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Clinical Characteristics of Nail Unit Melanoma in Türkiye: The Experience of Two Tertiary Dermatology Centers

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Background: The literature on the clinical presentations of nail unit melanoma (NUM) in different countries is limited.

Aims: To assess the specific clinical characteristics of NUM in Türkiye.

Study Design: A retrospective cross sectional study.

Methods: Patients with NUM in two centers were retrospectively evaluated for their clinicopathological features, including the location, laterality, destruction of the nail plate, erosion or ulceration, presence of longitudinal melanonychia (LM), Hutchinson's sign (HS), and the absence of pigmentation and Breslow thickness. These variables were compared in terms of the main location of the NUMs (fingernail versus toenail).

Results: A total of 37 patients (54.1% female) of mean age 61.9 ± 14.8 years were enrolled. In most cases, NUMs were located in the fingernails (62.2%), with the most common location being the thumbnails (45.9%), followed by the big toenails (32.4%). Five cases had in situ melanoma presenting with LM. The mean Breslow thickness of invasive NUM lesions (n = 26) was 4.7 ± 4.1 mm (median: 3). Although all in situ NUMs were located on the hands, no statistically significant difference was noted in the Breslow thickness of invasive NUMs on the toenails and fingernails. NUMs were hypomelanotic/amelanotic in 10 (27%) patients. LM was clinically evident in 40.5% of the patients and was significantly more frequently observed on fingernails. The HS of the nail folds was noted in 40.5% of the patients, with the proximal (73.3%) and distal (73.3%) nail folds being most commonly involved. Total or partial destruction of the nail plate was recorded in 24.3% and 51.4% of the patients, respectively. Erosion and/or ulceration on the surface of the NUM was clinically present in most (75.7%) cases. Invasive NUMs associated with LM (n = 10) displayed partial destruction of the nail plate (n = 9), erosion and/or ulceration on the tumor surface (n = 7), and HS (n = 6).

Conclusion: The clinical characteristics of patients with NUM, such as more common localization on the hands, a high rate of preference for thumbnail and big toe, and the ratio of HS, were similar to the studies reported from diverse countries. Partial destruction of the nail plate is an important clinical feature of NUM. Furthermore, LM is more frequently observed in NUMs on the fingernails.

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INTRODUCTION

Nail unit melanoma (NUM) is a distinct variant of acral melanoma that originates from the nail bed, matrix, or periungual skin.[1-3] Although NUM is detected with almost equal prevalence among all ethnic groups, its frequency varies among ethnicities, with an incidence rate of < 5% among all melanomas in most Caucasian populations. However, it is a major subtype of melanoma in regions such as Africa, Asia, and Latin America, with a relative frequency of up to 20% among all melanomas due to the rare occurrence of other melanoma subtypes in these populations. NUM also differs from other melanoma subtypes in its etiology and pathogenesis in terms of the lack of association with ultraviolet radiation exposure, a lower mutation burden, and unique genetic mutation rates.[1-8]

Early diagnosis is the crucial determinant of the prognosis of NUM. However, it has a worse prognosis when compared with other major melanoma subtypes, probably in relation to the frequent diagnosis at a more advanced stage in this location.[1,2,5,9,10] There is limited information available on the differences in the clinical features of NUM reported in patients from different countries.[2,5] We retrospectively evaluated the main clinical and histopathological features of NUM in Turkish patients and compared them in terms of the main location of the tumor. We also examined the differences between our results and the relevant literature.

MATERIALS AND METHODS

Consecutive patients diagnosed with NUM who visited the departments of Dermatology and Venerology of İstanbul Faculty of Medicine (first center) during 1997-2022 and University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital (second center) during 2011-2020 were included in this retrospective analysis. The demographic characteristics of the patients were recorded. In addition, a comprehensive review of their medical records and routine clinical photographs at the time of diagnosis was conducted, with a focus on the clinical features of NUM lesions including the location of the affected nail, laterality (right-left), total/partial destruction of the nail plate, presence of longitudinal melanonychia (LM), erosion or ulceration, and the absence of pigmentation (hypomelanotic/amelanotic melanoma). Hutchinson's sign (HS), which represents an extension of pigmentation of the NUM to either one or more of the nail folds (distal, proximal, and lateral), and satellite metastases around the NUMs were also evaluated. Furthermore, the main histopathological features of the melanoma, including the invasion level and exact depth (Breslow thickness), were recorded. In patients for whom the total excision histopathology records were not available, Breslow thicknesses in the biopsy materials obtained from the thickest part of the NUMs were evaluated.

