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Dermoscopic Features of Spitz Nevi by Age and Anatomic Site

A Clinicodermoscopical Study of 378 Spitz Nevi

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Yuka de Mestier du Bourg

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Professor Giuseppe Argenziano, MD, PhD

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DEDICATION

I dedicate my thesis work to my loving husband, Nicolas,

and my dear daughter, Lucile Aika Marie.

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Yuka de Mestier du Bourg

Medizinische Universität Graz

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1. INTRODUCTION

Spitz nevi are benign melanocytic nevi which have been a matter of debate since first described by Sophie Spitz in 1948 due to their overlapping features with melanoma both clinically and histopathologically (1). The clinical appearance of Spitz nevi vary from pink nodules to dark pigmented macules (2-4). Histopathologically, epithelioid melanocyte and/or spindle-like melanocyte proliferation is observed in Spitz nevi (3, 5). Although histopathological examination is the gold standard for the diagnosis of Spitz nevi, there are no definite histopathological criteria to date making the differentiation of Spitz nevi from melanoma extremely difficult or impossible at times (6, 7).

Dermoscopy, also known as epiluminescence microscopy (8), surface microscopy (9) or incident light microscopy (10), is a non-invasive, in vivo imaging technique that visualizes subsurface structures and colors that are undetectable to the naked eye (11). The first concept of dermoscopy dates back as early as the 17th century when Kohlhaus started skin surface microscopy (12). However, the technique itself was profoundly refined especially from the end of the 19th century and during the course of the 20th century. There are two types of methods in dermoscopy: nonpolarized dermoscopy and polarized dermoscopy. The first technique, nonpolarized dermoscopy, is the traditional approach which is performed by applying liquid or gel over the skin surface and placing an illuminating optic device, dermoscope, over it (8, 11, 13). The second technique, polarized dermoscopy, is a new method that does not require direct skin contact or liquid interface by incorporating a cross-polarization system (14). Hand held polarized dermoscopes became available in the year 2000 and this has accelerated the use of dermoscopy to be widely accepted in everyday clinical practice (15).

With the introduction of dermoscopy in clinical settings, the diagnostic accuracy of Spitz nevi has improved greatly (16-18). Dermoscopically, Spitz nevi display a multitude of morphological patterns (8, 16, 19-25). The hallmark of pigmented Spitz nevi is the starburst pattern with a bluish to black central homogeneous structureless area which is surrounded by darkly pigmented radiating streaks or pseudopods (16). In addition to this pattern, the globular pattern, the homogeneous pattern, the reticular pattern, the inverse network pattern and the dotted vessel pattern are also observed (**Table 1**).

Atypical patterns, namely, the multicomponent pattern and the nonspecific pattern are seen as well. However, a Spitzoid pattern under dermoscopy is not specific for the diagnosis of Spitz nevus, since melanoma may display the same features. In fact, even with the use of dermoscopy, as much as 13.3 % of dermoscopically unequivocal Spitzoid lesions are histopathologically diagnosed as melanomas (26). Furthermore, the probability of these lesions turning out to be melanomas rises immensely after puberty (26, 27). Consequently, surgical excision and subsequent histopathological evaluation of Spitz nevi is recommended as management of postpubertal lesions (28). Therefore, identifying Spitzoid lesions is important especially in older individuals.

Despite the fact that many large studies of Spitz nevi have been conducted focusing on the histopathological aspects (3, 4, 21, 29-34), there are very few large studies related to the dermoscopic features (21, 33). Moreover, previous studies in other melanocytic nevi, such as congenital nevi and common acquired nevi, have demonstrated the association of dermoscopic pattern with age and anatomic distribution (35-39). In both types of nevi, the globular pattern is reported to be more frequent on the trunk in younger individuals. No studies have been conducted to explore this in Spitz nevi as yet.

In the present study, we aimed to better understand the clinical and dermoscopical characteristics of Spitz nevi with focus on the relationship of the dermoscopic features with age and the anatomic site.

2. METHODS

This study was conducted at the Skin Cancer Unit of the Arcispedale Santa Maria Nuova IRCSS in Reggio Emilia, Italy. We searched the image database from May 2002 to October 2014. Ethics committee approval was waived by the ethics committee of Reggio Emilia.

We retrieved clinical and dermoscopic images of all lesions with histopathological diagnosis of Spitz nevus. We excluded all lesions with histopathological diagnosis of atypical Spitzoid tumor from the study. In addition, we included lesions with clinicodermoscopical diagnosis of Spitz nevus for those patients 12 years of age and younger undergoing follow up. In these cases, digital images from the first visit were obtained. The following clinical data of the patients were recorded from our database: (1) age, (2) sex and (3) anatomic site of the lesion. Clinical and dermoscopic images were evaluated individually by two observers. In case of disagreement, a third observer made the final assessment.

2.1 Evaluation of digital images

Clinical images were obtained with dedicated digital camera (Canon Inc.). Palpability of the lesions was evaluated according to the following definitions. A papule was defined as a solid elevated lesion with a diameter 5 mm or less. A plaque was defined as elevated lesion with a flat top. A nodule was defined as a solid dome shaped elevated lesion with a diameter more than 5 mm.

Dermoscopic images were taken with a digital photo-camera with polarized and non-polarized DermLite® Photo 3 Gen (San Juan Capistrano, CA, USA). Dermoscopic features were defined by taking previously published literature into account (19, 21, 24, 40, 41). The following features were assessed: (i) pigmentation, (ii) ulceration, (iii) global pattern, (iv) streaks, (v) homogeneous pigmentation, (vi) globules, (vii) pigment network, (viii) superficial black network, (ix) white lines, (x) blue white veil, (xi) regression, (xii) vessel type and (xiii) vessel distribution. The detailed definitions of the dermoscopic features are shown in **Table 2**. 'Irregular' was scored for local dermoscopic patterns when presence of any irregularity was observed in terms of color, morphology or distribution. 'Amelanotic' was defined as a lesion with absolutely no pigmentation dermoscopically. A lesion was considered as 'hypopigmented' when the pigmented area of a given lesion was less than 50%. 'Homogeneous pigmentation' was defined as any area of structureless color varying from black, brown, blue to pink, red.

The global pattern was classified into a total of 8 patterns. Detailed definitions of the global patterns are shown in **Table 1**. We divided the typical pigmented Spitzoid pattern into the following 4 patterns: starburst pattern, globular pattern, homogeneous pattern and reticular pattern. Nonpigmented or hypopigmented Spitzoid pattern was divided into inverse network pattern and dotted vessel pattern. Multicomponent pattern was scored when multiple patterns were present in a single lesion. Nonspecific pattern was chosen when none of the aforementioned patterns were recognizable in the lesion or when a lesion presented with an ulceration regardless of the background pattern. 'White lines' was scored when either crystalline structures or inverse network was present.

2.2 Statistical analysis

In the age group analysis, the cases were divided into two groups depending on age for comparison; (I) 12 years old and younger and (II) 13 years old and older. Additionally, the association of white lines with clinical features and dermoscopical patterns were analyzed.

In the anatomical site analysis, clinical and dermoscopical features were analyzed according to anatomic site of the lesion. Dermoscopical features were compared between the anterior trunk and the posterior trunk. In order to evaluate the presence of statistical difference between distal and proximal locations in terms of melanoblast migration, we paired anatomic sites in the following manner and compared the two groups: (a) anterior trunk and acral sites, representing the distal sites and (b) head and neck area combined with the posterior trunk, representing the proximal sites.

χ^2 test of independence was used to evaluate the differences in clinical and dermoscopical features. When less than 20% of the cells of a table presented with an expected value of less than 5, Fisher's exact test was applied. Mann Whitney U test was used to compare medians. $P<.05$ was considered statistically significant and all P values are two tailed.

3. RESULTS

3.1 Study population

The study set comprised 378 lesions from 373 patients. One case with diffuse eruptive Spitz nevi was excluded from the study. Five individuals had been diagnosed with multiple Spitz nevi either simultaneously or at separate timings, these cases were included in the study. In two cases only the dermoscopic image was available. Clinical and dermoscopic characteristics of the 378 lesions are presented in **Table 3** (**Figures 1-15**). Mean age and median age was 27.12±15.08 years and 28 years, respectively, ranging from 0 to 67 years. Of the 378 cases, 149 (39.4%) were male and 229 (60.6%) were female. The most frequent anatomic site was the lower extremity (151/378, 39.9%), followed by the trunk (115/378, 30.4%) and the upper extremity (68/378, 18.0%). The most prevalent dermoscopic global pattern was the starburst pattern, seen in 29.4% of the lesions (111/378), followed by the multicomponent pattern (79/378, 20.9%) and the nonspecific pattern (50/378, 13.2%) (**Figures 1-7**). Regular streaks and regular homogeneous pigmentation were present in 29.6% (112/378) and 59.3% (224/378) of Spitz nevi, respectively. The most frequent type of globules seen was the irregular globules, present in 33.9% (128/378) of Spitz nevi. Atypical pigment network was noted in 20.1% (76/378). Superficial black network and white lines were observed in 6.9% (26/378) and 25.1% (95/378) of all lesions, respectively. Blue white veil and regression were both infrequent features, detected in 1.3% (5/378) and 5.3% (20/378) of cases, respectively. A total of 132 lesions (34.9%) presented with vessels. Of these, the most common vessel type was the dotted vessels (74/132, 56.1%) followed by polymorphic vessels (42/132, 31.8%). These two vessel types comprised 87.9% (116/132) of the lesions that exhibited any vessels. The most frequently observed vessel distribution was diffuse distribution (66/132, 50.0%) followed by irregular distribution (29/132, 22.0%).

Figure 16 shows the age distribution of Spitz nevi. A bimodal pattern was observed. The first peak saw the highest number of lesions at age 6 to 10 years. The number dropped drastically at age 11 to 15 years. The second peak hits a high at age 26 to 30 years forming a duller curve than the former. The number of Spitz nevi declined sharply at age 51 to 55 years again and from then on the number remained extremely low.

3.2 Analysis by age groups

In the first analysis, all cases were divided into two age groups (**Table 4**). The first group, 12 years and younger, consisted of 96 lesions which comprised 25.4% of all Spitz nevi. Of the 96 lesions, 12 (12.5%) were excised for histopathological examination and 84 (87.5%) were lesions under follow up. The second group, 13 years of age or older, amounted to 282 cases (74.6% of all lesions).

3.2.1 Clinical characteristics and age group

We observed striking difference in the clinical and dermoscopical analysis between the two age groups (**Table 4**). The age group analysis revealed that in the younger group, the male to female ratio was 1:1.1, while that for the older age group it was 1:1.9. Nodules were more common in the younger group (18.8% vs 8.6%, P=0.006), as opposed to flat macular lesions which were seen more frequently in the older group (30.2% vs 46.6%, P=0.006). Amelanotic Spitz nevi were seen significantly more often in the young group as compared to the older group (11.5% vs 5.0%, P=0.027). Age distribution of amelanotic Spitz nevi is shown in **Figure 17**. One peak is noted at age 6 to 10 years that drops to 0 at age 16 to 20 years and remains relatively low in number afterwards.

Difference in the anatomic site of lesions among the two age groups were also observed. Lesions of the head/neck (9.4% vs 1.4%, P<.001) and acral sites (16.7% vs 5.0%, P<.001) were more frequent in the younger group, whereas lesions of the trunk (15.6% vs 35.5%, P<0.001) were more common in the older group.

3.2.2 Dermoscopic pattern and age group

Significant differences were noted in the dermoscopic patterns with respect to age groups. The globular pattern (12.5% vs 3.6%, P=0.001) and the dotted vessel pattern (11.5% vs 2.5%, P=0.001) were more characteristic of the younger age group. Age distributions of the globular pattern and the dotted vessel pattern are presented in **Figure 18** and **Figure 19**, respectively. Both followed a similar pattern with a peak at age 6 to 10 years, a decline right after and low number of lesions later on. The multicomponent pattern (12.5% vs 23.8%, P=0.019) was more prevalent in the older age group. Superficial black network, white lines, presence of pigment network and presence of vessels were seen at a significantly higher frequency in the older age group than the younger age group. As for detailed local dermoscopic patterns, regular homogeneous pigmentation and diffuse vessel distribution was more common in the younger group, whereas irregular homogeneous pigmentation and irregular vessel distribution were more prevalent features of the older age group. **Table 5** shows the results of the analysis of white lines with clinical features and dermoscopic patterns.

3.3 Analysis by anatomic site

3.3.1 Clinical characteristics and anatomic site

In the second analysis, difference between sex was observed according to the anatomic site of the lesion (**Table 6**). Males had a higher tendency to develop lesions on the trunk than females (36.9% vs 26.2%, P=0.027). In contrast, females had a predilection to acquire lesions on the lower extremities (31.5% vs 45.4%, P=0.007).

