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ORIGINAL ARTICLE

Predictor of Subungual Melanoma against Benign Longitudinal Melanonychia: A Retrospective Cohort Study from Korea

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Background: Longitudinal melanonychia (LM) is a common clinical finding. Most cases of LM are benign, and a wait-and-see approach is preferred in the management of this condition. Nevertheless, it is important for clinicians to distinguish subungual melanoma (SUM) from other benign LMs. **Objective:** To evaluate the demographic and clinicopathologic characteristics of LM in the Korean population and to identify the predictor of SUM against other benign conditions. **Methods:** This was a single-center retrospective cohort study including patients who underwent nail biopsy for LM from January 2000 to May 2019. To identify the predictor of SUM, receiver operating characteristic (ROC) analyses was performed. **Results:** A total of 68 cases of biopsy-proven LM were included in the analysis. Among the 68 cases, 8 were SUM. In univariable analysis, patients diagnosed with SUM were older ($p=0.035$) and had a longer disease duration ($p=0.004$). They also showed multicolor pigmentation of LM ($p=0.022$), a larger width of LM ($p<0.001$), and associated nail plate dystrophy ($p=0.010$) than patients diagnosed with benign conditions. In multivariable logistic regression, width of LM showed statistical significance (odds ratio, 1.083; 95% confidence interval, 1.018～1.153). ROC analysis suggested that an LM width >28% of the whole nail was the predictor of SUM (area under the curve=0.883; $p<0.001$). **Conclusion:** SUM has distinct demographic and clinical features. The width of LM can predict SUM against other benign LMs. **(Ann Dermatol 33(2) 147～153, 2021)**

-Keywords-
Longitudinal melanonychia, Melanocytic activation, Melanocytic proliferation, Subungual melanoma, Width

INTRODUCTION

Longitudinal melanonychia (LM) refers to a brown-black pigmented streak in the nail plate that runs from the proximal nail fold and extending to the distal nail plate longitudinally[1,2]. LM can be caused by exogenous pigments or hyperactivation or hyperplasia of melanocytes. Chronic local trauma, infections, medication, and ethnic melanonychia (occurring in dark-skinned persons) are the common causes of increased activation of melanocytes, whereas hyperplasia of melanocytes is due to lentigo of the matrix, nail matrix nevus or subungual melanoma (SUM)[1-3]. Although most cases of LM are benign and a wait-and-see approach is preferred in the management of this condition, it is important for clinicians to distinguish SUM from other benign LMs[1-3].

SUM is considered a variant of acral lentiginous melano-

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ma that arises from the nail matrix and may also arise from the nailbed although the latter cannot produce a pigmented streak[4]. Even though melanoma is not a common disease in Asian populations, the incidence of acral lentiginous melanoma and SUM is relatively high[5,6]. Clinical features such as widening of the streak, pigmentary change of the surrounding nail fold (Hutchinson's sign), nail plate dystrophy, darkening, or pigment variegation can be signs for suspecting SUM; however, it is difficult to differentiate SUM from other benign conditions in the early stage[1,2,5]. Owing to delayed diagnosis, the prognosis of SUM is poor[1,2,5]. To enable early recognition of SUM, previous studies have suggested criteria for distinguishing SUM from other benign conditions[2,5,7].

In this study, we retrospectively evaluated the demographic and clinicopathologic characteristics of LM in the Korean population. In addition, we also sought to identify demographic and clinical features for distinguishing SUM from other benign conditions.

MATERIALS AND METHODS

Patients and data acquisition

After obtaining approval from the institutional review board at Chungnam National University Hospital (approval no. 2019-03-032-002), we retrospectively reviewed patients who visited our hospital and underwent nail biopsy for LM from January 2000 to May 2019.

We retrieved the data of demographic and clinical characteristics, such as age, sex, past medical history, duration of LM, involved digit, change in LM features, and pathologic report of nail biopsy from the electronic medical records. Clinical photographs were also reviewed, and the color, width, pigment variegation (monochromic: LM in a single color and heterochromic: LM in multiple colors), and border of LM were evaluated. In addition, the presence of nail plate dystrophy and Hutchinson's sign was also assessed. The width of LM was measured at the line perpendicular to the longitudinal axis of the nail at the midpoint of the nail plate. The width of LM was calculated as the ratio of the LM to the whole nail.

All patients enrolled in the study underwent nail biopsy for histologic diagnosis. The procedure for nail biopsy was as follows: lidocaine was injected for local anesthesia; the nail plate was extracted after making longitudinal incisions at the lateral ends of the proximal nail fold; and the nail matrix was exposed. The specimen was obtained at the darkest matrix portion of LM.