Statistical analysis

Numerical variables were presented as the mean ± standard deviation (range: minimum-maximum), and categorical variables were presented as frequencies and percentages. The clinical and histopathological variables were compared between the NUM lesions in terms of location (fingernail versus toenail) using Fisher's exact tests. A significance level of $p < 0.05$ was considered indicative of statistical significance. IBM SPSS for Windows version 23.0 was applied for the statistical analysis. This study was conducted under the ethical standards of the İstanbul University, İstanbul Faculty of Medicine Institutional Committee and with the Declaration of Helsinki (approval number: E-29624016-050.04-2746117, date: 25.07.2024).

RESULTS

A total of 37 patients with NUM visited both centers, and the diagnosis was established in their first presentation to the outpatient clinics. None of them had a history of another prior melanoma. All the patients were Caucasian. They were adults and of mean age at the time of diagnosis of 61.9 ± 14.8 (age range: 29-92) years. There was a slight female predominance (n = 20, 54.1%) (Table 1).

In most cases, NUMs were located in the fingernails (n = 23, 62.2%). The most common location was thumbnail (n = 17, 45.9%) (Figure 1a), followed by big toenail (Figure 1b) in 12 (32.4%) cases, second fingernail in five (13.5%) cases, fifth toenail (Figure 1c) in two (5.4%) cases, and fourth fingernail in one case (2.7%). While the right and left feet were equally affected, NUMs were slightly more common on the right hand (60.9%) compared with the left hand (39.1%) (Table 1).

Histopathological examination revealed in in situ melanoma in five cases (4 female, 1 male) and all of them were located on the fingernails (Figure 1d-f). One patient with axillary lymph node metastasis presented with regressed NUM on the second fingernail (Figure 2a). Other (n = 31) patients showed invasive melanoma (Figures 1a-c, 2b-f, 3a-f). Data concerning Breslow thickness could not be obtained in five of these patients. The mean Breslow thickness recorded in 26 invasive NUM lesions was 4.7 ± 4.1 mm (median: 3, range: 0.9-18) based on the histopathological examination of the excision material in most (n = 21) of them (Table 1).

Besides 34 patients in whom melanoma primarily originated from the nail matrix or nail bed, the main mass of NUMs was located on the finger pulp and exhibited a remarkable extension to the nail unit in three patients (Figure 2e). The NUMs were hypomelanotic/amelanotic in 10 (27%) patients. Most of these NUMs (n = 6) were located on the big toenails (Figures 1b, 2b), and the remaining amelanotic lesions (n = 4) were located on the thumbnails (Figure 3b). The LM was clinically evident in 15 (40.5%) patients (Figures 1d-f, 2c-e), of whom 13 were located on the fingernails. Total (Figures 1b, 2b, 2f) or partial (Figures 1a, 2c, 3a-d) destruction of the nail plate was noted in 9 (24.3%) and 19 (51.4%) patients, respectively. Erosion (Figure 2f) and/or ulceration (Figures 1a, 1b, 3f) on the surface of the NUM was clinically present in most (n = 28, 75.7%) patients. While LM was the isolated clinical finding in four patients with in situ NUMs (Figure 1d-f), partial destruction of the nail plate accompanied LM in one patient with in situ NUM. In the remaining cases (n = 10), LM was associated with the partial destruction of the nail plate (n = 9) (Figure 2c, d), erosion and/or ulceration on the tumor surface (n = 7), and HS (n = 6) histopathologically showing invasive melanoma.