3.3.2 Dermoscopic pattern and anatomic site

The starburst pattern was the most prevalent pattern for all locations except for the head and neck region and the upper extremity. Reticular pattern (3/13, 23.0%) and homogeneous pattern (3/13, 23.0%) were the two most common sites for head and neck, while that for the upper extremities was the multicomponent pattern (18/68, 26.5%). **Table 7** shows that, compared to lesions without streaks, lesion with streaks were more common on the anterior trunk (13.8% vs 4.6%, P=0.002) and acral sites (11.3% vs 4.6%, P=0.017). On the other hand, the posterior trunk was significantly associated with absence of streaks (16.3% vs 26.3%, P=0.017). This led us to further compare the dermoscopic patterns between the anterior trunk and the posterior trunk (**Table 8**). As much as 77.8% of the lesions of the anterior trunk showed streaks, whereas the percentage of that for the posterior trunk was only 41.8% (P<0.001). Compared to the posterior trunk, the anterior trunk was nearly five times more likely to exhibit streaks (OR=4.879, 95% CI: 1.976-12.049, P<0.001). The starburst pattern and the reticular pattern were both significantly more frequently seen on the anterior trunk than the posterior trunk

(47.2% vs 26.6%; P=0.029, 13.9% vs 2.5%; P=0.030, respectively). **Table 9** shows that among body sites, the highest prevalence of the starburst pattern was observed in the anterior trunk (17/36, 47.2%) and the acral site (12/31, 38.7%). This was followed by the lower extremity (43/151, 28.5%) and the posterior trunk (21/79, 26.6%). Additionally, the comparison between the anterior trunk and other body sites showed that the starburst pattern was seen significantly more frequently on the anterior trunk relative to the posterior trunk, upper extremity and the lower extremity. **Table 10** shows the results of the comparison analysis between the distal and proximal anatomic locations in terms of melanoblast migration. The distal sites consisted of the anterior trunk and acral sites, whereas the proximal group comprised the head and neck area together with the posterior trunk. Presence of streaks, the starburst pattern and the reticular pattern were all significantly more frequently present in distal locations in terms of melanoblast migration (P<0.001, P=0.015, P=0.023, respectively).

4. DISCUSSION

To the best of our knowledge, this is the largest study with detailed dermoscopic features of Spitz nevi. Both the age group analysis and the anatomic site analysis suggested that Spitz nevi entail biologically distinct subsets. A major finding in this study was that the anatomical site seem to influence the dermoscopic appearance of Spitz nevi.

4.1 Study population

4.1.1 Clinical features

The most frequent anatomic site of the lesions in our series was the lower extremity (39.9%) followed by the trunk (30.4%) and the upper extremity (18.0%). Most prior literatures have found the lower extremity to be the most common site (4, 29-32, 34), however, Weedon *et al*. reported that to be the trunk (3). As for the second most frequent location, some past series have reported that to be the trunk followed by the upper extremity, like in the case of the present study (31, 34). In contrast, others have found the upper extremity to be the second most frequent body site followed by the trunk (29, 30, 32). In agreement with previous studies, the head and neck area was the least common location of Spitz nevus (3.4%) in our study (29-32, 34). However, the percentage for the head and neck area was relatively smaller compared to other series which ranged from 5% to 24% (3, 4, 21, 29-32, 34). The reason for this may be that this study has taken place at a pigmented lesion screening facility where total body skin examinations are done as routine and therefore more lesions in uncovered sites may have been detected.

Classically, Spitz nevi have been known to be a type of nevi common in children (2-4). In contrary to this belief, recent publications have indicated that they are rather common in adults (30, 34). In our present study, 66% of the lesions occurred in individuals older than 20 years of age (data not shown). There are a number of previous literatures with large studies of Spitz nevi to date (3, 4, 21, 29-34). However, most are based on histopathological evaluation following excision of the lesion. What sets our study apart from others is that we included not only histopathologically confirmed Spitz nevi but also the dermoscopically diagnosed Spitz nevi that are being monitored for age 12 years and under. This enabled us to better understand the actual age distribution of Spitz nevi. Additionally, in studying the age distribution, our large study population allowed for the subdivision of cases into smaller age groups. As shown in **Figure 16**, the age distribution of Spitz nevi followed a bimodal pattern with the first and biggest peak at the age group 6 to 10 years, followed by a sharp decrease at age groups 11 to 15 years and 16 to 20 years. Subsequently, the second and smaller peak was seen at 26 to 30 years. This peak was flatter with a wider base and gentle slopes, with high number of lesions between 26 to 45 years. Recent studies have shown that Spitz nevi in young age involute over time (20, 42, 43). In a study of 64 Spitz nevi with a mean age of 10.4 years and a mean follow up period of 25 months, Argenziano *et al*. documented that 79.7% of Spitz nevi showed signs of involution (42). This leads us to believe that the dip at age 11 to 20 years reflects this involution of prepubertal Spitz nevi. If this is the case, the subsequent peak with numbers of Spitz nevi diminishing after age 40 years would indicate that another wave of Spitz nevi emerge around adolescence and involute over a longer course of time than prepubertal Spitz nevi. Spitz nevi are mimickers of melanoma with up to 13.3% of symmetric Spitzoid lesions turning out to be melanoma which prompts excision of postpubertal lesions (26). Therefore, follow ups of Spitz nevi over time in adulthood are generally not performed and there are no reports documenting the life course of adulthood Spitz nevi. However, our results suggests that the rapid evolution and involution are characteristic of prepubertal Spitz nevi. The dynamic involution of prepubertal Spitz nevi in contrast to the slower life of adulthood Spitz nevi implies that these two are distinct subsets with different biological behaviors.

Finally, a female predominance was observed in our series (60.6%). Previous studies have found similar results, ranging from 57.8% to 69.9% (3, 4, 21, 29-31, 34).

4.1.2 Dermoscopic features

The results of this study show that the most prevalent dermoscopic pattern was the starburst pattern which was seen in 29.4% of Spitz nevi. This is in line with past studies that classified Spitz nevi patterns dermoscopically, although in the study conducted by Pellacani *et al.*, the globular pattern tied the starburst pattern as the most common dermoscopic pattern (21, 33). Ferrara *et al*. demonstrated that the second most frequent dermoscopic pattern was the globular pattern, followed by the atypical pattern and Pellacani *et al.* showed that the multicomponent pattern followed subsequently as the third most common pattern (21, 33). These results differ from the present study. In our series, the second most common pattern was the multicomponent pattern (20.9%) and the third was the nonspecific pattern (13.2%). Moreover, globular pattern was seen only in 5.8% of Spitz nevi in the current study which revealed stark contrast to that of Ferrara *et al*. (19.3%) and Pellicani *et al* (22.5%) (21, 33). The mean age of the study population in our series was 27.1 years while that of Ferrara *et al*. was 20.9 years (21). In the current study, we found that the globular nevi were significantly associated with age 12 years and under. Therefore, the study population in the study by Ferrara *et al*. may have had more younger patients with Spitz nevi exhibiting the globular pattern. While the mean age in the study by Pellicani *et al*. was not mentioned, it may possibly have been a factor for the discrepancy.

4.2 Analysis by age groups

4.2.1 Clinical features

We found that the male to female ratio decreased from 1:1.1 in the younger age group to 1:1.9 in the older age group. Similar data has been published with the male to female ratio ranging from 1:0.9 to 1.5 in the younger age group, whereas that for the older age group decreased to 1:2.0 to 2.7 when age groups were divided at either age 10 or 15 years (30, 31, 34). Dal Pozzo *et al*. also reported that before 10 years of age, the proportion of males was slightly higher and it became vice versa after 15 years of age (4). On the other hand, in a Hispanic population, Berlingeri-Ramos *et al*. demonstrated that the male to female ratio was 1:1.4 for patients up to 12 years of age and the ratio increased to 1:1.2 in patients older than 12 years of age revealing an opposite trend (29). This reverse trend may be explained by the smaller sample size in the latter study, 108 patients to be exact, in contrast to a range of 187 to 349 patients in the former studies. Another possibility may be that it is due to ethnic difference, since the studies with the male to female ratio decreasing in the older age groups were conducted in Italy, Spain and Germany presumably from a Caucasian population.

In the present study, the most frequent anatomic site was the lower extremity in both the younger age group and the older age group (**Table 4**). This is in line with data documented by Berlingeri-Ramos *et al*. and Betti *et al* (29, 34). Requena *et al*. demonstrated that the most affected body site was the lower extremity in all age groups except for the group with patients older than 45 years in which that was the trunk (31). Cesinaro *et al*. reported that the lower extremity was the most common location in females in all age groups, whereas the upper extremity and the trunk were the most common site in males older than 30 years and older than 40 years, respectively (30). In our current study, the lower extremity was followed by the upper extremity and acral sites in the younger age group and by the trunk and the upper extremity in the older age group.

Comparison of the two age groups showed that lesions on the head and neck region were seen more frequently in the younger age group (9.4% vs 1.4%, P<0.001). On the contrary, lesions on the trunk showed an opposite trend, less frequent in the younger group with respect to the older group (15.6% vs 35.5%, P<0.001). This is in accordance with other studies by Betti *et al*. and Dal Pozzo *et al.* (4, 34). Requena *et al.* showed similar results in that the head and neck were frequent locations in children compared to adults and that the trunk was the most common anatomic site for patients older than 45 years of age (31).

On the other hand, unlike existing studies, the present study revealed that the acral site was a common location for Spitz nevi in the younger age group compared to the older age group (**Figures 8 & 9**). This high frequency in the younger age group may be attributable to the fact that in our study, not only the palms and soles with glabrous skin, but also the dorsum of the hands, feet, fingers and toes were included in the acral site. Most previous reports did not analyze acral sites as a separate location and included these lesions in either the lower extremity, upper extremity or limbs (3, 4, 21, 29-31, 34). Lott *et al.* demonstrated that Spitz nevi on the dorsum of the hands and feet were relatively common with the prevalence ranging from 5 to 8%. However, the anatomic site of Spitz nevi by age was not analyzed (32).

Our results indicated that nodular lesions were significantly associated with the younger age group, whereas macules were significantly associated with the older age group (**Figure 10**). Dal Pozzo *et al*. examined palpability by clinically grouping Spitz nevi into the following three groups: dome-shaped nonpigmented type, dome-shaped pigmented type and the flat pigmented type (4). They found that the mean age for the dome-shaped nonpigmented type was 9.3 years which was lower compared to the other two types, with statistical significance for the flat pigmented type ($p<0.01$). The mean ages for the dome-shaped pigmented type and flat pigmented type were 12.8 years and 16.4 years.

4.2.2 Dermoscopic features

We observed that dermoscopically amelanotic lesions were seen more often in the younger age group compared to the older age group (**Figure 10**). This is in line with previous studies that clinically assessed pigmentation. Betti *et al*. reported that clinical absence of pigmentation was seen more frequently in age group under 15 years than in that of 15 years and older (34). In the series by Dal Pozzo *et al*., age groups 0 to 5 years and 6 to 10 years together comprised over 70% of the dome-shaped nonpigmented type, each accounting for more than 30% (4). In contrast, in the age group 11 to 15 years, the prevalence of the dome-shaped nonpigmented type dropped between 10 to 15% and in the age group older than 15 years, remained low between 15 to 20%. The present study showed a similar tendency upon studying the age distribution of amelanotic Spitz nevi. As shown in **Figure 17**, the number of amelanotic Spitz nevi peaks at 6 to 10 years and sharply drops after that to become 0 at 16 to 20 years. Afterwards, the number of lesions is relatively low at older age. In the previously mentioned study conducted by Argenziano *et al*. with a mean age of 10.4 years, it was observed that nearly half of the Spitz nevi in involution were amelanotic (42). In addition, they observed that the more than 90% of growing lesions were either pigmented or partially pigmented. With these observations in consideration, our results suggest that amelanotic Spitz nevi is characteristic of childhood and involutes during youth. The aformentioned decrease in the prevalence of dome-shaped nonpigmented type in the age group 11 to 15 years and the low prevalence remaining in the age group over 15 years described by Dal Pozzo *et al*. also supports this view (4).

Comparison of dermoscopic global pattern between the two age groups revealed that the globular pattern was significantly associated with the younger age group (**Figure 8**). Recent literature have shown that Spitz nevi evolve and involute exhibiting different dermoscopical patterns depending on the stage of evolution (20, 42-45). The starburst pattern is representative of the growth of the lesion and can be preceded by the globular pattern (42). Subsequent to growth, starburst Spitz nevi become stable displaying the homogeneous pattern or the reticular pattern. After a certain period of time, they lose pigmentation and involute. Natural changes in dermoscopic pattern of globular Spitz nevi have been documented. Pizzichetta *et al*. first reported a globular Spitz nevus that evolved into a starburst pattern in 3 months (44). Piccolo *et al*. also observed two cases of globular Spitz nevi that developed into the starburst pattern in 3 months and 6 months respectively (45). Later on, the former changed into the reticular pattern and the latter into the homogeneous pattern. Argenziano *et al*. described a globular Spitz nevus that started to display an involution pattern in a period of a month (20). Although the number of reported cases is limited, the prominent common factors among these cases are their rapid speed of change in dermoscopic patterns and the young age at presentation (mean age 4.5 years old, ranging from 1 to 11 years). As shown in **Figure 18**, in the current study, we observed that the number of globular nevi reaches a peak at 6 to 10 years and plunges to 0 at 11 to 15 years. After 16 years of age, the number stays low. This drastic decrease in the number of globular nevi after 11 years of age most likely reflects the rapid evolution of globular nevi. After 46 years of age, there no longer were any lesions that exhibited the globular pattern. Our results suggest that the globular pattern is a distinctive feature of childhood Spitz nevi and that they evolve rapidly and become very uncommon soon after puberty. In addition, the starburst pattern, homogeneous pattern and the reticular pattern, which can be succeeding patterns of the globular pattern, all peaked in number at the age group 6 to 10 years and sharply decreased at age group 11 to 15 years (data not shown), resembling the tendency seen in the globular pattern for ages 0 to 20 years. This implicates that they evoluted and involuted speedily within this time frame. This is in line with our postulation that the evolution and involution of Spitz nevi in childhood is a rapid process in prepuberty.

