Yes	0.305 (0.099-0.943)	0.0392	0.269 (0.080-0.907)	0.0343

IM, Invasive melanoma; *NUM*, Nail unit melanoma; *OR*, Odds ratio; *CI*, Confidence interval.
*Univariate model included all variates. Only significant variates are displayed here.
**Multivariate model by stepwise selection using significant variates from univariate model
****P* values less than .05 are significant

5. Factors affecting invasion depth in patients with NUM

Among 77 patients, invasion depth (Breslow thickness) was available in the pathologic reports for 55 patients. Univariate and multivariate linear regression revealed nail plate splitting as the only significant factor correlating with invasion depth. The beta coefficient value was 0.734, indicating that on average, those with nail plate splitting had an invasion depth 0.734 millimeter greater than those without nail plate splitting (Table 6).

Table 6. Univariate and multivariate linear regression analysis for factors affecting invasion depth in NUM

Characteristic	Univariate and multivariate model*	
	Beta (SE)	*P* value**
Nail plate splitting		
No	ref	
Yes	0.734 (0.253)	0.0055

NUM, Nail unit melanoma; *SE*, standard error
*Univariate and multivariate linear regression analysis revealed the same finding
***P* values less than .05 are significant

IV. DISCUSSION

LM poses a diagnostic challenge as the possibility of NUM must always be considered in the differential diagnosis. Nail matrix biopsy is required for the definitive diagnosis of NUM. However, nail matrix biopsy is associated with risks such as permanent nail dystrophy or insufficient specimen. Ideally, such an invasive biopsy would be performed as a confirmatory measure only for patients with LM with high clinical suspicion of malignancy. Therefore, in this study, we aimed to aid clinicians in distinguishing NUM in patients with LM by comparing various clinical factors between patients with benign LM and NUM. Using multivariate logistic regression analysis, we showed that patients with LM with high band color intensity, variegation, nail plate splitting, Hutchinson's sign, and band change were more likely to show malignancy. In other words, nail matrix biopsy should be considered in patients presenting with the aforementioned factors.

In a retrospective cohort of 60 cases of benign LM and eight patients with NUM, Yim et al. performed multivariate logistic regression analysis and found LM width percentage as a significant indicator. They suggested that involvement of > 28% of the whole nail is suggestive of NUM rather than benign LM.[15] In another cohort of 76 cases of benign LM

and eight patients with NUM, Ko et al. did not perform multivariate analysis, but suggested the cutoff point as LM width > 40% of the whole nail.[2] In our large cohort of 97 benign LM and 80 patients with NUM, width > 1/3 of the whole nail showed significant difference between the two groups, but importantly was not significant upon multivariate analysis. We suggest this discrepancy may be due to difference in sample size of patients with NUM.

In our study, nail plate splitting was not only an indicator of malignancy but also a significant indicator of invasiveness and invasion depth. Changes in the nail plate are known to be dependent on the location and extent of the nail matrix injury. While the distal matrix produces the deeper two-thirds of the nail plate, the proximal matrix produces the superficial third. Therefore, a small damage to the distal nail matrix results in little or no nail distortion since the normal superficial third (produced by the unaffected proximal nail matrix) covers the defective deeper two-thirds.[20] On the other hand, alteration of the proximal or the entire matrix leads to the production of a thin nail plate that easily breaks even with daily life activities, resulting in nail splitting.[21] Considering that NUM arises from abnormal nail matrix melanocytes, it is reasonable to associate nail splitting to locally advanced melanoma, which is an association supported by previous studies.[8,21] Therefore, the presence of nail splitting in patients with LM may indicate destruction of a large part of the nail matrix, which suggests NUM rather than benign LM, and IM rather than MIS.

There are several limitations to our study. First, not all patients with benign LM were biopsy-confirmed. Given that most LM are benign and do not change, it is not standard of care to perform biopsy in most of these patients. Thus, it remains very difficult to obtain an adequate number of biopsy-confirmed benign patients with LM to match the number of patients with NUM. Second, we could not analyze the dermoscopic findings because dermoscopy was not widely used in the early study period. However, our aim was to provide a clinical guideline for early selection of patients with LM at risk for NUM, and

we believe that analysis of clinical photographs suffices. Lastly, our study was limited in that it was retrospective in nature. Future studies should include a large, prospective cohort study of patients with LM undergoing biopsy, with both clinical and dermoscopic photographs.