The HS of the nail folds was noted in 16 (43.2%) patients, which was mostly (n = 10) seen in the NUM of the hands. The proximal (Figure 3b-e) (n = 11), distal (Figure 3a, c) (n = 11), and lateral nail folds (Figure 3e) (n = 6) were involved in patients with HS. In seven patients, only one nail fold was involved, specifically, proximal in three and distal in four patients (Figure 3a). The HS involving two (Figure 3c-e) and three nail folds was present in five and three patients, respectively. In one patient, HS was present in all four nail folds. Furthermore, two cases demonstrated satellite metastases as periungual papules (Figure 3d, f).

A comparison of the NUMs on the fingernails and toenails revealed that LM was significantly more frequently observed on the NUMs of the fingernails (Table 1). The NUMs on the fingernails and toenails did not show any significant difference in terms of the demographic and other clinical features (Table 1). Although all in situ NUMs were located on the hands, no statistically significant difference was noted in the median Breslow thickness of invasive NUMs on the toenails (2.6 mm) and fingernails (4.1 mm) (Table 1).

DISCUSSION

The frequency of the types of melanoma displayed racial differences, and this is more prominent in acral melanomas including the lesions located on the palms, soles, fingers, toes, and nails.[9] The rate of NUM among all cutaneous melanomas reported from various European countries and Canada ranged from 1.5 to 5.2%.[1,4-6] The rate of NUM was much higher among African and Asians than that among Caucasians, and melanoma in this location may account for approximately 9-18% of cutaneous melanoma cases.[2,7] Türkiye has a Caucasian population, but Fitzpatrick skin types 3 and 4 are the most common. A study originating from one of our centers investigating all cutaneous melanomas during 1997-2015 revealed that 19% of all primary cutaneous melanoma cases were from the acral lentiginous melanoma (ALM) type, displaying a higher rate estimated for a Caucasian population.[11] Furthermore, 32.5% of these ALM patients were NUMs, representing a ratio of 6.3% among the 227 primary cutaneous melanomas in the above-mentioned study.[11] In other studies from Türkiye published during 2014 and 2024, the ratio of ALM was also higher (8.95%, 11.4%, 13.25%, 17.1%) in comparison to that in Western countries.[12-15] However, the ratio of NUM among ALM patients was not mentioned in three of them[12,13,15] and, in the fourth, a lower NUM ratio (2.5%) was reported among 612 cutaneous melanoma cases.[14] Although ALM seems to be a relatively common subtype of melanoma in Türkiye, the specific clinical features of NUM were evaluated with a relatively large series in the present study for the first time in Turkish patients.

NUM is different from other subtypes of melanoma not only in terms of its racial differences in incidence but also in its etiology and pathogenesis.[2,5,9,16] Irrelevance to ultraviolet radiation exposure, low mutation burden, and different genetic mutation profiles are