The histopathologic diagnosis of LM was categorized as follows: melanocytic activation (increased pigmentation in the basal layer of the matrix without an increase in the number of melanocytes), melanocytic proliferation (increased number of melanocytes in the basal layer of the matrix without atypia), and SUM.

Statistical analysis

The demographic, clinical, and histologic variables were analyzed to determine the differences among the causes of LM. For comparing continuous variables, Mann–Whitney test and Kruskal–Wallis test were used for statistical analysis. Categorical variables were analyzed using Fisher's exact test. To identify the features distinguishing SUM from oth-

Table 1. Demographic features of patients according to histopathologic diagnosis

Variable	Total patients (n=68)	Melanocytic activation (n=49)	Melanocytic proliferation (n=11)	Subungual melanoma (n=8)	*p*-value
Age (yr)	35.2±20.1	36.8±18.0	18.7±20.2	48.5±20.4	0.005
Sex					0.153
Male	30 (44.1)	18 (36.7)	7 (63.6)	5 (62.5)	
Female	38 (55.9)	31 (63.3)	4 (36.4)	3 (37.5)	
Duration of LM (mo)	42.8±64.9	29.0±45.5	22.5±26.1	141.0±99.6	0.016
Comorbidity					-
Diabete	2 (2.9)	0 (0)	0 (0)	2 (25.0)	
Hypertension	5 (7.4)	1 (2.0)	1 (9.1)	3 (37.5)	
Latent tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)	
Renal insufficiency	0 (0)	0 (0)	0 (0)	0 (0)	
Chronic hepatitis	0 (0)	0 (0)	0 (0)	0 (0)	
Heart disease and stroke	0 (0)	0 (0)	0 (0)	0 (0)	
Hyperlipidemia	1 (1.5)	0 (0)	0 (0)	1 (12.5)	
Immune suppressing disease	1 (1.5)	1 (2.0)	0 (0)	0 (0)	
Immune suppressants	2 (2.9)	2 (4.1)	0 (0)	0 (0)	

Values are presented as mean±standard deviation or number (%). LM: longitudinal melanonychia, -: not available.

er benign conditions, multivariable logistic regression analysis was performed on variables that showed statistically significant in Kruskal–Wallis test, and Fisher's exact test. Lastly, to investigate the predictor of SUM and to calculate its sensitivity and specificity, we performed a receiver operating characteristic (ROC) analysis. Results are expressed as mean±standard deviation, and a *p*-value of <0.05 was considered statistically significant. Data were analyzed using IBM SPSS software (ver. 24.0; IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, we enrolled 68 patients with LM whose pathologic diagnosis was hyperactivation or hyperplasia of melanocytes (Table 1, Fig. 1). Of the 68 enrolled patients, 49 (72.1%) had LM due to melanocytic activation, 11 (16.2%) had LM due to melanocytic proliferation, and 8 (11.8%) had SUM. The average age of the 68 patients was 35.2±20.1 years. Compared with the average age of patients with melanocytic activation and melanocytic proliferation (36.8±18.0 and 18.7±20.2 years, respectively), the average age of patients with SUM was higher (48.5±20.4 years) ($p=0.005$). With respect to the duration of LM, patients with SUM had a longer duration (141.0±99.6 months) than patients with melanocytic activation or melanocytic proliferation (29.0±45.5 months for melanocytic activation and 22.5±26.1 months for melanocytic proliferation) ($p=0.016$).

In the 68 patients, 36 (52.9%) LMs involved the left side, whereas 75.0% of SUMs involved the right side ($p=0.046$; Table 2). With respect to the locations of LM, 53 (77.9%) were on the hand and 15 (22.1%) were on the foot. However, all SUMs were located on the hand ($p=0.253$). The mean width of LM (ratio of the LM to the whole nail) was 0.21±0.17. The width of LM in SUM cases (0.49±0.26) was wider than that in cases due to melanocytic activation or melanocytic proliferation (0.17±0.11 and 0.16±0.13, respectively) ($p=0.002$). Among the 68 patients, 15 (22.1%) complained of nail plate dystrophy. The frequency of nail plate dystrophy in SUM cases (62.5%) was higher than that in cases due to melanocytic activation and melanocytic proliferation (18.4% and 9.1%, respectively) ($p=0.015$). Hutchinson's sign, pigmentary change of the surrounding nail fold, was found in 23.5% of the overall LM cases. In particular, the Hutchinson's sign was present in 54.5% of cases due to melanocytic proliferation and 50.0% of SUM cases ($p=0.002$).