Globular pattern is known to be the predominant pattern in youth in both congenital melanocytic nevi and acquired melanocytic nevi. Changchien *et al*. observed that in congenital melanocytic nevi, the globular pattern was more common in individuals younger than 12 years and that they became much less frequent thereafter (39). Seidenari *et al*. also documented that the globular pattern prevailed in congenital melanocytic nevi of individuals under 11 years of age (37). In acquired melanocytic nevi, Zalaudek *et al*. reported that the mean age for globular nevi was 14 years while that for nevi other than the globular type was 34 years and older (36). In another study by Zalaudek *et al.* in which they examined acquired melanocytic nevi, globular nevi were significantly more prevalent in age 2 to 20 years compared to all other older age groups (35). In their study, they observed an almost linear decrease in the number of globular nevi in adulthood. This decline was not as radical as in the case of the present study and the authors speculated that this may be due to the evolution of a certain portion of childhood globular nevi. One portion of globular nevi remains as globular nevi in puberty, gradually lose pigmentation and acquire a more structureless pattern with age. The other portion evolves into nevi with peripheral rim of globules, which is a sign of growth, during puberty and turn into nevi with either a globular or structureless central area with peripheral network. Predominance in youth and eventual evolution are similarities between the globular pattern in Spitz nevi and in both congenital melanocytic nevi and acquired melanocytic nevi, although the evolution of globular Spitz nevi is far more dynamic and rapid. It is intriguing that all these nevi exhibiting globules share similar biological behavior: appearing in youth and evoluting into another pattern.

In addition to the globular pattern, we found that the dotted vessel pattern was also significantly associated with the younger age group (**Figure 10**). This pattern, also called the nonpigmented homogeneous pattern, is known to be common in children (24). This is in line with our findings. As shown in **Figure 19**, the number of dotted vessel pattern nevi reaches a peak at 6 to 10 years, plummets at age 16 to 20 years and remains low in number thereafter. Although the amelanotic nevi in the present study entails not only the dotted vessel pattern but also some lesions from the inverse network pattern and the unspecific pattern, the age distribution of the dotted vessel pattern parallels that of the amelanotic nevi. Our results suggests that Spitz nevi harboring the dotted vessel pattern are also characteristic of childhood and involute at young age.

We found that dermoscopic patterns and features of irregular or atypical nature were associated with the older age group, namely the multicomponent pattern, irregular homogeneous pigmentation, atypical network and irregular distribution of vessels. On the other hand, in lesions with vessels, diffuse vessel distribution was more common in the younger age group. Broganelli *et al*. pointed out that Spitzoid lesions in prepubertal children usually have typical morphologic aspect and clinical course and that nevi which do not fall into this category are uncommon in children (28). Our results are congruent with their view.

Superficial black network is a distinctive type of network seen in pigmented Spitz nevi which was first documented by Argenziano *et al.* (46). It appears as prominent black network ending at the periphery which overlies a bluish black to whitish bluish diffuse pigmentation. This dermoscopic feature histopathologically corresponds to focal areas of pigmented parakeratosis. In the present study, we found that 6.9% of Spitz nevi presented the superficial black network (**Figure 11**). Argenziano *et al*. reported similar observations with 10.5% of Spitz nevi harboring this feature. Furthermore, our results indicated that superficial black network was associated with the older age group which is a new finding. As a matter of fact, all but one lesion exhibiting the superficial black network fell into the older age group (96.2%). Superficial black network seems to be common among individuals in their twenties, thirties and forties (24/26 lesions, 92.3%) and there were no lesions with this dermoscopic feature observed before 10 years of age or after 50 years of age.

White lines in our study consists of both the inverse network and crystalline structures (**Table 2**). Crystalline structures appear as linear bright white lines that show up upon polarized dermoscopy which corresponds histopathologically to increased collagen in the dermis (47, 48). Inverse network, otherwise known as the negative pigment network, is a white network that is thought to correspond histopathologically to hypopigmented elongated rete ridges (23). Both crystalline structures and inverse network are features seen in Spitz nevi and melanoma (23, 47-51). In the present study, 25.1% (95/378) of the lesions exhibited white lines (**Figure 12**). In contrast, Botella-Estrada *et al*. reported that 55.6% (5/9) of Spitz nevi showed either the crystalline structures or the inverse network (50). This discrepancy may be due to the smaller number of cases in their study. We found that nearly half of lesions with white lines (47/95, 49.5%) appeared on the lower extremity. Furthermore, white lines were significantly associated with females, nodular lesions, hypopigmentation, multicomponent pattern, inverse network pattern and ulceration ($P=0.022$, $P=0.015$, $P<0.001$, $P<0.001$, $P<0.001$ and $P=0.027$ respectively) (**Table 5**). In agreement with Broganelli *et al*., this atypical dermoscopic feature was observed more frequently in the older group (28).

In recent years, evidence has compiled supporting the notion that morphological features and growth patterns of melanocytic tumors are associated with their underlying genetic alterations.

In nevi, association between different mutations in the MAPK pathway and different types of melanocytic nevi have been found. NRAS mutations are seen in congenital melanocytic nevi, especially large and giant types (52). GNAQ mutations are common in blue nevi (53). BRAF mutations are seen in 78% of acquired melanocytic nevi (54). In terms of dermoscopy, Marchetti *et al*. showed that the BRAF V600E mutation was more frequent in globular nevi compared with reticular nevi (91.7% vs 30.1%, P=0.004) (55). Significant associations between five single-nucleotide polymorphisms and either reticular or globular nevi in children have been described by Orlow *et al*. as well (56).

In melanoma, Fargnoli *et al*. reported that melanomas of MCR1 R carriers have lower total dermoscopic score value, less number of dermoscopic structures and lower prevalence of atypical pigment network (57). Sanchez *et al*. documented that melanomas with KIT exon 17 mutations harbor a dermoscopic pattern of dark homogeneous structureless areas and streaks in the periphery (58). This report is particularly interesting because this dermoscopic pattern bears a resemblance to the starburst pattern of Spitz nevi. We can speculate that a certain specific mutation may be responsible for the starburst pattern in Spitz nevi. Furthermore, Pozzobon *et al*. demonstrated that BRAF and NRAS mutations were associated with dermoscopic peppering in melanoma (59).

As for Spitzoid tumors, there are studies investigating the genetic alterations and dermoscopical features. However, to our knowledge, none have demonstrated the genetic signature to correspond to a certain dermoscopic feature. Moscarella *et al*. studied the genotypic characteristics of randomly distributed multiple Spitz nevi and their dermoscopic pattern along with clinical and histopathological features (60). In their study, all six cases examined were found to be wild type for genetic sequences of BRAF gene codons 599-601 (exon 15) and also N-/H-/K-RAS genes codons 12-13 (exon 2) and 61 (exon 3). Nevertheless, studies have been published revealing the relationship between genotypical and the histopathological characteristics in Spitzoid tumors (61-63). There are mainly 3 types of genetic alterations that are identified so far in Spitzoid tumors: HRAS gene alterations, kinase fusions and BRAF mutations combined with bi-allelic

BAP1 loss (64). Of these 3 types, HRAS gene alterations and kinase fusions have been reported in Spitz nevi. These two types seem to be exclusive to each other and together comprise nearly 70% of Spitz nevi.

Genetic alterations of the HRAS gene (including both mutations and copy number gain) was seen in 48 of 293 (16.3%) in Spitz nevi summarized from multiple studies (54). HRAS is an oncogene in the MAPK pathway along with the aforementioned NRAS, BRAF, and GNAQ (65). Mutations in HRAS are generally exclusive to Spitz nevi (54). Bastian *et al*. documented that copy number gain in chromosome 11p was seen in 11.8% of Spitz nevi and that it was significantly associated with mutations in the HRAS gene (63). In addition, the copy gain of the 11p chromosome was associated with the following histopathological features: large size of the lesion, intradermal growth, single cells between collagen bundles, desmoplasia, vesicular nuclei, ample eosinophilic cytoplasm, eosinophilic membranes, and marked nuclear pleomorphism. Similar results have been reported by Van Engen-van Grunsven *et al*. in which 18.3% of Spitz nevi harbored HRAS mutations (61). In their study, Spitzoid tumors (including both Spitz nevi and STUMPs) with HRAS mutations exhibited the following histopathological features: predominantly intradermal localization, relatively low cellularity, single cells between collagen bundles, desmoplasia and infiltrative base. Studies indicate a favorable prognosis in these subtypes (54, 61, 63, 66, 67).

Spitz nevi with kinase fusions have been described by Wiesner *et al.* (68). Kinase fusions were seen in 41 of 75 (55%) Spitz nevi in a mutually exclusive pattern. Genes identified in this group were membrane bound receptor tyrosine kinases ROS1 (25%), NTRK1 (11%), ALK (11%), and RET (3%) and the serine/threonine kinase BRAF (5%).

None of Spitz nevi in this group had HRAS mutation. Histopathological correlation with genetic types of these tumors have not been document yet.

Atypical Spitz tumors with BRAF V600E mutations accompanied by bi-allelic BAP1 loss have been shown to be a distinct subset also by Wiesner *et al* (62). All tumors were negative for HRAS mutations. Histopathological features frequent in these tumors were as follows: mostly dermal location, epithelioid cells, cytoplasmic amophilia, well-defined cytoplasmic borders, vesicular chromatin, binucliation or multinucleation and marked tumor infiltrating lymphocytes. In this subset of atypical Spitz tumors, anatomical preference was also reported. Of the 32 atypical Spitz tumors, BAP1-negative tumors were significantly more frequently located on the trunk and less likely to be present on the limbs when compared with BAP1-positive tumors. In some melanocytic tumors, it seems that not only the morphological features and growth patterns but also the anatomical location is influenced by genetic signatures.

It is known in melanocytic tumors that morphological features among histopathology, dermoscopy and also in vivo confoncal microscopy correlate with each other (69-71). The presence of association between genetic characteristics and histopathological features means that there probably is an association between dermoscopic features and genetic characteristics as well. Thus, we speculate that there is a genetic alteration corresponding to each dermoscopic subtype of Spitz nevi which exhibit unique biological behavior.

4.3 Analysis by anatomic site

4.3.1 Clinical features

In our analysis, according to anatomic site, we found difference between males and females (**Table 6**). Females had higher chance to present lesions on the lower extremities (P=0.007), whereas males were more likely to present lesions on the trunk (P=0.027). At the same time, the most frequent location for males was the trunk (36.9%) and that for females was the lower extremity (45.4%). This is consistent with the findings of Requena *et al.* (31). In their study, they found the lower extremity to be the most affected body site for females (48%). The trunk was the most common site for males (37%) with statistical difference (P<.0001). Cesinaro *et al*. also reported that the lower extremity was the most frequent site of lesions for females in all age groups and that the trunk was significantly more affected in males over the age 40 (30). In contrast, Berlingeri-Ramos *et al*. have reported that the most common anatomic site was the lower extremities for both males and females in a Hispanic population (29). Interestingly, the trend with frequent truncal lesions in males and lesions of lower extremity in females found in our study has also been reported in melanomas in multiple documents from different countries (72-78). Some attribute this to behavioral difference in males and females, such as modes of clothing, sun-related behavior, and propensity to seek medical care (72, 74). Others point out the possibility of the influence of sex hormones (76). Another point of view presented by Bataille *et al*. suggests that difference in melanocyte differentiation between sex and anatomical site programmed early on during embryogenesis may play a role (79). The reason for this coinciding tendency in Spitz nevi and melanoma may share common grounds.

4.3.2 Dermoscopic features

Analysis of dermoscopic features by anatomic location revealed association between streaks and body sites. Presence of streaks was significantly associated with the anterior trunk and the acral site, while the posterior trunk was significantly associated with the absence of streaks (**Table 7**). To our knowledge, this is the first study to demonstrate dermoscopic difference related to anatomic sites in Spitz nevi. Congruent with this result, the anterior trunk and the acral site had relatively higher prevalence of the starburst pattern than the other body sites, amounting to nearly 50% and 40% each (**Table 9, Figures 9, 13, 14**). The anterior trunk displayed the starburst pattern significantly more frequently than all other anatomic locations with the exception of the acral sites. The remarkable difference between the anterior and posterior trunks prompted us to further compare dermoscopic features between the two. In addition to streaks, the anterior trunk exhibited both the starburst pattern and reticular pattern significantly more frequently than the posterior trunk (**Table 8, Figures 13-15**). This is in agreement with the observation that Spitz nevi evolve from the starburst pattern to the reticular pattern described in previous literature (43, 45).

Differences in dermoscopic patterns among various anatomic sites are reported in congenital nevi and common nevi. In congenital nevi, Seidenari *et al*. observed that the trunk was a common site for globular nevi whereas that for reticular nevi was the limbs (37). Changchien *et al*. also showed that the head, neck and trunk were frequent sites for globular nevi, while that for the reticular nevi was the extremities (39). In common nevi, Zalaudek *et al*. found that the upper body segments were the most frequent location for globular nevi in children and adolescents and that the shoulders and midback were the most common sites for reticular nevi (35). Moreover, like the case in our study, difference between the anterior trunk and the posterior trunk was observed. Reticular nevi, unspecified nevi and nevi with mixed pattern that harbor a central globular or structureless area with peripheral network were common on the posterior trunk relative to the anterior trunk. Fonseca and Marchetti *et al.* found that the complex nevi and the globular nevi were more frequent on the back compared with the legs, whereas the reticular nevi were more frequent on the legs with respect to the back (38). They further went on to analyze the dermoscopic features between the two locations. Network was significantly more common on the legs, whereas dots and globules of any type were more common on the back. Another study describing the difference in the distribution of acquired melanocytic nevi between the anterior trunk and posterior trunk has been documented by Blake *et al.* (80). It was demonstrated that 70% of trunk nevi belonged to the posterior trunk and that the density of nevi decreased continuously following a dorsolateral pattern from the midline of the posterior trunk to the midline of the anterior trunk that could be described mathematically.

