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Clinical and dermoscopic features of Atypical Spitz Tumors: a multi-center, retrospective, case-control study

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Abstract

Background—Few studies have described the clinical and dermoscopic features of atypical Spitz tumors (AST).

Objective—To describe the clinical and dermoscopic features of a series of AST as compared to those of conventional Spitz nevi (SN).

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Methods—Multicenter, retrospective, case-control study, analyzing the clinical and dermoscopic characteristics of 55 AST and 110 SN that were excised and diagnosed histopathologically.

Results—The majority of AST presented clinically as a plaque or nodule, dermoscopically typified by a multicomponent or nonspecific pattern. A proportion of lesions (16.4%) exhibited the typical non pigmented spitzoid pattern of dotted vessels and white lines under dermoscopy.

Nodularity, ulceration, linear vessels, polymorphic vessels, white lines, and blue/white veil were associated with AST by univariate analysis, but only nodularity and white lines remained significant after multivariate analysis. In contrast, a pigmented typical spitzoid pattern was a potent predictor of SN, associated with 6.5-fold increased probability.

Limitations—Differentiation from spitzoid melanoma and other non melanocytic lesions was not investigated.

Conclusion—Atypical Spitz tumors are polymorphic melanocytic proliferations with a nodular clinical appearance. Dermoscopically they demonstrate a multicomponent and nonspecific pattern. A typical non pigmented spitzoid pattern on dermoscopy (with dotted vessels and white lines) does not exclude AST.

Introduction

Atypical Spitz tumors (AST) are defined as melanocytic proliferations with intermediate histopathologic features between Spitz nevi (SN) and spitzoid melanoma, carrying uncertain malignant potential.¹⁻⁹ The exact clinico-pathologic definition of AST is a matter of ongoing debate among dermatopathologists. Currently, some opinion leaders assert that only two diagnostic categories can be ascribed to spitzoid lesions, namely, SN and spitzoid melanoma.⁵ Others suggest that spitzoid lesions are a 'morpho-biologic spectrum' ranging from benign to clear-cut malignant lesions, with AST placed in the middle of this spectrum.⁶ Since the first description, by Smith and co-worker in 1989,² several studies have investigated the histopathologic features of AST. There remains a lack of consensus, with diagnostic agreement among dermatopathologists consistently lower than for non-spitzoid melanocytic neoplasms.⁴ AST is a diagnostic definition increasingly used by pathologists, presenting the clinician with difficult patient management decisions.¹⁰⁻¹² Despite numerous histopathologic studies, few have described the clinical and dermoscopic features of AST.^{8,10,12,13}

We compared clinical and dermoscopic images of a series of AST with those of a control group of conventional SN in order to identify diagnostic features that might be used in the differential diagnosis between these two entities.

Material and Methods

We conducted a multicenter, case-control study analyzing clinical and dermoscopic characteristics of 55 AST and 110 SN that were excised and diagnosed histopathologically. Clinical and dermoscopic images of AST were collected from the databases of 7 pigmented lesions clinics in Italy (Reggio Emilia, Naples, Modena, Turin, Milan) and Spain (Barcelona, Tarragona). The inclusion criterion was the availability of a clinical and

dermoscopic image of a histopathologically diagnosed AST. A control group of 110 consecutively selected SN was obtained from the database of the Skin Cancer Unit, ASMN-IRCCS, Reggio Emilia. The study period was 2003–2014. All lesions were examined by dermatopathologists specialized in the diagnosis of melanocytic skin tumors. Clinical images were acquired using a high resolution digital camera. Dermoscopic images were captured using polarized or non polarized dermoscopes (DermLite Foto, 3Gen LLC, Dana Point, CA).

Clinical information included the age and sex of each patient, and location of the tumor. For the AST group, additional information included sentinel lymph node biopsy (SLNB) status, performance of wide excision (with at least 1 cm clear margins) after initial biopsy, years of follow up, and outcome.