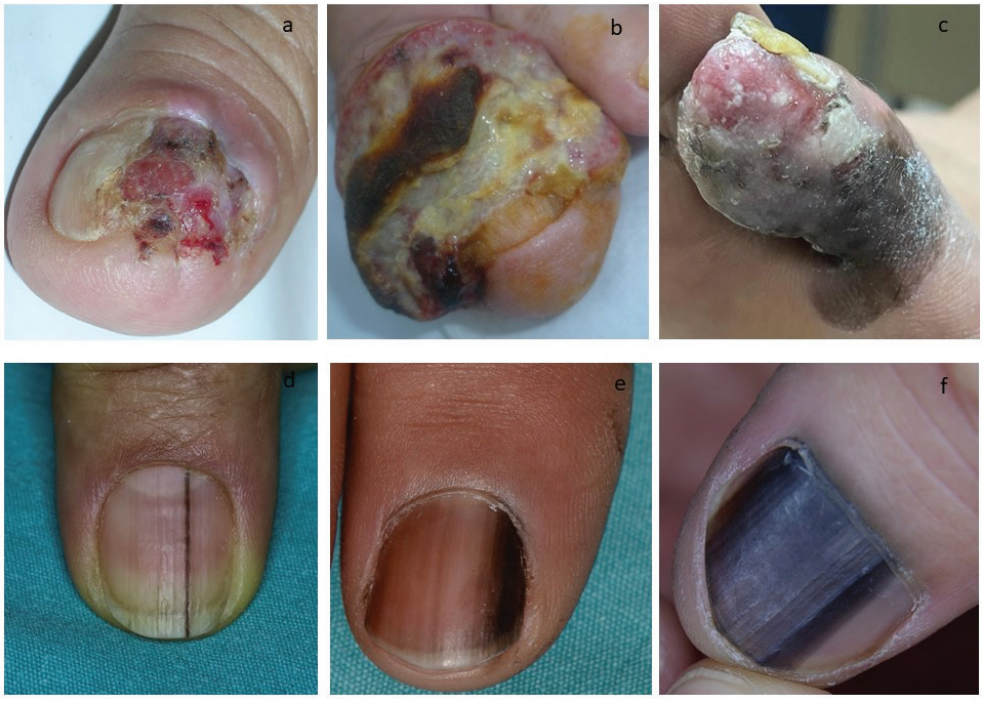

FIG. 1. (a) A hypomelanotic/amelanotic nailbed melanoma causing partial nail plate destruction*; (b) Ulcerated hypomelanotic/amelanotic nailbed melanoma with complete nail plate destruction*; (c) Melanoma extending from the distal nail fold to the plantar area*; (d) A longitudinal melanonychia as a very thin brown-black band representing in situ melanoma**; (e) Multiple bands of longitudinal melanonychia on the fingernail representing in situ melanoma**; (f) A dark-colored longitudinal melanonychia covering the great majority of the nail plate, histopathologically diagnosed as in situ melanoma** (cases from the first* and second** centers).