Studies of anatomic site related and age related dermoscopic difference in nevi have given rise to the dual concept of nevogenesis (81, 82). This concept proposes that there are at least two pathways in nevogenesis. The first pathway, the constitutional pathway, is responsible for the development of globular nevi. Melanocytes in globular nevi are believed to arise from melanoblasts that migrate through the dorsolateral migratory pathway, from the neural crest in a cephalo-caudal and dorso-lateral sequence (83-85). Melanoblasts emigrate to the dermis at 6-8weeks estimated gestational age (EGA) (86). Then, by 12-13 weeks EGA, they are present in the suprabasal layers of the epidermis and by 15-17 weeks EGA, they localize to the basal layer of the epidermis and populate the hair follicles thereafter (86). It is hypothesized that there is a delay or an arrest in the early stage of migration in the above mentioned progression sequence (81). This presumably results in the arrest of melanoblasts in the dermis and in proximal and dorsal body sites like the head and neck region and the upper posterior trunk which is in accordance with the documented anatomic characteristics of globular nevi (35, 39). The second pathway, the acquired pathway, give rise to the reticular nevi. It is proposed that reticular nevi arise from epidermal melanocytes at the dermoepidermal junction responding to intermitted ultraviolet radiation.

We grouped anatomic sites in terms of melanoblast migration sequence to compare the dermoscopic features: proximal sites, head and neck region and the posterior trunk as one group and distal sites, anterior trunk and acral sites as another. Comparison of dermoscopic features between the two groups revealed that the presence of streaks, starburst pattern and reticular pattern were all significantly more frequent in the distal group ($P<.001$, $P=0.015$, $P=0.023$, respectively) (**Table 10**). This is also in accordance with the dermoscopic patterns seen in the evolution of starburst Spitz nevi (43, 45). Our results shows that streaks, starburst pattern and the reticular patterns are more common in anatomic sites in which melanoblasts arrive at a later timing as opposed to early arriving locations such as the head and neck region and the posterior trunk. This may be an implication that the nevogenesis of the starburst pattern Spitz nevi is influenced by the timing of melanoblast migration. We postulate that the starburst pattern Spitz nevi harbor a specific genetic alteration associated with later timing in the melanoblast migration and that this gives rise to this characteristic anatomical distribution. An interesting study documenting pigmentation defects in mutant mice observed during the course of melanoblast migration has been reported by Jordan *et al.* (87). Adult mice heterozygous for rump-white (*Rw*/+) have depigmented areas in the posterior abdomen and hindlimbs which are more prevalent ventrally than dorsally and in digits of both the forelimbs and hindlimbs. Rump-white mutation is a dominant lethal mutation which is embryonically lethal when homozygous. The mutation results in the ectopic expression of tyrosine kinase KIT receptor in the embryonic dermatome of the somites at mouse embryonic day (E) 10.5 (88). KIT receptors are expressed by melanoblasts and are essential along with its ligand KITL for the survival and proliferation of melanoblasts and also for the migration from the dermis to the epidermis at E14.5 (89-91). The misexpression of KIT receptor leads to the sequestration of KITL which becomes unavailable any further for the dispersal and/or survival of melanoblasts during migration. Their study compared *Rw*/+ and wild type mice melanoblast migration by marking melanoblast lineage cells with reporter transgene *Dct-lacZ*. In *Rw*/+ mice, melanoblasts failing to migrate and survive resulted in reduced number of melanoblasts which started at E11.5 and formed a large area in the trunk with a low number of melanoblasts that persisted until E15.5. Although a second wave of melanocytes emerged at E16.5, melanocytes remained absent in the hindlimbs and decreased in number in lumbar and ventral abdominal regions. The authors surmise that the anatomical distribution of the depigmented areas may be explained by a later timing of KIT receptor misexpression in *Rw*/+ mice. The location of the depigmented body sites in the study share similarities with the anatomical sites in which streaks, starburst pattern and the reticular pattern were observed in our study. Their study supports our view that the starburst pattern affected body sites may have a link with the migration of the melanoblasts.

In addition to the aforementioned dorsolateral migratory pathway of melanoblasts, recent studies have shed light on an alternative migration route called the ventral migratory pathway (92). This was originally believed to be the route for the development of the peripheral nerve system but now has been identified to generate the second wave of melanoblasts. In this pathway, neural crest derived cells migrate between the neural tube and the anterior somite in a ventral direction as they form the dorsal root ganglia (93). Cells that do not acquire a neuronal fate adopt a glial fate and become multipotent Schwann cell precursors that can generate both Schwann cells and melanoblasts (93). As the Schwann cell precursors travel along the nerves towards the periphery, a subset of these acquires a melanocyte fate by detaching and losing contact with the nerves (92). These melanoblasts proliferate in number and migrate towards the skin to become melanocytes populating the hair follicles and epidermis. Whether there is a biological difference between the melanocytes arising from the two pathways is not clear. However, it is certainly possible that a particular subset of nevi originates from melanocytes of the second wave.

Besides the melanoblast migration, local environmental factors that supposedly have an effect on the regulation of melanocyte proliferation may differ among anatomic locations and as a result, it may also influence the biologic behavior of nevi in terms of anatomic distribution.

Our study has several limitations. This is a retrospective observational study and is prone to misclassification bias. We tried to eliminate this by having two individuals evaluate the dermoscopical features based on recorded images and when in disagreement, having a third individual perform the decisive assessment. This applied to the evaluation of the tumor palpability by clinical images as well. In addition, the study is based on images from the first visit, meaning that, in pediatric cases, we did not consider all of the dynamic dermoscopic changes that appear during follow up due to the evoluting and involuting nature of Spitz nevi. The images are dependent on the timing of the presentation and as a result, may not entirely portray the longitudinal change of Spitz nevi. Furthermore, in children under age 12 years and under, we included cases which were dermoscopically diagnosed as Spitz nevi without histological confirmation because they were undergoing follow up. However, these cases basically exhibited typical features of Spitz nevi and were otherwise excised for histopathological examination.

4.4 Conclusion

In conclusion, we found age and anatomic location related difference in the clinical and dermoscopical features of Spitz nevi. This suggests that dermoscopic subtypes of Spitz nevi each exhibit distinct biological behavior which is presumably determined by an underlying signature genetic alteration. The life span of childhood Spitz nevi seemed to have a shorter life cycle, with involution around puberty as compared with that of adulthood Spitz nevi. Age group analysis showed that clinical features associated with the younger age group were near 1.0 male to female ratio, nodules, head and neck location and the acral site (**Figures 8-10**). As for the dermoscopic features, Spitz nevi in the younger age group were more likely to be amelanotic, to exhibit the globular and dotted vessel pattern, and to present with homogeneous structureless areas and diffuse distribution of vessels (**Figures 8 & 10**). In addition, they were more unlikely to display pigment network. The globular pattern is a hallmark of prepubertal Spitz nevi which evolves rapidly and becomes uncommon thereafter. The dotted vessel pattern appeared to be characteristic of prepubertal Spitz nevi which involutes in childhood. On the other hand, clinical features associated with the older age group were prevalence in females, macules and truncal lesions. Regarding the dermoscopic features, Spitz nevi in the older age group were more likely to be pigmented, to exhibit the multicomponent pattern, to present with irregular homogeneous pigmentation, superficial black network, white lines, pigment network, atypical network and to have an irregular distribution of vessels (**Figures 11 & 12**). Analysis by anatomic sites showed that females frequently had lesions on the lower extremity and the men on the trunk. Streaks were significantly associated with the anterior trunk and acral sites. Streaks, starburst pattern and the reticular pattern were seen more frequently in the anterior trunk and acral sites which are body sites where melanoblasts arrive towards the end of migration (**Figures 9, 13-15**). The starburst pattern nevi may be a biologically distinct subset with a genetic alteration that is linked with late melanoblast migration.

Future studies on the relationship between dermoscopic and genetic alterations may offer better insight into the intriguing mechanism of the nevogenesis of Spitz nevi. Nonetheless, we believe this study enables us to add depth to the understanding of the morphologically and biologically diverse life of Spitz nevi.

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APPENDIX

Table 1. Definition of the observed dermoscopic global patterns

Dermoscopic pattern	**Definition**
Starburst pattern	Bluish to black central homogeneous structureless area surrounded by darkly pigmented radiating streaks or pseudopods.
Globular pattern	Numerous, variously sized, round to oval globules and/or globules of various shades of brown, black, or bluish gray/black that is often distributed through out the entire lesion with a regular brown to grey-blue central structureless area.
Homogeneous pattern	Diffuse, brown, gray, blue or black pigmentation in the absence of other distincive local features.
Reticular pattern	Pigment network covering most parts of the lesion.
Dotted vessel pattern	Dotted vessels distributed regularly over a pink homogeneous structureless area.
Inverse network pattern	White network surrounding vascular structures or pigmented globules over most parts of the lesion.
Multicomponent pattern	Lesion that displays more than one pattern described above.
Nonspecific pattern	Lesion that does not fall into any of the patterns or lesion with any ulceration.

Table 2. Definition of the observed dermoscopic features

Dermoscopic feature	Definition
Amelanotic lesion	Lesion with absolutely no pigmentation upon dermoscopy.
Hypopigmented lesion	Lesion with less than 50% of pigmented area.
Streaks	Brownish-black linear structures of variable thickness, not clearly combined with pigmented network lines. Scored as regular (regularly distributed at the periphery of the lesion) or irregular.
Homogeneous pigmentation	Areas of structureless color varying from black, brown, blue, pink and red.
Superficial black network	Distinctive type of pigment network, visible on the surface of heavily pigmented lesions.
Regular globules	Sharply circumscribed, usually round to oval structures with regular distribution.
Irregular globules	Globules with any of the following features: variously sized and/or colored globules or globules with irregular distribution.
White lines	White crossing lines in between the vascular structures or the pigmented globules (inverse network) and/or white parallel or orthogonal and disordered linear streaks or short lines (crystalline structures).
Typical pigment network	Light- to dark-brown pigmented, regularly meshed and narrowly spaced network.
Atypical pigment network	Black, brown or gray, irregularly meshed network, distributed more or less irregularly throughout the lesion and usually ending abruptly at the periphery.
Blue white veil	Confluent, gray-blue to whitish blue, diffuse pigmentation.
Regression	Gray-blue areas, white areas, peppering

**Courtesy of* Dr. Elvira Moscarella

Table 3. Clinical and dermoscopic charateristics of 378 Spitz nevi lesions

Total (n=378) N,%			
Age (years)		**Homogeneous pigmentation**	
Mean±SD	27.12±15.08	Regular	224 (59.3%)
Median age	28	Irregular	96 (25.4%)
Sex		Absence of homogeneous pigmentation	58 (15.3%)
Male	149 (39.4%)		
Female	229 (60.6%)	**Globules**	
Palpability (n=376)		Brown regular	7 (1.9%)
Macule	159 (42.3%)	Blue/gray regular	41 (10.8%)
Papule	107 (28.5%)	Black regular	3 (0.8%)
Plaque	68 (18.1%)	Pink globules	1 (0.3%)
Nodule	42 (11.2%)	Irregular	128 (33.9%)
Pigmentation		Absence of globules	198 (52.4%)
Amelanotic	25 (6.6%)	**Pigment network**	
Hypopigmented	69 (18.3%)	Typical	19 (5.0%)
Pigmented	284 (75.1%)	Atypical	76 (20.1%)
Ulceration		Absence of pigment network	283 (74.9%)
Presence of ulceration	8 (2.1%)	**Superficial black network**	
Anatomic site		Presence of superficial black network	26 (6.9%)
Head & neck	13 (3.4%)		
Trunk	115 (30.4%)	**White lines**	
Upper extremity	68 (18.0%)	Presence of white lines	95 (25.1%)
Lower extremity	151 (39.9%)	**Blue white veil**	
Acral	31 (8.2%)	Presence of blue white veil	5 (1.3%)
Global pattern		**Regression**	
Starburst	111 (29.4%)	Presence of regression	20 (5.3%)
Globular	22 (5.8%)	**Vessels**	
Homogeneous	33 (8.7%)	Linear	8 (2.1%)
Reticular	35 (9.3%)	Comma	2 (0.5%)
Multicomponent	79 (20.9%)	Hairpin	0 (0.0%)
Nonspecific	50 (13.2%)	Polymorphic	42 (11.1%)
Inverse network	30 (7.9%)	Dotted	74 (19.6%)
Dotted vessel	18 (4.8%)	Coiled	3 (0.8%)
Streaks		Arborizing	3 (0.8%)
Regular	112 (29.6%)	Absence of vessels	246 (65.1%)
Irregular	91 (24.1%)	**Vessel distribution** (n=132)	
Absence of streaks	175 (46.3%)	Central	27 (20.5%)
		Peripheral	10 (7.6%)
		Diffuse	66 (50.0%)
		Irregular	29 (22.0%)

Table 4. Analysis of clinical and dermoscopical characteristic differences between different age groups; 12 years & younger and 13 years & older