In addition, we divided the enrolled patients into two groups (benign LM and SUM) and performed subgroup analysis (Table 3). The patients who diagnosed with SUM have an older age ($p=0.035$), longer duration ($p=0.004$) and wider width of LM ($p<0.001$). The results showed that pigment variegation of LM and nail plate dystrophy were more frequently in the SUM group ($p=0.022$ for pigment variegation and $p=0.010$ for nail plate dystrophy).

We performed multivariable logistic regression analysis for the clinical features of LM showing statistical significance in Kruskal–Wallis test and Fisher's exact test between benign LM and SUM (age, width of LM, color of LM, and nail plate dystrophy). The analysis revealed that the width of LM had statistical significance (odds ratio: 1.083; 95% confidence interval: 1.018~1.153) (Table 4). Lastly, the ROC analysis revealed that when cutoff point for the width of LM was 0.28, the sensitivity and specificity was 0.750 and 0.883, respectively (area under the curve=0.883, $p<0.001$) (Fig. 2).

DISCUSSION

In this study, we found that SUM has distinct demographic and clinical features from those of other benign melanocytic lesions. Patients with SUM were older and their disease duration was longer. In addition, they more frequently

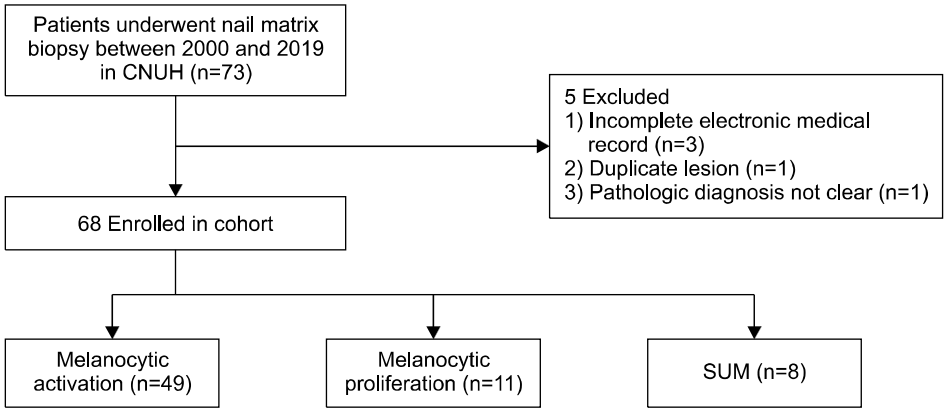

Fig. 1. Flowchart of study. CNUH: Chungnam National University Hospital, SUM: subungual melanoma.

Table 2. Clinical features of LM according to histopathologic diagnosis

Variable	Total patients (n=68)	Melanocytic activation (n=49)	Melanocytic proliferation (n=11)	Subungual melanoma (n=8)	*p*-value
Location of LM					
Hand or foot					0.253
Hand	53 (77.9)	36 (73.5)	9 (81.8)	8 (100)	
Foot	15 (22.1)	13 (26.5)	2 (18.2)	0 (0)	
Right or left					0.046
Right	32 (47.1)	24 (49.0)	2 (18.2)	6 (75.0)	
Left	36 (52.9)	25 (51.0)	9 (81.8)	2 (25.0)	
Involved digit					-
1st	26 (38.2)	18 (36.7)	4 (36.4)	4 (50.0)	
2nd	14 (20.6)	11 (22.4)	3 (27.3)	0 (0)	
3rd	6 (8.8)	5 (10.2)	0 (0)	1 (12.5)	
4th	11 (16.2)	9 (18.4)	1 (9.1)	1 (12.5)	
5th	11 (16.2)	6 (12.2)	3 (27.3)	2 (25.0)	
Width of LM (ratio)	0.21±0.17	0.17±0.11	0.16±0.13	0.49±0.26	0.002
Color of LM					0.050
Monochromic	36 (52.9)	28 (57.1)	7 (63.6)	1 (12.5)	
Heterochromic	32 (47.1)	21 (42.9)	4 (36.4)	7 (87.5)	
Hutchinson sign	16 (23.5)	6 (12.2)	6 (54.5)	4 (50.0)	0.002
Border of LM					0.919
Well defined	43 (63.2)	30 (61.2)	7 (63.6)	6 (75.0)	
Blurred	25 (36.8)	19 (38.8)	4 (36.4)	2 (25.0)	
Nail plate dystrophy	15 (22.1)	9 (18.4)	1 (9.1)	5 (62.5)	0.015
Longitudinal ridge	12	7	1	4	
Split of nail plate	1	0	0	1	
Nail plate dystrophy	1	1	0	0	
Horizontal groove	1	1	0	0	
Recent change of LM*	21 (30.9)	13 (26.5)	3 (27.3)	5 (62.5)	0.147
Change of color	12	8	3	1	
Change of width	11	7	0	4	
Change of length	1	0	0	1	