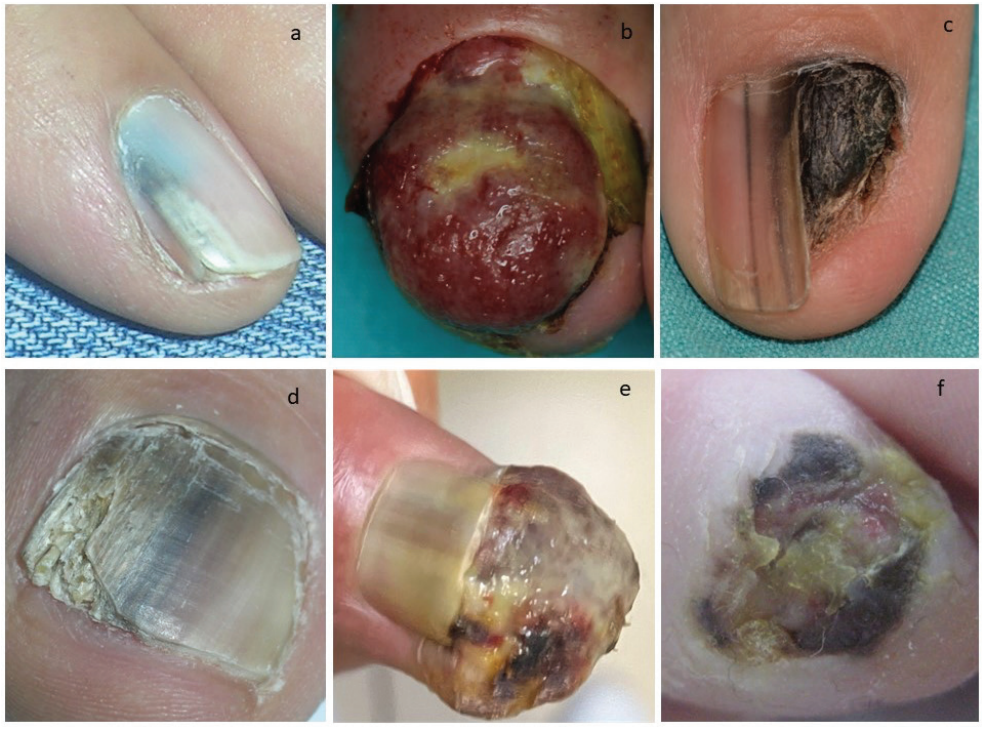

FIG. 2. (a) Ill-defined bluish pigmentation on the nailbed associated with focal nail plate dystrophy, histopathologically showing features of a completely regressed melanoma*; (b) Hypomelanotic/amelanotic melanoma presenting as a large exophytic nodule on the nailbed**; (c) Invasive melanoma causing partial nail destruction and longitudinal melanonychia**; (d) Invasive melanoma causing longitudinal melanonychia and nail dystrophy on one side of nail plate*; (e) Large ulcerated nodule of invasive melanoma on the finger pulp associated with longitudinal melanonychia*; (f) Pigmented melanoma on the nailbed showing eroded surface and total nail plate destruction* (cases from the first* and second** centers).

considered important baseline characteristics of NUM. The question of whether trauma is associated with the development of ALM, including NUM, has been raised by several authors but remains unresolved.[3,16] In a study on the role of trauma in NUM, 21.8% of 87 patients reported a previous trauma history, and trauma-related NUMs were more likely to involve the toenails.[3] In our study, thumbnails and big toenails, which are more exposed to trauma, comprised 78.8% of all NUM locations. Additionally, the right and left feet were equally affected, and the right hand (60.9%), which is more exposed to physical trauma, was more commonly involved than the left hand (39.1%) in our series. However, no further comments could be made on this issue owing to the lack of data regarding the patient's history of trauma in the present study.

A meta-analysis of NUM evaluating studies reported from Australia, Europe, America, and Asia published between 2000 and 2018 representing a period from 1914 to 2017 with a total of 1,340 patients revealed an average age range of diagnosis of 41.1-67 years, with a peak incidence around the sixth decade.[2] Similar to many studies on NUM,[2,5,7,16-18] the age at the time of diagnosis was usually in late adulthood and elderly (mean: 61.9 ± 14.8 years) in our series. Furthermore, all of our NUM patients were adults, the youngest being 29 years old. Although extremely rare cases of NUM have been reported in children,[1,16] in most studies NUM was not recorded in the pediatric age group,[7,8] as in our study which support the notion that unnecessary intervention should not be performed on pigmented nail lesions, including LM cases in children.[1,16] Interestingly, the mean age of patients with NUM on the foot was more than that on the hand in our series, albeit the difference was not statistically significant. This finding has also been stated in some other studies and can be attributed to the fact that hands are more easily observed in everyday life, which brings earlier medical attention to a suspicious lesion.[5] The slight female predominance seen in our series has also been recorded in many other similar studies.[7,8]

NUM most commonly appears in the nails of the thumb, big toe, and index finger, but it has been reported in all digits.[1,17] The thumbnails (45.9%) and big toenails (32.4%) are the most common locations for NUM in our cohort, similar to previously reported data.[8,9,16] Although the majority of ALMs are diagnosed in the lower extremities, most upper-limb ALMs manifest as fingernail unit lesions.[9] As in many case series, the number of NUMs in the hands (62.2%) was higher than that in the feet (37.8%) in our study.[2,3,10,16]

Approximately two-thirds of all NUMs present clinically as LM, which can be defined as a longitudinally oriented band of brown-to-black pigmentation extending through the length of the nail plate which may be irregular in width and color.[1,16] This finding was recorded in 40.5% of our patients, most commonly on the fingernails (86.7%). While 33.3% of patients with LM lesions had in

TABLE 1. Comparison of Clinical and Histopathological Features of Nail Unit Melanomas on the Fingernails and Toenails.