V. CONCLUSION

In summary, malignancy should be suspected and biopsy should be performed in patients with LM with high band color intensity, variegation, nail plate splitting, Hutchinson's sign, and band change. Nail plate splitting, especially, indicates the presence of invasive melanoma and greater Breslow depth, raising greater alarm in management.

REFERENCES

1. Baran R, Kechijian P. Longitudinal melanonychia (melanonychia striata): diagnosis and management. *J Am Acad Dermatol.* 1989;21(6):1165-75.
2. Ko D, Oromendia C, Scher R, Lipner SR. Retrospective single-center study evaluating clinical and dermoscopic features of longitudinal melanonychia, ABCDEF criteria, and risk of malignancy. *J Am Acad Dermatol.* 2019;80(5):1272-83.
3. Singal A, Bisherwal K. Melanonychia: Etiology, Diagnosis, and Treatment. *Indian Dermatol Online J.* 2020;11(1):1-11.
4. Haneke E, Baran R. Longitudinal melanonychia. *Dermatol Surg.* 2001;27(6):580-4.
5. Tosti A, Baran R, Piraccini BM, Cameli N, Fanti PA. Nail matrix nevi: a clinical and histopathologic study of twenty-two patients. *J Am Acad Dermatol.* 1996;34(5 Pt 1):765-71.
6. Mole RJ, MacKenzie DN. Subungual Melanoma. *StatPearls*. Treasure Island (FL)2022.
7. Kim JH, Park JH, Lee DY. Site distribution of cutaneous melanoma in South Korea: a retrospective study at a single tertiary institution. *Int J Dermatol.* 2015;54(1):e38-9.
8. Lee DJR, Arbache ST, Quaresma MV, Nico MMS, Gabbi TVB. Nail Apparatus Melanoma: Experience of 10 Years in a Single Institution. *Skin Appendage Disord.* 2018;5(1):20-6.
9. Giblin AV, Thomas JM. Incidence, mortality and survival in cutaneous melanoma. *J Plast Reconstr Aesthet Surg.* 2007;60(1):32-40.
10. Ishihara Y, Matsumoto K, Kawachi S, Saida T. Detection of early lesions of "ungual" malignant melanoma. *Int J Dermatol.* 1993;32(1):44-7.
11. Tan KB, Moncrieff M, Thompson JF,McCarthy SW, Shaw HM, Quinn MJ, et al. Subungual melanoma: a study of 124 cases highlighting features of early lesions, potential pitfalls in diagnosis, and guidelines for histologic reporting. *Am J Surg Pathol.* 2007;31(12):1902-12.
12. Jellinek N. Nail matrix biopsy of longitudinal melanonychia: diagnostic algorithm including the matrix shave biopsy. *J Am Acad Dermatol.* 2007;56(5):803-10.
13. Levit EK, Kagen MH, Scher RK, Grossman M, Altman E. The ABC rule for clinical detection of subungual melanoma. *J Am Acad Dermatol.* 2000;42(2 Pt 1):269-74.
14. Lee JH, Park JH, Lee JH, Lee DY. Early Detection of Subungual Melanoma In Situ: Proposal of ABCD Strategy in Clinical Practice Based on Case Series. *Ann Dermatol.* 2018;30(1):36-40.