Clinical and dermoscopic images were evaluated in agreement by two observers (EM and GA) blinded with respect to the histopathologic diagnosis. When no agreement was achieved, a third evaluator (AL) was involved. Clinical evaluation included the assessment of palpability (macule, papule, plaque, nodule). The presence of ulceration and pigmentation were evaluated on dermoscopic images. Ulceration was scored as present or absent. Each lesion was defined as amelanotic (absence of pigmentation), hypomelanotic (pigmentation involving less than 50% of the lesion), or pigmented (pigmentation involving more than 50% of the lesion).¹⁴

Concerning dermoscopic characteristics, each lesion was assigned to a global pattern according to the following definitions: 1) Multicomponent pattern: combination of at least 2 different predominant features within a given lesion; 2) Typical pigmented spitzoid pattern: a pigmented lesion with regular starburst appearance (composed of streaks or large globules symmetrically distributed at the periphery); 3) Typical non-pigmented spitzoid pattern: a hypopigmented/amelanotic lesion with dotted vessels and/or reticular depigmentation;¹⁵ 4) Globular pattern: brown globules involving most of the lesion; 5) Reticular pattern: pigment network occupying most of the lesion; 6) Homogeneous pattern: homogeneous pigmentation involving most of the lesion; 7) Nonspecific pattern: global pattern not ascribable to any of the above categories.

The presence of local dermoscopic features was also assessed, according to the definitions summarized in table 1. Lesions were scored for the presence of network, streaks, globules, regression, blue white veil, vascularity, homogeneous pigmentation, regression structures, and white lines.¹⁶ The latter feature included both inverse network and crystalline structures defined as shiny white parallel, orthogonal or disordered linear streaks or short lines that are only seen with polarized light dermoscopy.^{17–20} Because our study sample was composed of images taken either with polarized or with non polarized light dermatoscopes, we decided to consider inverse network and crystalline structures as one parameter called white lines (Table 1).

The definite histopathologic diagnosis of AST or Spitz nevus was used as the main outcome. Demographic, clinical and dermoscopic variables were included in the analysis. Colinearity was assessed via a correlation matrix, using Spearman's Rho correlation coefficient.

Variables that were statistically significantly correlated were included in the logistic regression analyses. Student's t test and Non parametric Man-Whitney U-test were used to compare means, after normality explorations. Pearson's Chi Square was used for non-parametric cross tabulation comparisons. Relative risks were calculated for dichotomous variables. Crude and adjusted odds ratios and corresponding 95 percent confidence intervals (95% CI) were calculated by univariate and conditional multivariate logistic regression, respectively. The Type I error probability associated with all tests in this study was set to 0.05. An alpha less than 0.10 is considered to signify a trend. All statistical calculations were made with the SPSS 17.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, Ill.).

Results

In all, 165 patients (65 males and 100 females) were included. Mean age was 28.4 ± 13.5 for females and 26.4 ± 31.9 years for males. Mean age was 20.8 ± 313.8 in the AST group, and 31.0 ± 312.3 in the SN group (Student's t-test, $p < 0.0001$).

Frequencies of the observed clinical and dermoscopic variables are reported in Tables 2 and 3. The majority of AST presented as nodular lesions (32/55, 58.2%), whereas SN were more frequently macules (47/110, 42.7%) or plaques (42/110, 38.2%). Approximately half of AST were pigmented (29/55, 52.7%) and half were hypo- or non-pigmented (26/55, 47.3%). The majority of SN were pigmented (78/110, 70.9%) (Table 2).

The most frequent global dermoscopic pattern in AST was the multicomponent pattern, seen in 24/55 AST (43.6%), followed by nonspecific (11/55, 20.0%) and non-pigmented typical spitzoid (9/55, 16.4%), while a typical pigmented spitzoid pattern was found only in 2/55 AST (3.6%) (Table 3). In contrast, the typical pigmented spitzoid pattern was the most frequent global dermoscopic pattern of SN (40/110, 36.3%), followed by multicomponent (29/110, 26.4%) and non-pigmented typical spitzoid patterns (18/110, 16.4%).

According to the univariate logistic regression analysis, the most potent clinical predictors of AST were the nodular surface and the presence of ulceration, posing a 15-fold and 11-fold probability of AST, respectively. In contrast, the presence of pigmentation was associated with a 2.5-fold reduced probability of AST. The univariate analysis revealed several dermoscopic predictors of AST and SN. Specifically, the presence of linear or polymorphic vessels, blue white veil and white lines were independent predictors of AST, whereas the pigmented typical spitzoid pattern and the presence of regular streaks were suggestive of SN (table 4).

After employing the multivariate conditional logistic regression model, which adjusted for all variables included in the model, nodularity and white lines remained significant predictors of AST, posing a 10-fold and 11-fold probability, respectively. In contrast, the presence of a pigmented typical spitzoid pattern was a potent predictor of SN, associated with 6.5-fold increased probability in the same multivariate model (table 5).