Variables		Hand (n = 23)	Foot (n = 14)	*p*
Sex	Male	10	7	0.69
	Female	13	7	
Age (mean ± SD, years)		58.5 ± 14.6 (median: 57, range: 29-92)	67.5 ± 13.9 (median: 66.5, range: 45-89)	0.09
Localization		- Thumbnail (n = 17) - Second fingernail (n = 5) - Fourth fingernail (n = 1)	- Big toenail (n = 12) - Fifth toenail (n = 2)	NA
Laterality		Right (n = 14) Left (n = 9)	Right (n = 7) Left (n = 7)	0.73
Invasion level and Breslow thickness (mean ± SD, mm)*		In situ (n = 5)	-	
			Invasive NUM	
		- 5.4 ± 4.4 (median: 4.1, range: 0.9-18) (n = 13) - Complete regression (n = 1) - Unknown (n = 4)	- 4 ± 3.8 (median: 2.6, range: 1.4-15) (n = 13) - Unknown (n = 1)	0.63
Melanotic		19 (82.6%)	8 (57.1%)	0.13
Amelanotic/hypomelanotic		4 (17.4%)	6 (42.9%)	
Presence of longitudinal melanonychia		13 (56.5%)	2 (14.3%)	0.01
Presence of HS		10 (43.5%)	6 (42.8%)	0.10
Total destruction of the nail plate		4 (17.4%)	5 (35.7%)	0.21
Partial destruction of the nail plate		12 (52.2%)	7 (50%)	0.89
Erosion and/or ulceration on the surface of the NUM		15 (65.2%)	13 (92.8%)	0.10

NA, non-available; SD, standard deviation; HS, Hutchinson's sign; NUM, nail unit melanoma; *The Breslow thickness recorded in 21 invasive NUM lesions was based on the histopathological examination of the excision material and in five patients on the biopsy material.

situ melanoma, other patients with LM (66.7%) exhibited clinical signs of NUM associated with the invasive stage of melanoma.

Hypomelanotic/amelanotic melanoma is a rare variant of melanoma, but up to 30% of NUMs may present with hypomelanotic/amelanotic lesions.[1,16] In a study originating from the United Kingdom, hypomelanotic/amelanotic NUM was reported in 23% of 105 patients.[6] Similarly, hypomelanotic/amelanotic lesions were observed in 27% of our patients, most commonly (60%) on the big toenail. Previously, a study evaluating 87 patients with NUM reported that trauma-related NUMs were more likely to involve the toenails, with a high proportion of hypomelanotic/amelanotic melanomas.[3]

The HS presents as an extension of brownish pigmentation from the NUM onto the nail folds,[1,16,17] as was seen in 40.5% of our cases. Although it is among the diagnostic clues for this neoplasm, minimal evidence supports the overall prognostic significance of this clinical sign.[7] A recent study focusing on the clinical implications of HS in 61 NUM patients indicated that 75.4% of them showed HS, with fingers (52.2%) and toes (47.8%) almost equally affected.[7] However, our study found that HS was more common in fingernails (86.7%). In nearly half of our cases with HS, more than one of the nail folds were involved, with both the proximal (73.3%) and distal (73.3%) nail folds being the most common ones. In the above-mentioned study from Korea, in 37.6% of patients, more than one of the nail folds was involved with HS, and different from our series, the involvement of the distal nail fold (69.6%) was the most common pattern, followed by the proximal nail fold (67.4%) and the lateral nail folds (36.9%).[7] Furthermore, satellite metastasis of NUM was observed as periungual papules in two of our patients (Figure 3d, f), which may be an underreported finding in this location.[19]

The destruction of the nail plate is a well-known feature of NUM.[7,14,16] It has been reported that nail destruction occurred in 75.4% of 61 patients with NUM, without specifying partial or total destruction.[7] Remarkably partial destruction, which has been rarely mentioned in previous studies, was recorded in more than half of the patients in our series, making it nearly two times more common than the ratio of total destruction. It has been previously emphasized that the presence of HS is usually associated with nail plate destruction.[7] Similarly, in our series, in all patients with NUM showing HS, total (n = 4) or partial (n = 11) destruction of the nail plate was also recorded. Furthermore, most of the patients with invasive NUMs exhibited erosion and ulceration on the surface of the tumors clinically.