Values are presented as number (%), mean±standard deviation, or number only. LM: longitudinal melanonychia, -: not available. *The detailed symptoms appeared independently or in combination, the number of 'recent change of LM' and the number of detailed symptoms can be different.

showed involvement of the right side of the extremities. The other distinct characteristics of SUM included a wider width than benign LM and being accompanied by nail plate dystrophy. Although statistically insignificant, SUM showed the following different features from LM due to melanocytic activation or melanocytic proliferation: 87.5% of SUMs showed pigment variegation ($p=0.050$) and 62.5% of patients with SUM experienced recent change in their LM. Moreover, when we divided enrolled patients into two groups (benign LM and SUM), pigment variegation of LM was more frequently found in the patients of SUM ($p=0.022$). The results of our study are in line with those of previous studies[2,3,5-7]. Previously, Lee et al.[5] and Saida and Ohshima[6] summarized the characteristic features of SUM. They suggested that SUM had distinct features such as LM onset in adult age, width >6 mm, brown band with shades of black, nail deformity, Hutchinson's sign, and involvement of one digit[5,6]. Chakera et al.[8] also reported the clinical characteristics of SUM of hand. They found that SUM occurred more frequently in male and mainly affected the thumb, which was also observed in our study. However, their study showed that the SUM involved predominantly left hand, in contrast to the result of our study. Among these features of SUM, this study again found that LM onset in older age, larger width, and accompanying nail plate dystrophy are characteristic features of SUM.

Many studies have attempted to identify the predictor of SUM against other benign LMs. In this study, we performed multivariable logistic regression and ROC analyses to determine the predictor of SUM. The analysis revealed

Table 3. Demographics and clinical features between two groups of benign LM and subungual melanoma

Variable	Total patients (n=68)	Benign LM (n=60)	Subungual melanoma (n=8)	*p*-value
Age (yr)	35.2±20.1	33.5±19.6	48.5±20.4	0.035
Duration of LM (mo)	42.8±64.9	27.6±41.8	141.0±99.6	0.004
Location of LM				
Hand or foot				0.184
Hand	53 (77.9)	45 (75.0)	8 (100)	
Foot	15 (22.1)	15 (25.0)	0 (0)	
Right or left				0.135
Right	32 (47.1)	26 (43.3)	6 (75.0)	
Left	36 (52.9)	34 (56.7)	2 (25.0)	
Width of LM (ratio)	0.21±0.17	0.17±0.12	0.49±0.26	<0.001
Color of LM				0.022
Monochromic	36 (52.9)	35 (58.3)	1 (12.5)	
Heterochromic	32 (47.1)	25 (41.7)	7 (87.5)	
Hutchinson sign	16 (23.5)	12 (20.0)	4 (50.0)	0.062
Border of LM				0.700
Well defined	43 (63.2)	37 (61.7)	6 (75.0)	
Blurred	25 (36.8)	23 (38.3)	2 (25.0)	
Nail plate dystrophy	15 (22.1)	10 (16.7)	5 (62.5)	0.010
Longitudinal ridge	12	8	4	
Split of nail plate	1	0	1	
Nail plate dystrophy	1	1	0	
Horizontal groove	1	1	0	
Recent change of LM*	21 (30.9)	16 (26.7)	5 (62.5)	0.096
Change of color	12	11	1	
Change of width	11	7	4	
Change of length	1	0	1	

Values are presented as mean±standard deviation, number (%), or number only. LM: longitudinal melanonychia. *The detailed symptoms appeared independently or in combination, the number of 'recent change of LM' and the number of detailed symptoms can be different.

Table 4. Multivariable logistic regression analysis for clinical features of LM

Variable	Odds ratio	95% CI
Age	1.047	0.975~1.124
Width of LM	1.083	1.018~1.153
Color of LM		
Monochromic	1	
Heterochromic	8.217	0.456~149.977
Nail plate dystrophy		
Absence of dystrophy	1	
Nail plate dystrophy	2.352	0.267~20.714

CI: confidence interval, LM: longitudinal melanonychia.