Discussion

Our study provides novel insights into the clinical and dermoscopic morphology of AST, as compared to SN. According to our findings, AST develop either as pigmented nodular lesions with multicomponent or unspecific pattern dermoscopically, or as non-pigmented nodular lesions with a typical spitzoid pattern on dermoscopy. In contrast, detection of a pigmented typical spitzoid pattern (the so-called starburst pattern) is highly suggestive of SN.

Our observations might be valuable for improving the clinical recognition of AST and avoid its misinterpretation as SN. This is clinically relevant, since the management of these 2 entities differs significantly. AST are controversial tumors, because of their clinical and histopathologic morphologic overlap with spitzoid melanoma³⁻⁵. Accordingly, optimal management is wide local excision.

In contrast, SN is a benign tumor, similar to other benign melanocytic nevi. It is typified on dermoscopy by the so-called “starburst pattern”, consisting of symmetrically distributed peripheral streaks or pseudopods. A non-pigmented SN typically displays regularly distributed dotted vessels, with or without white lines intercrossing the red dots (reticular depigmentation or inverse network)¹⁰.

Spitzoid melanoma can also display some of these features (peripheral streaks, dotted vessels or inverse network), but usually lacks the characteristic symmetry of SN. Accordingly, lesions not overall characterized by one of the 2 typical spitzoid patterns should be excised, even in the presence of local spitzoid features.

Our results demonstrate that the majority of AST do not display a typical spitzoid, but a multicomponent or unspecific pattern. Consequently, the use of dermoscopy might prompt clinicians to excise these tumors, facilitating their appropriate management.

Diagnostic difficulty with spitzoid tumors is not only associated with dermoscopically asymmetric lesions, but also with those displaying a perfectly symmetric typical spitzoid pattern. Although the vast majority of these are SN, some will turn out to be melanomas and, others AST. In our study, 16.4% of AST were dermoscopically characterized by a typical non-pigmented spitzoid pattern, namely dotted vessels and white lines. In contrast, the pigmented typical spitzoid (starburst) pattern was a potent predictor of SN. This information, added to the previously existing knowledge on the morphologic diversity of spitzoid lesions, might further enhance their optimal management.

To overcome the problem of accurately interpreting a spitzoid-looking lesion, some clinicians are prone to remove all of them, while others follow a more conservative approach, especially in children.²¹⁻²⁴ As shown by a recent study, the possibility of a perfectly symmetric spitzoid-looking lesion to be a melanoma significantly increases with age, being exceedingly low until the age of 20 years and rising to 50% after the age of 50 years²⁵. Conservative management of Spitz nevi in children is increasing, as highlighted by a survey recently published.²⁶ In this study, respondents included 175 pediatric dermatologists from the United States and around the world, with about 80% utilizing

dermoscopy. In children with a clinical diagnosis of Spitz nevus, the option of clinical follow-up was chosen by 49.3% of respondents in the context of small, stable, non-pigmented lesions and by 29.7% in the context of pigmented lesions with a typical starburst pattern on dermoscopy.²⁶ Thus, pigmented lesions, even if exhibiting a typical starburst pattern, seemed to be of most concern to the majority of respondents.

Our results highlight that the presence of a starburst pattern on dermoscopy almost invariably corresponds to SN. Monitoring such a lesion seems a safe management strategy. In contrast, surgical excision might represent the optimal choice for hypopigmented and amelanotic nodules dermoscopically displaying dotted vessels and white lines, since these findings characterize almost 20% of AST.

One limitation of our study is that we included only melanocytic lesions (SN and AST) in the analysis. We did not investigate either the differential diagnosis with spitzoid melanoma, or non melanocytic lesions, such as angioma and pyogenic granuloma, which can simulate AST both clinically and dermoscopically.^{8,10,12,27,28} Further studies are needed to evaluate this differential diagnosis. An additional limitation can be identified in the selection of the study sample, with multicenter collection of AST, whereas SN were selected in a single center. This was due to the relative rarity of AST compared to SN.

In conclusion, AST are polymorphic melanocytic tumors typically appearing as nodular lesions and dermoscopically typified by a multicomponent or unspecific pattern. Amelanotic and hypomelanotic nodules with a typical spitzoid pattern under dermoscopy cannot be safely classified as SN. Elucidation of the clinical and dermoscopic features of histopathologically equivocal spitzoid lesions may help the clinician select lesions that merit excision irrespective of patient age.