Early diagnosis is crucial for a better prognosis in NUM. However, in situ NUM ratios have been reported in a wide range between 9% and 63% from different countries.[2] In our series, five (13.5%) cases were

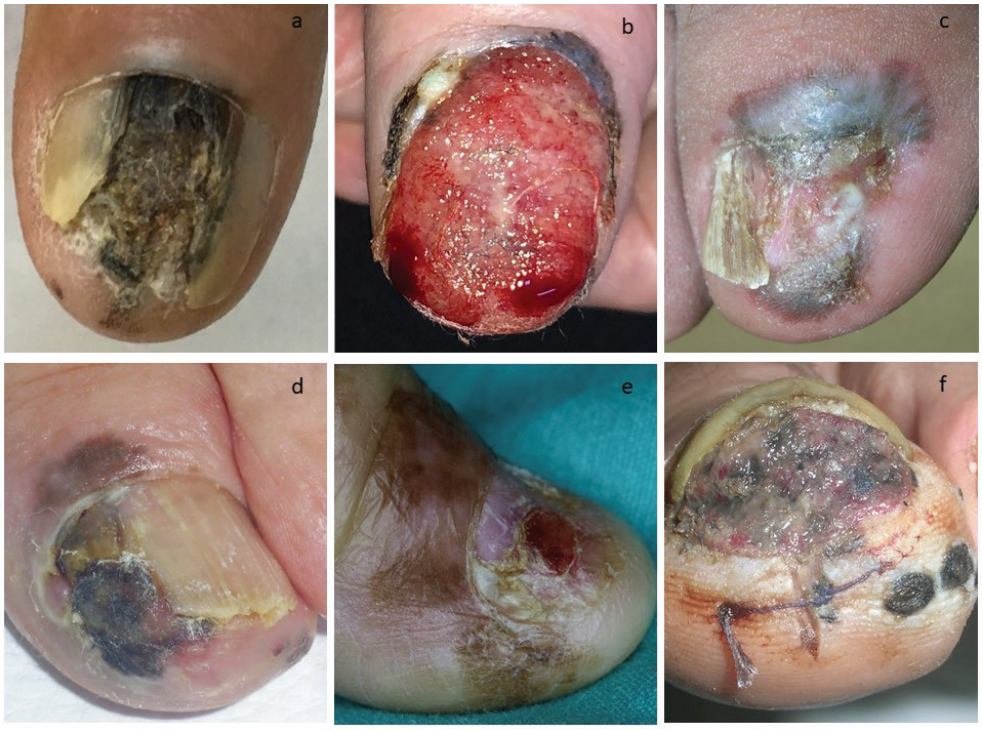

FIG. 3. (a) Pigmented mass of invasive melanoma on the nail bed causing partial nail plate destruction (on the midline) associated with distal nail fold pigmentation (Hutchinson's sign)*; (b) Hypomelanotic/amelanotic melanoma on the nailbed associated with Hutchinson's sign on the proximal nail fold*; (c) Invasive nail melanoma associated with Hutchinson's sign on the distal and proximal nail folds*; (d) Invasive nail melanoma causing unilateral nail plate destruction associated with Hutchinson's sign on the proximal and distal nail folds and satellite papules on the toe pulp*; (e) Invasive melanoma causing complete nail destruction and Hutchinson's sign on the proximal and lateral nail folds**; (f) Ulcerated subungual melanoma associated with two satellite papules* (cases from the first* and second** centers).

diagnosed at the in situ stage. In a recent meta-analysis, the mean Breslow thickness in invasive NUM case series ranged from 0.82 to 8.70 mm.[2] The relatively low median Breslow thickness (3 mm) in our series may be related to the fact that they were diagnosed in two experienced tertiary referral centers. However, the Breslow thickness of seven (18.9%) patients was > 4 mm in our study. As our hospitals were tertiary centers where melanoma surgery is frequently performed, some patients first addressed to the plastic surgery departments were later referred to our dermatology departments for diagnostic confirmation before considering the surgery. This might be the reason for these advanced cases. Similarly, the median Breslow thickness was 3.2 mm in a case series of 124 NUMs reported from Australia.[20] In a recent cohort of 103 patients diagnosed with NUM of the hands from Australia, the median Breslow thickness of invasive tumors (n = 94) was 3.1 mm.[21] In other similar large studies reported from various countries, including the United States of America and the United Kingdom, the median Breslow thickness was relatively high, in a wide range of 3.2 to 8.7 mm.[6,10,18,22-24] In a study from one of our centers that analyzed all cutaneous melanomas between 1997 and 2015, a high ratio of melanoma patients showed either in situ (23.19%) or thin melanomas, with a Breslow thickness of < 1 mm (30.9% of the cases with invasive melanoma).[11] Although the frequency of melanoma has increased over the years in our country,[25] a decrease in Breslow thickness over time has been demonstrated in one of our centers.[26] The present study on NUM performed in two centers was in contrast, suggesting that melanomas in this specific location present more commonly with higher Breslow thickness in Turkish patients in the period of the study. However, in recent years, with the rising awareness about NUM among patients and physicians in Türkiye as well as across the world along with the widespread use of nail biopsy techniques by dermatologists, it is expected that the rate of NUM cases diagnosed at an early stage, such as in situ or minimally invasive, will gradually increase.