	12 years & younger (n=96) N, (%)	**13 years & older (n=282)** N, (%)	*P* value
Sex			0.003
Male	50 (52.1%)	99 (35.1%)	
Female	46 (47.9%)	183 (64.9%)	
Palpability (n=376)			
Macule	29 (30.2%)	130 (46.4%)	0.006
Nodule	18 (18.8%)	24 (8.6%)	0.006
Pigmentation			
Amelanotic	11 (11.5%)	14 (5.0%)	0.027
Ulceration			
Presence of ulceration	3 (3.1%)	5 (1.8%)	0.424
Anatomic site			
Head & neck	9 (9.4%)	4 (1.4%)	<0.001
Trunk	15 (15.6%)	100 (35.5%)	<0.001
Upper extremity	18 (18.8%)	50 (17.7%)	
Lower extremity	37 (38.5%)	114 (40.4%)	
Acral	17 (17.7%)	14 (5.0%)	<0.001
Global pattern			
Starburst	32 (33.3%)	79 (28.0%)	
Globular	12 (12.5%)	10 (3.6%)	0.001
Homogeneous	9 (9.4%)	24 (8.5%)	
Reticular	8 (8.3%)	27 (9.6%)	
Multicomponent	12 (12.5%)	67 (23.8%)	0.019
Nonspecific	8 (8.3%)	42 (14.9%)	
Inverse network	4 (4.2%)	26 (9.2%)	
Dotted vessel	11 (11.5%)	7 (2.5%)	0.001
Streaks			0.226
Regular streaks	34 (35.4%)	78 (27.7%)	
Irregular streaks	18 (18.8%)	73 (25.9%)	
None	44 (45.8%)	131(46.5%)	
Homogeneous pigmentation			
Regular	66 (68.8%)	158 (56.0%)	0.028
Irregular	10 (10.4%)	86 (30.5%)	<0.001
Globules			0.787
Brown regular	2 (2.1%)	5 (1.8%)	
Blue/gray regular	11 (11.5%)	30 (10.6%)	
Black regular	0 (0.0%)	3 (1.1%)	
Pink globules	0 (0.0%)	1 (0.4%)	
Irregular globules	37 (38.6%)	91 (32.3%)	
None	46 (47.9%)	152 (53.9%)	
Pigment network			
Presence of pigment network	16 (16.7%)	79 (28.0%)	0.027
Atypical	10 (10.4%)	66 (23.4%)	0.006
Superficial black network			
Presence of superficial black network	1 (1.0%)	25 (8.9%)	0.009
White lines			
Presence of white lines	16 (16.7%)	79 (28.0%)	0.027
Blue white veil			
Presence of blue white veil	1 (1.0%)	4 (1.4%)	>0.99
Regression			
Presence of regression	2 (2.1%)	18 (6.4%)	0.104
Vessels			
Presence of vessels	23 (24.0%)	109 (38.7%)	0.009
Vessel type (n=132)			0.282
Vessel distribution (n=132)			
Diffuse	17 (73.9%)	49 (45.0%)	0.012
Irregular	1 (4.3%)	28 (25.7%)	0.025

Table 5. Analysis of white lines with clinical features and dermoscopical patterns.

	Presence of white lines		
	Yes (n=95) N, (%)	**No (n=283)** N, (%)	*P* value
Sex			
Male	28 (29.5%)	121 (42.8%)	0.022
Female	67 (70.5%)	162 (57.2%)	
Palpability (n=376)			
Macule	28 (29.5%)	131 (46.6%)	0.004
Nodule	17 (17.9%)	25 (8.9%)	0.015
Pigmentation			
Hypopigmented	40 (42.1%)	29 (10.2%)	<0.001
Pigmented	46 (48.4%)	238 (84.1%)	<0.001
Ulceration			
Presence of ulceration	5 (5.3%)	3 (1.1%)	0.027
Anatomic site			
Head & neck	2 (2.1%)	11 (3.9%)	
Trunk	27 (28.4%)	88 (31.1%)	
Upper extremity	15 (15.8%)	53 (18.7%)	
Lower extremity	47 (49.5%)	104 (36.7%)	
Acral	4 (4.2%)	27 (9.5%)	
Global pattern			
Starburst	3 (3.2%)	108 (38.2%)	<0.001
Globular	1 (1.1%)	21 (7.4%)	0.022
Homogeneous	2 (2.1%)	31 (11.0%)	0.082
Reticular	3 (3.2%)	32 (11.3%)	0.018
Multicomponent	37 (38.9%)	42 (14.8%)	<0.001
Nonspecific	15 (15.8%)	35 (12.4%)	
Inverse network	30 (31.6%)	0 (0.0%)	<0.001
Dotted vessel	4 (4.2%)	14 (4.9%)	

Table 6. Analysis of sex by anatomic site of lesion

	Sex		
	Male (n=149) N, (%)	**Female (n=229)** N, (%)	*P* value
Anatomic site			
Head & neck	8 (5.4%)	5 (2.2%)	
Trunk	55 (36.9%)	60 (26.2%)	0.027
Upper extremity	25 (16.8%)	43 (18.8%)	
Lower extremity	47 (31.5%)	104 (45.4%)	0.007
Acral	14 (9.4%)	17 (7.4%)	

Table 7. Analysis of streaks by anatomic site of lesion

	Presence of streaks		
	Yes (n=203) N, (%)	**No (n=175)** N, (%)	*P* value
Anatomic site			
Head & neck	6 (3.0%)	7 (4.0%)	
Anterior trunk	28 (13.8%)	8 (4.6%)	0.002
Posterior trunk	33 (16.3%)	46 (26.3%)	0.017
Upper extremity	32 (15.8%)	36 (20.6%)	
Lower extremity	81 (39.9%)	70 (40.0%)	
Acral	23 (11.3%)	8 (4.6%)	0.017

Table 8. Comparison of dermoscopic features between the anterior trunk and the posterior trunk

	Anatomic site		
	Anterior trunk (n=36) N, (%)	**Posterior trunk (n=79)** N, (%)	*P* value
Presence of streaks			
Yes	28 (77.8%)	33 (41.8%)	<0.001
No	8 (22.2%)	46 (58.2%)	
Presence of starburst pattern			
Yes	17 (47.2%)	21 (26.6%)	0.029
No	19 (52.8%)	58 (73.4%)	
Presence of reticular pattern			
Yes	5 (13.9%)	2 (2.5%)	0.030
No	31 (86.1%)	77 (97.5%)	

Table 9. Starbust pattern comparison between the anterior trunk and other anatomic sites

	Presence of the starburst pattern		
	Yes	**No**	
	N, (%)	N, (%)	*P* value*
Anatomic site			
Head & neck (n=13)	2 (15.4%)	11 (84.6%)	0.043
Anterior trunk (n=36)	17 (47.2%)	19 (52.8%)	
Posterior trunk (n=79)	21 (26.6%)	58 (73.4%)	0.029
Upper extremity (n=68)	16 (23.5%)	52 (76.5%)	0.014
Lower extremity (n=151)	43 (28.5%)	108 (71.5%)	0.030
Acral (n=31)	12 (38.7%)	19 (61.3%)	0.483

*In respect of the anterior trunk

Table 10. Comparison of dermoscopic features between distal and proximal sites in terms of melanoblast migration; Anterior trunk + acral site vs Head & neck + posterior trunk

	Anatomic site		
	Distal	**Proximal**	
	Anterior trunk + acral (n=67)	**Head & neck + posterior trunk (n=92)**	
	N, (%)	N, (%)	*P* value
Presence of Streaks			
Yes	51 (76.1%)	39 (42.4%)	<0.001
No	16 (23.9%)	53 (57.6%)	
Presence of Starburst Pattern			
Yes	29 (43.3%)	23 (25.0%)	0.015
No	38 (56.7%)	69 (75.0%)	
Presence of Reticular pattern			
Yes	11 (16.4%)	5 (5.4%)	0.023
No	56 (83.6%)	87 (94.6%)	

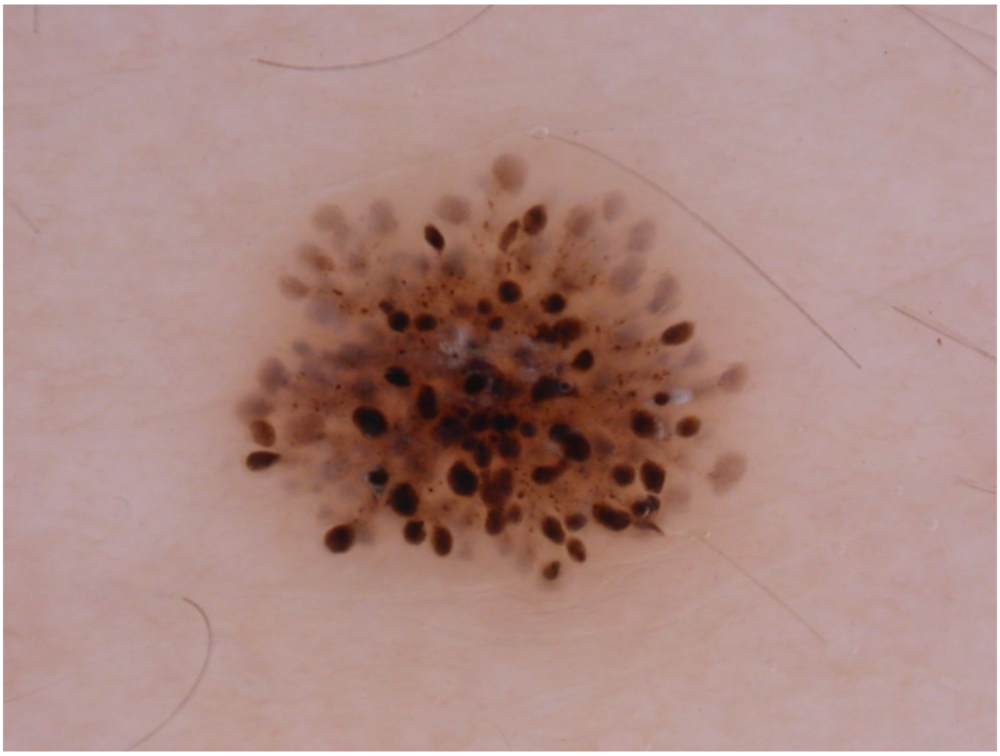

Figure 1. Spitz nevus exhibiting the globular pattern.

Figure 2. Spitz nevus exhibiting the starburst pattern.

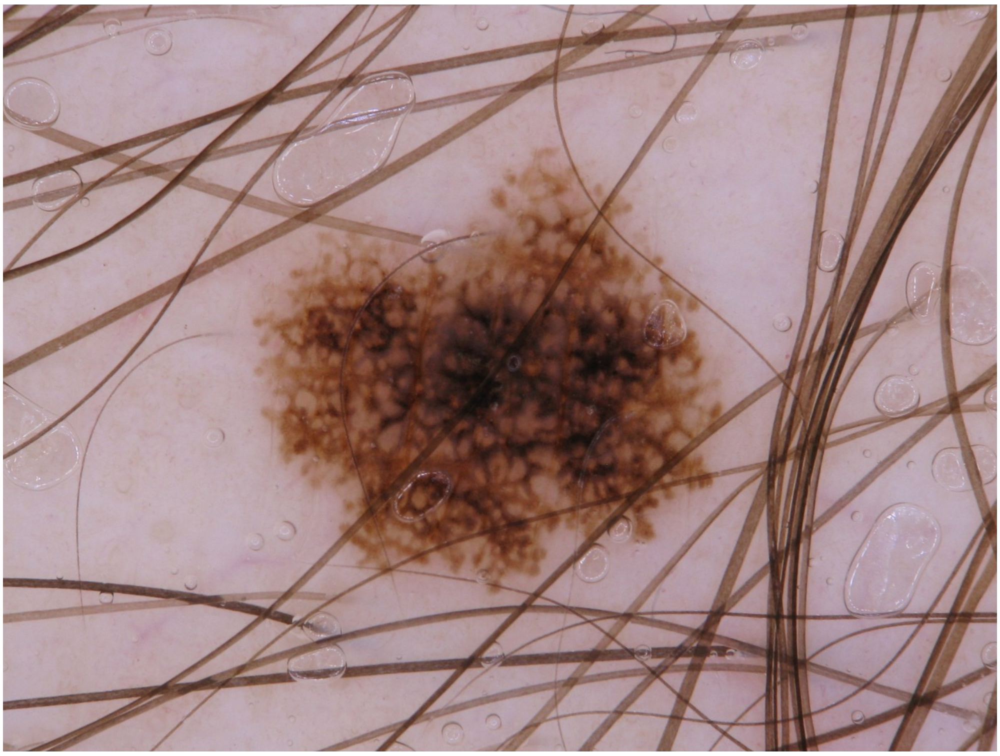

Figure 3. Spitz nevus exhibiting the reticular pattern.

Figure 4. Spitz nevus exhibiting the homogeneous pattern.

Figure 5. Spitz nevus exhibiting the dotted vessel pattern.

Figure 6. Spitz nevus exhibiting the inverse network pattern.

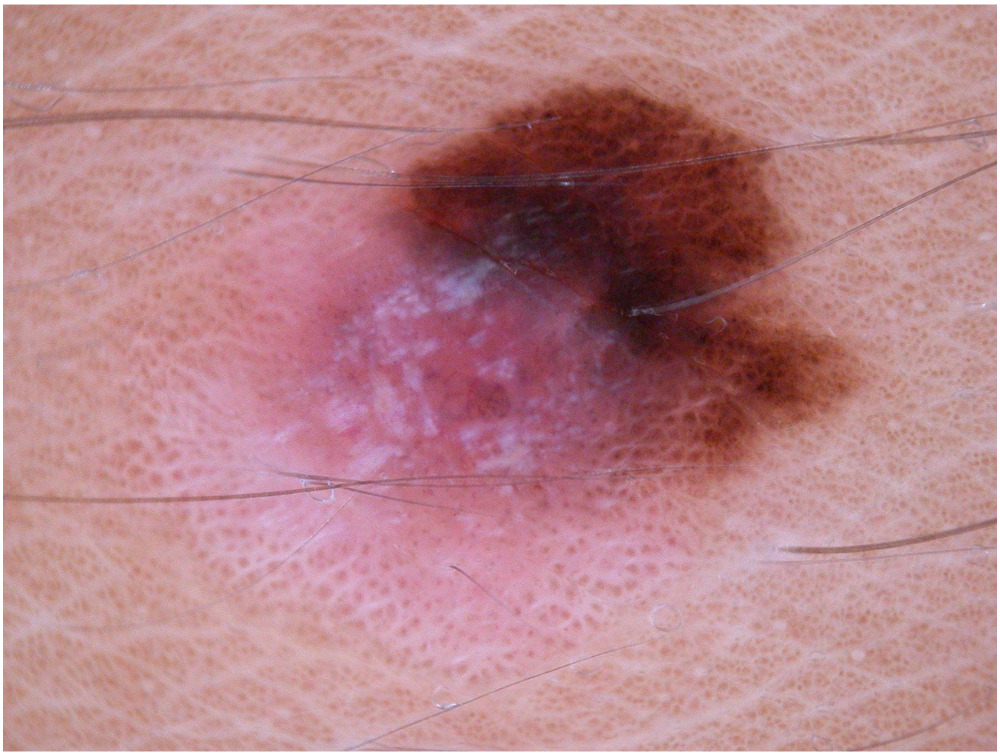

Figure 7. Spitz nevus exhibiting the multicomponent pattern.