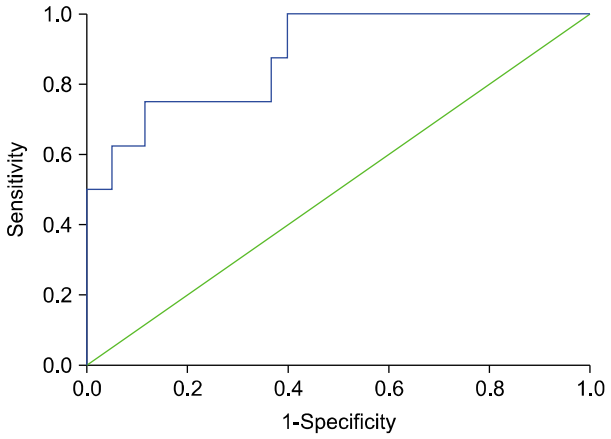

Fig. 2. Receiver operating characteristic curve for width of longitudinal melanonychia in the detection of subungual melanoma.

that the width of LM can be the predictor of SUM against other benign LMs. Our results suggested that LM width > 28% of the whole nail indicates SUM rather than other benign LMs. Recently, Ko et al.[2] also proposed that the width of LM can be a predictor of SUM against other benign LMs and suggested the cutoff point as LM width >40% of the whole nail. Although the cutoff point was different, our results highlight the importance of the width of LM in the differential diagnosis of this disease.

Hutchinson's sign has been considered a critical presumptive sign in the diagnosis of SUM[5,7,9]. The extension of pig-

mentation from the nail matrix or nail bed to the surrounding tissue represents radial growth of SUM[9]. However, extension of pigmentation to the surrounding tissue has also been found in other benign conditions and such findings were referred to as pseudo-Hutchinson's sign[9]. Previous studies reported that one-third of LMs due to nevi on the nail matrix or nail bed showed pseudo-Hutchinson's sign[9,10]. In this study, 54.5% of LMs due to melanocytic proliferation and 50.0% of SUMs showed pigmentary change of the surrounding nail fold. Among patients with melanocytic proliferation who showed pigmentary change of the surrounding nail fold, the histologic diagnosis in three patients was melanocytic nevus and two of these patients were younger than 5 years. Additionally, we further analyzed the presence of Hutchinson's sign or pseudo-Hutchinson's sign in enrolled patients over 12-year-old, considering the atypical LM found in children. Of the included 56 patients, 44 (78.6%) had LM due to melanocytic activation, 5 (8.9%) had LM due to melanocytic proliferation, and 7 (12.5%) had SUM. Hutchinson's sign or pseudo-Hutchinson's sign was observed in 16.1% of all patients over 12-year-old. When pediatric cases were excluded, the proportion of showing pseudo-Hutchinson's sign was found in 9.1% in melanocytic activation, 40.0% in melanocytic proliferation, and Hutchinson' sign was found in 42.9% in SUM. In particular, there were marked decrease in the melanocytic proliferation group. As melanin pigmentation can be densely observed in cases of melanocytic proliferation, such as melanocytic nevus, pseudo-Hutchinson's sign can be frequently observed. Ohn et al.[11] investigated the dermoscopic features of nail matrix nevi in adults and children and found that pseudo-Hutchinson's sign was observed in 62.1% of nail matrix nevi in children on dermoscopy. Although previous studies emphasized the importance of Hutchinson's sign in the early detection of SUM[5,6,12], clinicians should consider the possibility of pseudo-Hutchinson's sign, especially when managing LM in children. Therefore, LM in children should be approached with caution through serial inspection, photographs and dermoscopic examination with a longer follow-up period.

There are some limitations of this study. First, since this study was conducted on single tertiary medical center, there can be a selection bias. Only patients with severe lesion may have been enrolled in this study. Second, as our study was a retrospective study over a 19-year period, there can be missing information including follow-up. In addition, we could not investigate the dermoscopic findings since the examining the LM with dermoscopy has not been widely used in those periods. Prior study has described the characteristic dermoscopic findings of SUM *in situ* and reported width of pigmentation at least 3 mm, multicolor pigmentation, asymmetry, border fading, and Hutchinson's sign as the predictive signs for SUM *in situ*[13]. SUM is a malignant neoplasm of the nail unit with a poor prognosis. Only biopsy can definitely diagnose SUM; however, the risk of nail plate dystrophy after nail matrix biopsy, although the risk is depending on the technical skills, is another limitation in the early detection of SUM. In this retrospective study, we found that SUM had different demographic and clinical features from those of LM of benign causes. Our results also implied that the width of LM can be a predictor of SUM; that is, LM width $>28\%$ of the whole nail suggests SUM rather than other benign LMs. Clinicians should be cautious when dealing with patient whose the width of LM is over a quarter of the patient's whole nail width. Additional studies are needed to test the predictive values proposed in this study, which can be helpful in establishing the approach for early detection of SUM. In addition, further studies on the usefulness of dermoscopy in the diagnosis of SUM are needed for the early detection of SUM.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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