A study reported from Australia that compared the clinicopathological characteristics and melanoma-specific survival of 101 ALM patients in the invasive stage according to the tumor location revealed that nail ALM patients had a shorter survival when compared to patients in other locations of ALM on univariate analysis.[9] This report can be attributed to the greater Breslow thickness and ulceration on the diagnosis of NUMs. Hand ALMs in this study showed a higher Breslow thickness than foot ALMs, which can be attributed to the higher proportion of NUMs present in this location.[9] In our study, although all in situ NUMs were located on the hands, the median Breslow thickness of invasive NUMs in this location (4.1 mm) was higher than on the foot (2.6 mm), albeit without any statistical significance. There are limited data available on the impact of NUM-specific localization (fingernails

vs. toenails) on the overall prognosis.[1] In two of the recent relevant studies, the overall survival or recurrence-free survival of NUMs was not significantly correlated with the tumor location in terms of the involved digits.[18,27] In another study, a comparison of NUMs located on the hand versus those on the foot revealed more frequent ulceration in foot-located tumors, which correlates with more distant metastases and poorer overall survival.[10] In our study, erosion and/or ulceration on the surface of the NUM was more frequent on the toenails (92.8%) than on the fingernails (65.2%), albeit without statistical significance.

The main limitation of our study was its retrospective design, which restricted the availability of data such as the lesion duration, trauma history, lymph node involvement, distant metastasis frequency, prognosis, and treatment details.

In conclusion, the present study is the largest study on NUM in Türkiye to date and confirmed that NUM is a malignancy of adults. The clinical characteristics of patients with NUM in our study, such as the more common localization on the hands, a high rate of preference for the thumbnail and big toe, and the frequency rate of HS, were similar to those previously reported in the relevant literature. On the other hand, partial destruction of the nail plate seems to be a typical feature of invasive NUM. While LM is more frequently observed in NUM lesions located on the hand, the higher incidence of hypomelanotic/amelanotic NUM on the foot is a clinically noteworthy observation. During the study duration, besides early diagnosed in situ melanomas, especially those located on the fingernails, NUMs with high Breslow thickness were observed in any digits, especially in neglected cases.

Ethics Committee Approval: İstanbul Faculty of Medicine Institutional Committee and with the Declaration of Helsinki (approval number: E-29624016-050.04-2746117, date: 25.07.2024).

Informed Consent: Retrospective study.

Data Sharing Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- T.A., M.B.G., Ş.Ö.S., C.B., F.G.; Design- T.A., M.B.G., C.B., F.G.; Supervision- T.A., Ş.Y., N.B., P.G., Z.K.S., C.B., F.G.; Materials- T.A., M.B.G., Ş.Y., N.B., P.G., Ş.Ö.S., Z.K.S., C.B., F.G.; Data Collection or Processing- T.A., M.B.G., Ş.Ö.S., C.B., F.G.; Analysis or Interpretation- T.A., M.B.G., Ş.Y., N.B., P.G., Z.K.S., C.B., F.G.; Literature Review- M.B.G., C.B., F.G.; Writing- T.A., C.B., F.G.; Critical Review- T.A., Ş.Y., N.B., P.G., Ş.Ö.S., Z.K.S., C.B., F.G.

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