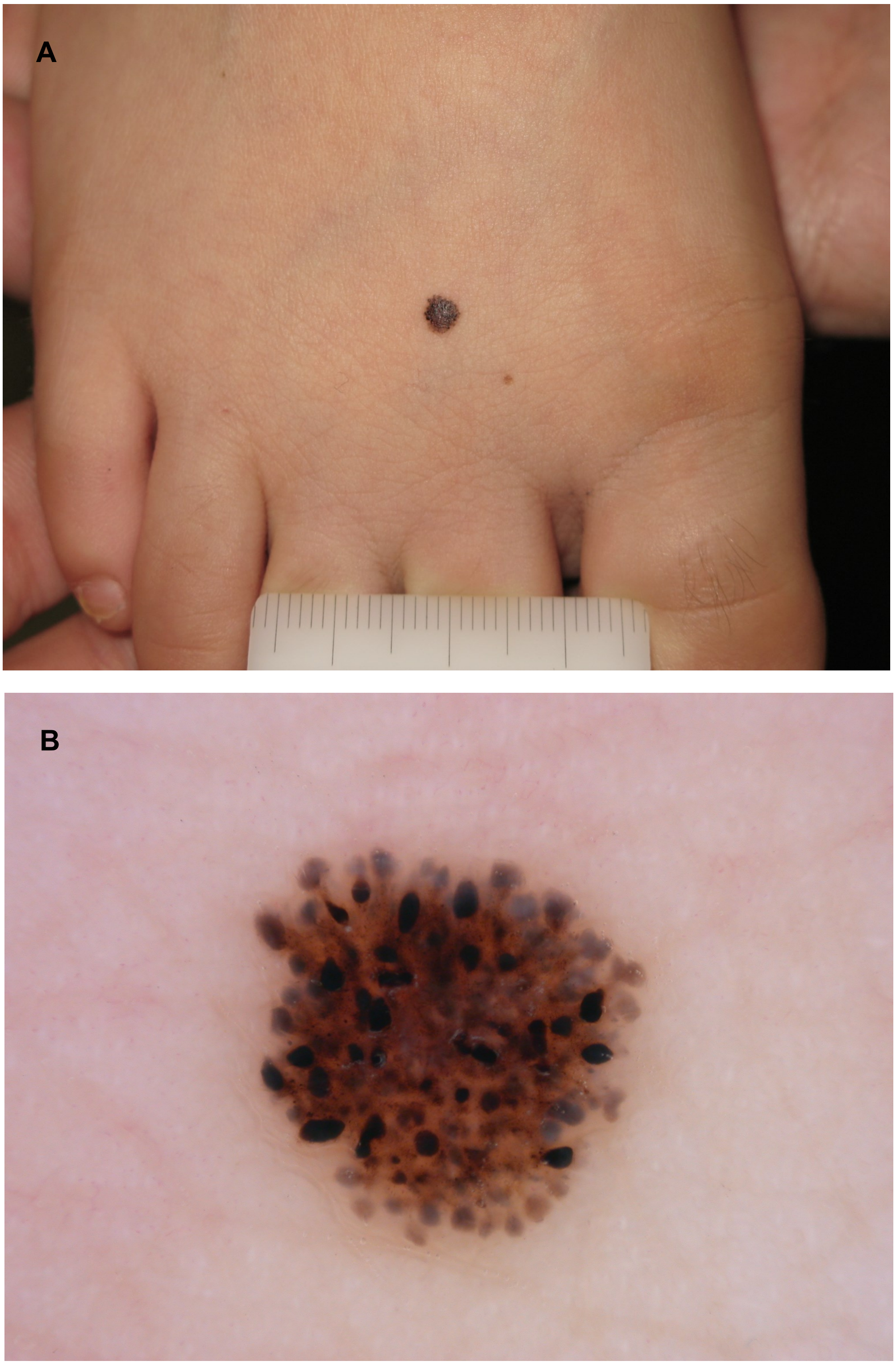

Figure 8. Spitz nevus on the dorsum of the foot of a 6 year old male.
A. Clinically, the lesion is slightly elevated and pigmented.
B. Dermoscopically, the lesion exhibits the globular pattern.

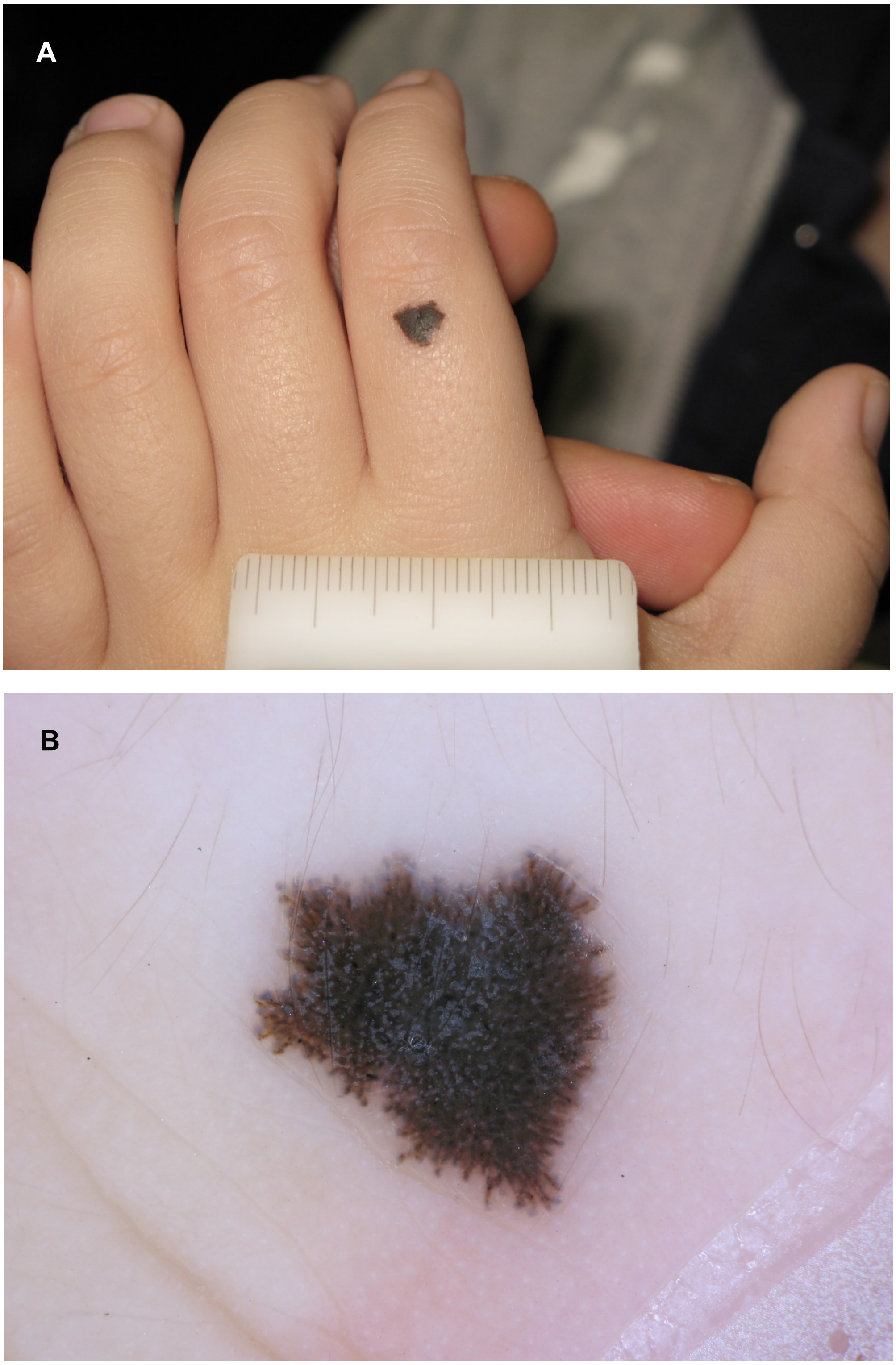

Figure 9. Spitz nevus on the dorsum of the finger of a 3 year old male.
A. Clinically, the lesion is elevated and pigmented.
B. Dermoscopically, the lesion exhibits the starburst pattern with streaks at the periphery .

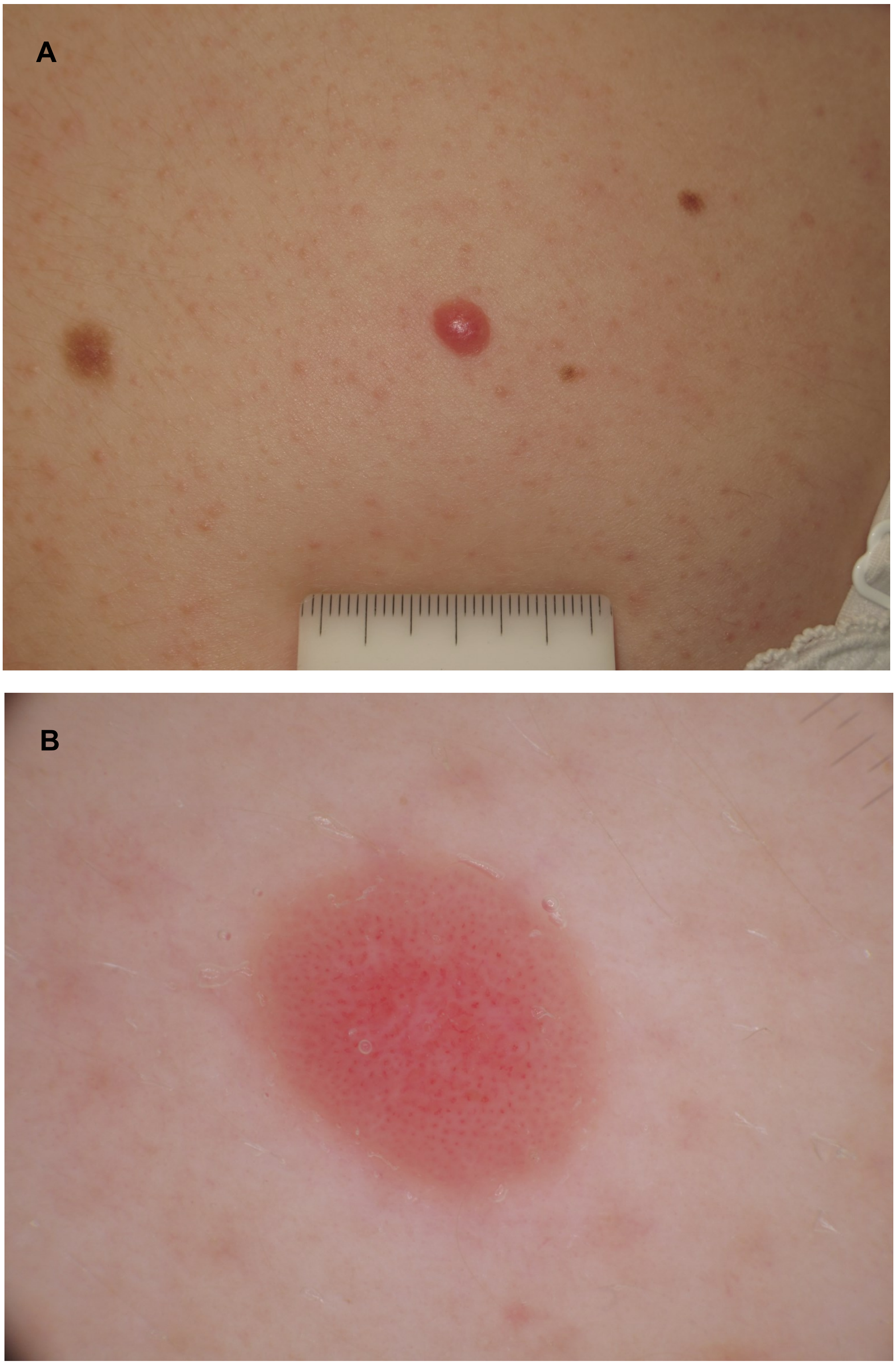

Figure 10. Spitz nevus on the posterior trunk of a 10 year old female.
A. Clinically, the lesion is a hypopigmented pink nodule.
B. Dermoscopically, the lesion exhibits the dotted vessel pattern.