15. Yim SH, Kwon IS, Hong D, Jung KE, Lee Y, Seo YJ, et al. Predictor of Subungual Melanoma against Benign Longitudinal Melanonychia: A Retrospective Cohort Study from Korea. *Ann Dermatol.* 2021;33(2):147-53.
16. Lipner SR, Scher RK. Evaluation of nail lines: Color and shape hold clues. *Cleve Clin J Med.* 2016;83(5):385-91.
17. Yoo H, Kim H, Kwon ST, Jo SJ, Mun JH, Lee C, et al. Tumor invasion in the hyponychium is associated with distant metastasis and poor prognosis in subungual melanoma: A histologic landscape of 44 cases. *J Am Acad Dermatol.* 2022;86(5):1027-34.
18. Ohn J, Hur K, Cho Y, Park J, Kim JY, Lee SJ, et al. Developing a predictive model for distinguishing invasive nail unit melanoma from nail unit melanoma in situ. *J Eur Acad Dermatol Venereol.* 2021;35(4):906-11.
19. Ohn J, Choe YS, Mun JH. Dermoscopic features of nail matrix nevus (NMN) in adults and children: A comparative analysis. *J Am Acad Dermatol.* 2016;75(3):535-40.
20. de Berker DA, Andre J, Baran R. Nail biology and nail science. *Int J Cosmet Sci.* 2007;29(4):241-75.
21. Inthasot S, Andre J, Richert B. Causes of longitudinal nail splitting: a retrospective 56-case series with clinical pathological correlation. *J Eur Acad Dermatol Venereol.* 2022;36(5):744-53.

ABSTRACT(IN KOREAN)

손발톱 흑색선에서 악성 흑색종 및 흑색종의 침범 여부를 시사하는 임상적 인자들에 관한 후향적 연구

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이 상 균

손발톱 흑색선은 반드시 악성 흑색종을 감별해야 하므로 진단적으로 중요한 의미를 갖는다. 손발톱바탕질 조직검사가 악성 흑색종을 감별할 수 있는 유일한 방법이지만, 이는 영구적인 손발톱 손상을 초래할 수 있기 때문에 손발톱 흑색선에서 임상적으로 악성 흑색종을 구분하는 것이 중요하다. 많은 문헌들에서 악성 흑색종을 시사하는 인자들을 보고하고 있으나, 아직까지 이를 다수의 환자들을 대상으로 통계적인 뒷받침을 하는 연구는 없는 상태이다. 이에 본 연구의 저자들은 이전에 알려진 인자들을 대상으로 어떤 인자들이 유의하게 악성 흑색종을 시사하는 지 통계적 증거를 제공하고자 한다.

본 연구는 후향적 임상분석연구로 진행되었다. 2005년부터 2021년 사이에 신촌 및 강남세브란스병원에서 손발톱 흑색선으로 내원한 환자들을 대상으로 하였다. 악성 흑색종 환자들은 모두 조직검사에서 흑색종으로 진단 되었으며, 양성 흑색선은, 조직검사에서 양성으로 진단되었거나, 조직검사 없이 5년 이상 경과 관찰한 경우로 정의하였다. 두 군 간 임상적 인자들 간의 차이에 대해 다변량 로지스틱 회귀 분석을 진행하였다.

총 177명의 환자들의 코호트가 구축되었고, 97명의 양성 흑색선, 그리고 80명의 악성 흑색종 환자들이 포함되었다. 다변량 로지스틱 회귀 분석에서 진한 흑색선 색도 (p = 0.0031), 색깔 얼룩덜룩함 (p = 0.0005), 손발톱판 갈라짐 (p = 0.0017), Hutchinson's sign (p = 0.0027), 선의 변화 (p = 0.001)가 흑색선에서 악성 흑색종과 유의미한 연관이 있었다. 또한, 이 중 손발톱판 갈라짐은 흑색종의 침범 여부와 침범 깊이와 연관이 있었다. 본 연구의 제한점으로는, 연구 특성 상 후향적 연구 이었다는 점과, 모든 양성 흑색선이 조직검사로 확인되지 못했다는 점이다.

손발톱 흑색선 환자에서 흑색선이 색깔이 진하거나, 얼룩덜룩 하거나, 손발톱판이 갈라지거나, Hutchinson's sign이 보이거나, 변화가 있는 경우에는 악성 흑색종을 의심하여 조직검사를 시행 하여야겠다.

핵심되는 말 : 손발톱 흑색선, 악성 흑색종, 손발톱 흑색종, 후향적 연구, Hutchinson's sign