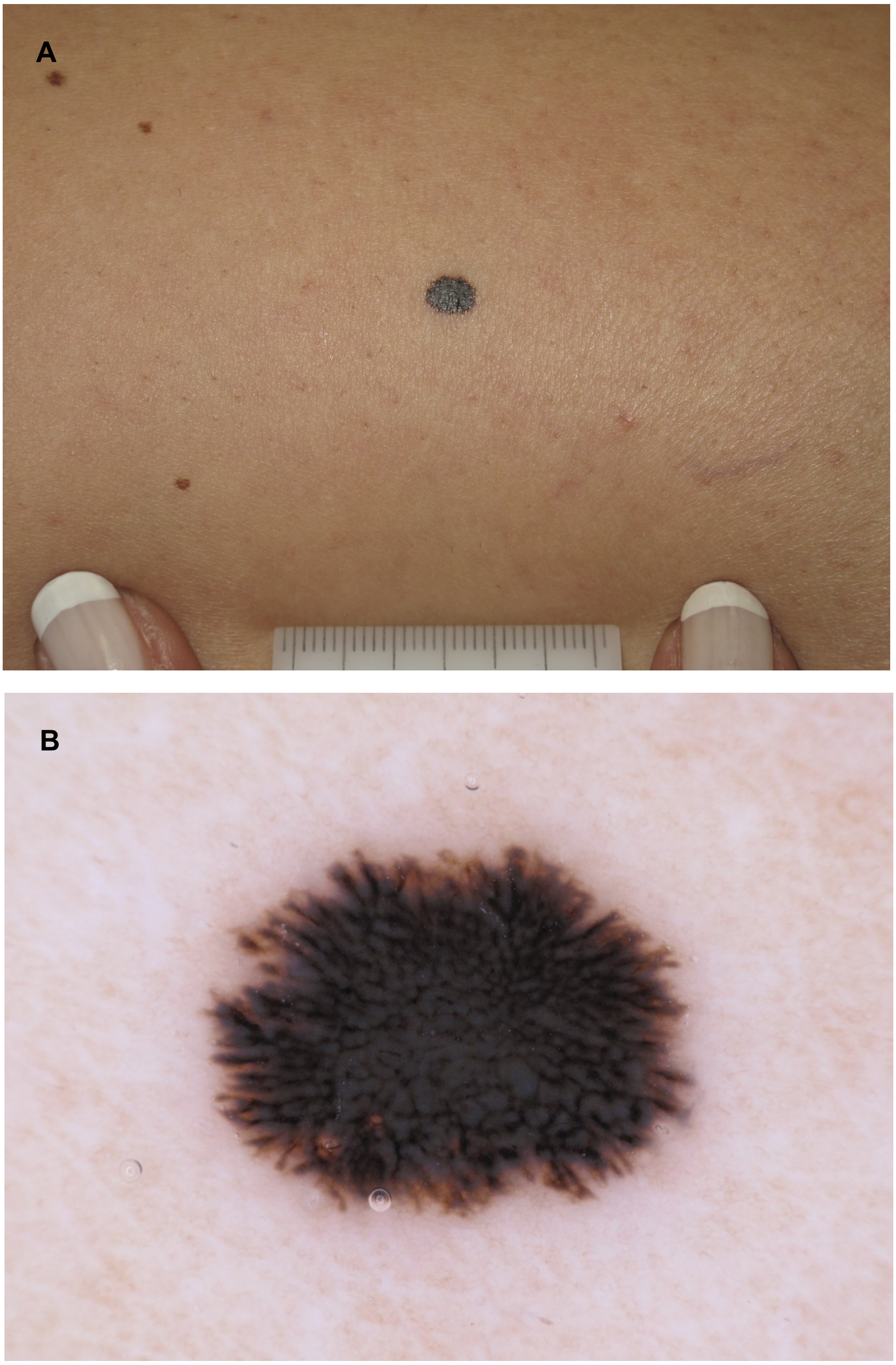

Figure 11. Spitz nevus on the lower extremity of a 28 year old female.
A. Clinically, the lesion is flat and pigmented.
B. Dermoscopically, the starburst pattern with superficial black network is observed.

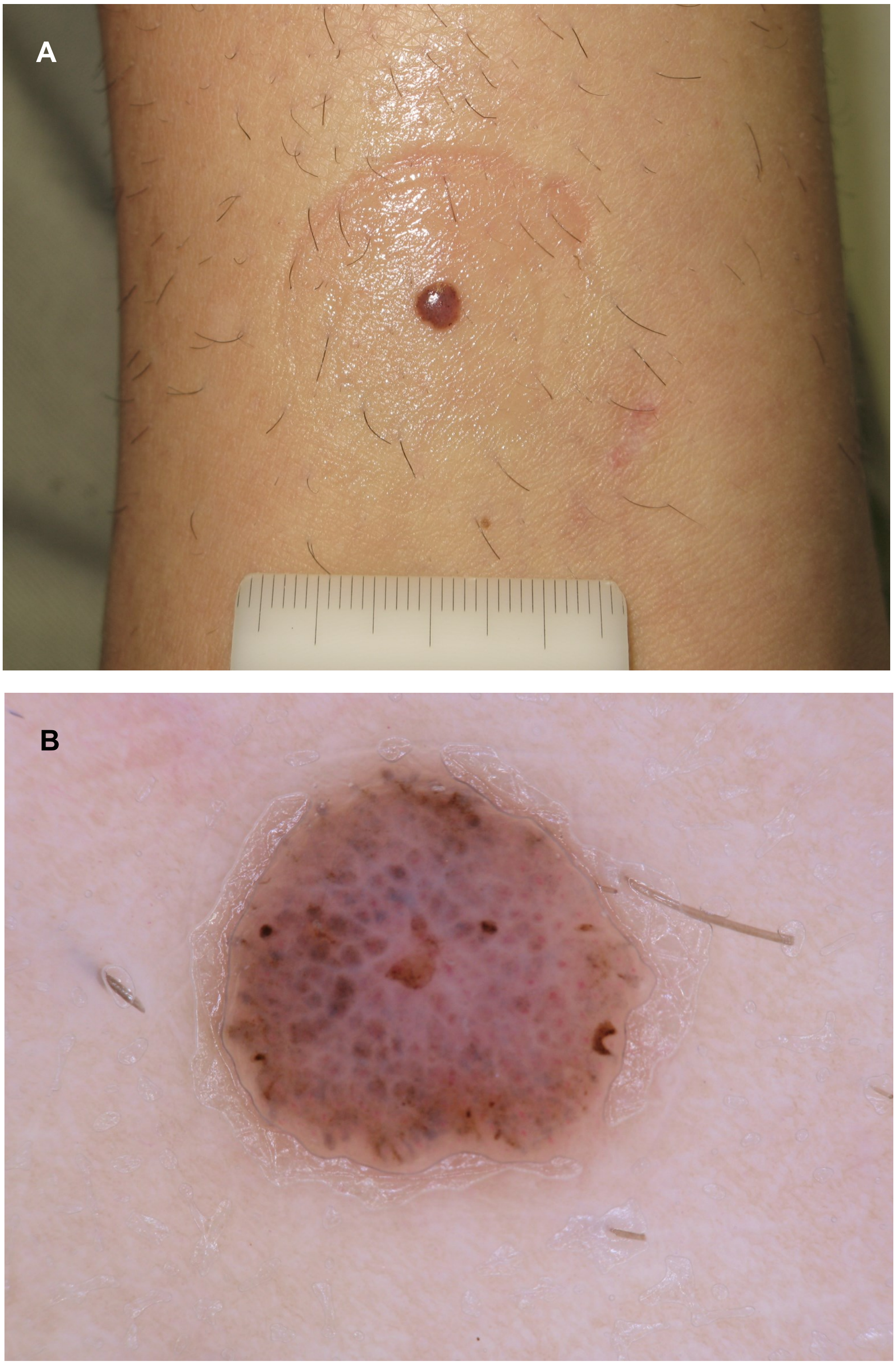

Figure 12. Spitz nevus on the lower extremity of a 17 year old male.

A. Clinically, the lesion is a pinkish brown papule.

B. Dermoscopically, ulceration is seen at the center of the lesion. White lines are also observed. This lesion falls into the nonspecific pattern due to the ulceration.

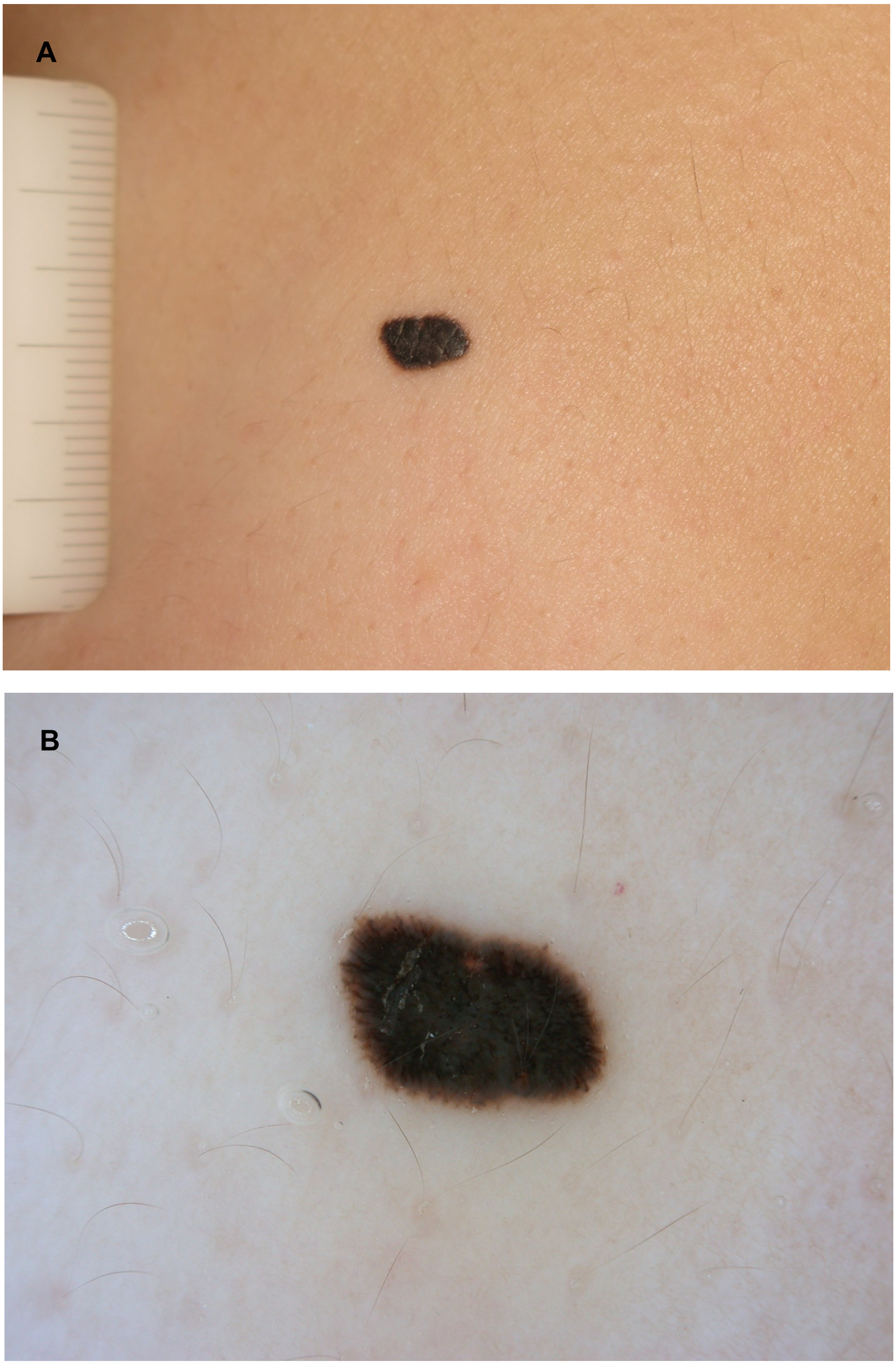

Figure 13. Spitz nevus on the anterior trunk of a 28 year old female.
A. Clinically, the lesion is slightly elevated and heavily pigmented.
B. Dermoscopically, the lesion exhibits the starburst pattern with streaks at the periphery.

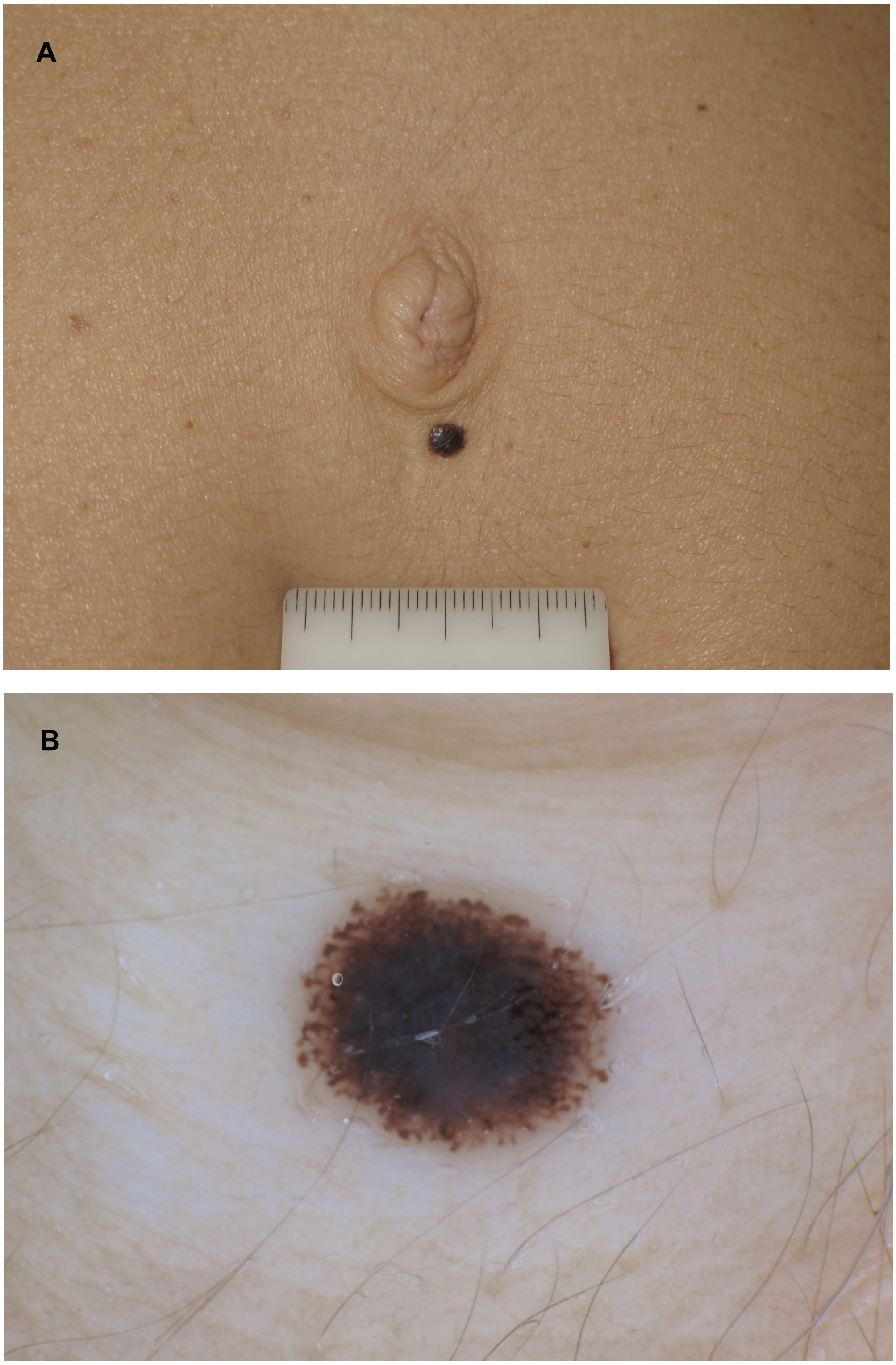

Figure 14. Spitz nevus on the anterior trunk of a 39 year old female.
A. Clinically, the lesion is a pigmented papule.
B. Dermoscopically, the lesion exhibits the starburst pattern with pseudopods.

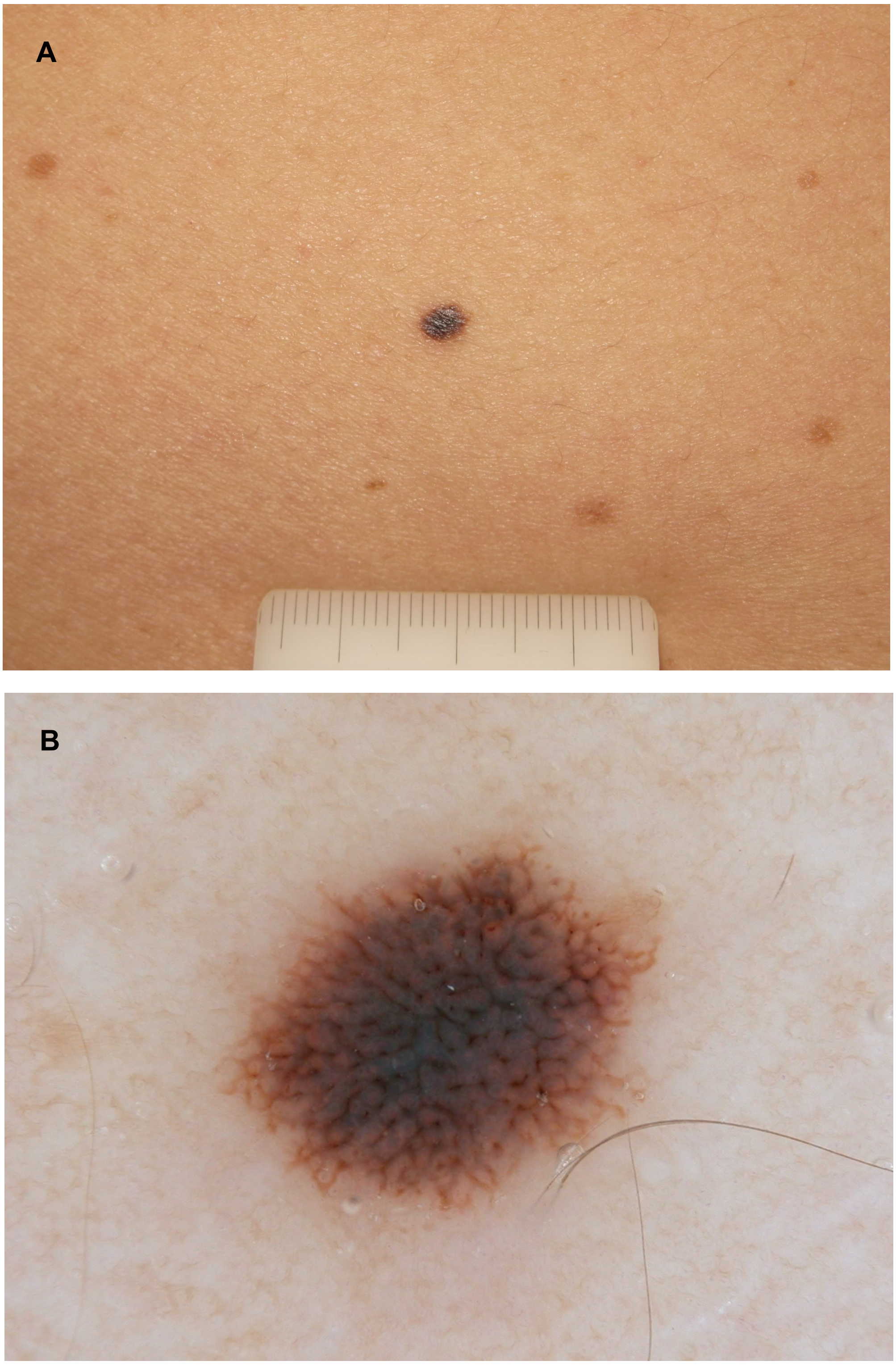

Figure 15. Spitz nevus on the anterior trunk of a 49 year old male.
A. Clinically, the lesion is a pigmented macule.
B. Dermoscopically, the lesion displays the reticular pattern with bluish gray background.

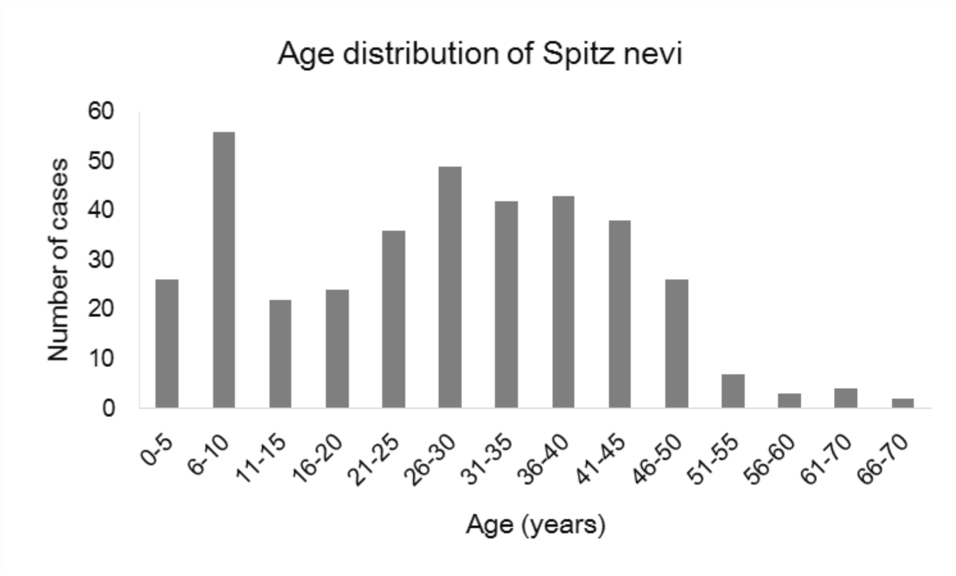

Figure 16. Distribution of Spitz nevi according to age.

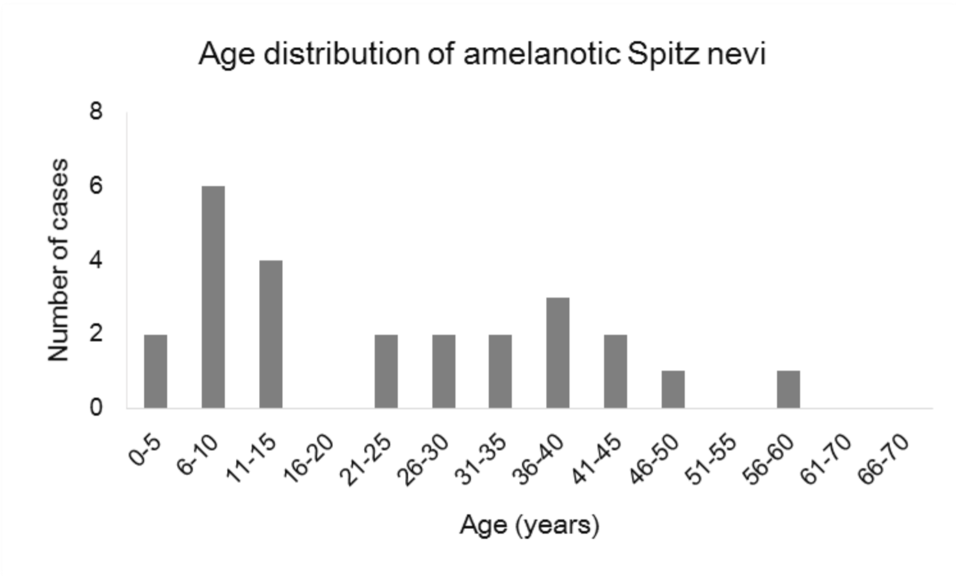

Figure 17. Distribution of amelanotic Spitz nevi according to age.

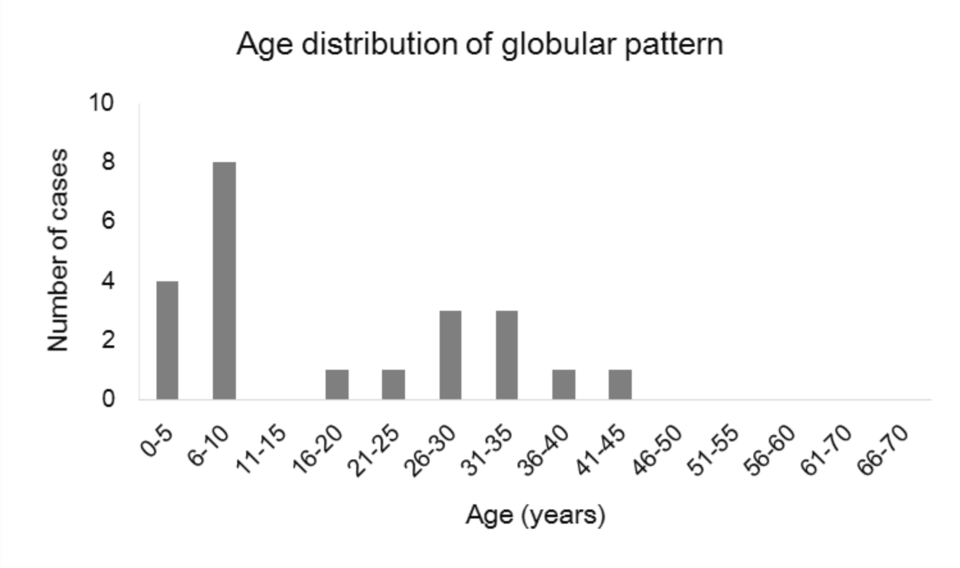

Figure 18. Distribution of globular pattern Spitz nevi according to age.

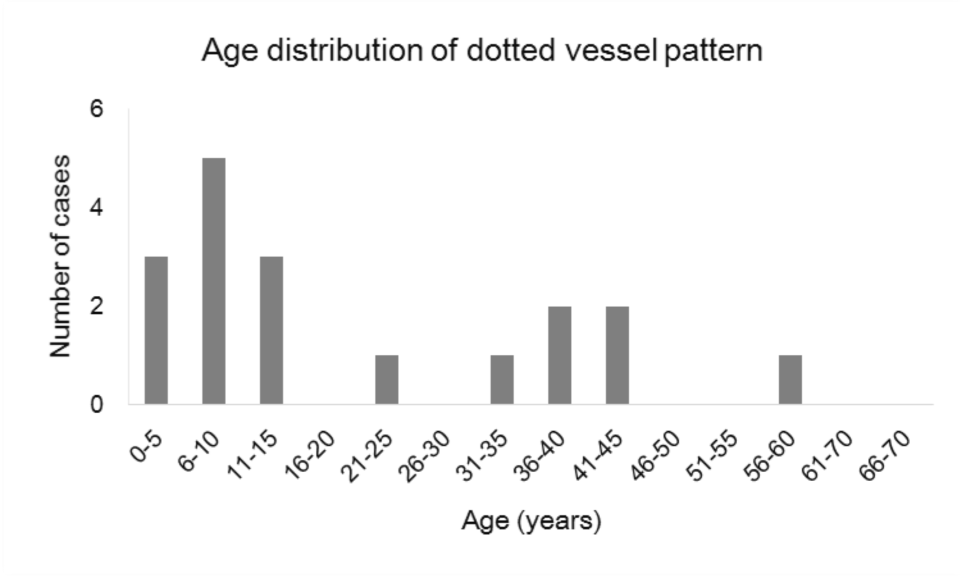

Figure 19. Distribution of dotted vessel pattern Spitz nevi according to age.