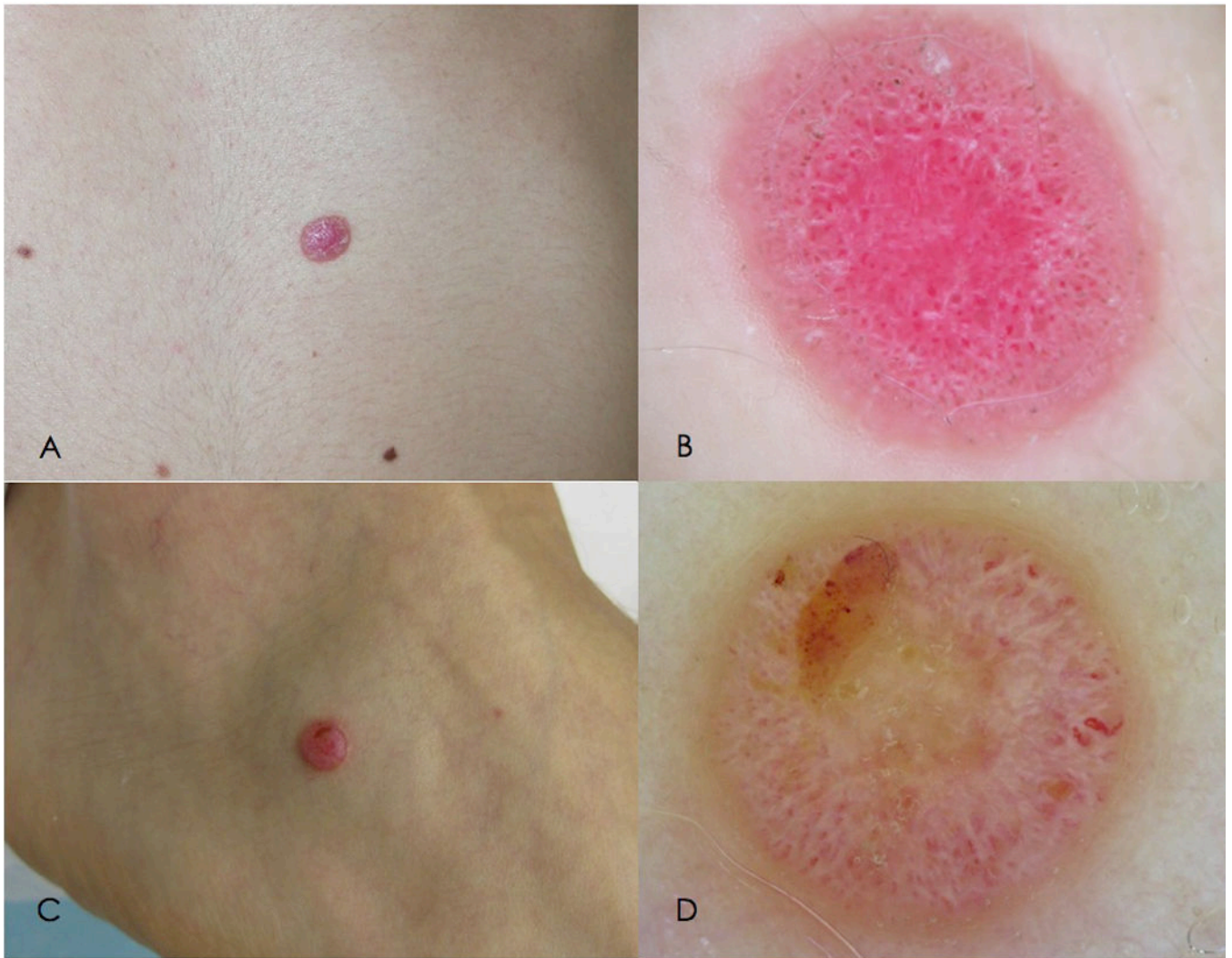
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**Figure 1.**

Clinical and dermoscopic features of amelanotic AST (atypical Spitz tumor). A. Clinical image of an amelanotic nodular lesion, arising on the abdomen of a 25 year-old woman. B. On dermoscopy, dotted vessels and white lines are visible over a pinkish background. C. Clinical image of an amelanotic nodule arising on the extremity of a 19 year-old boy. D. On dermoscopy, the lesion shows a nonspecific pattern, with polymorphic vessels, ulceration and white lines.

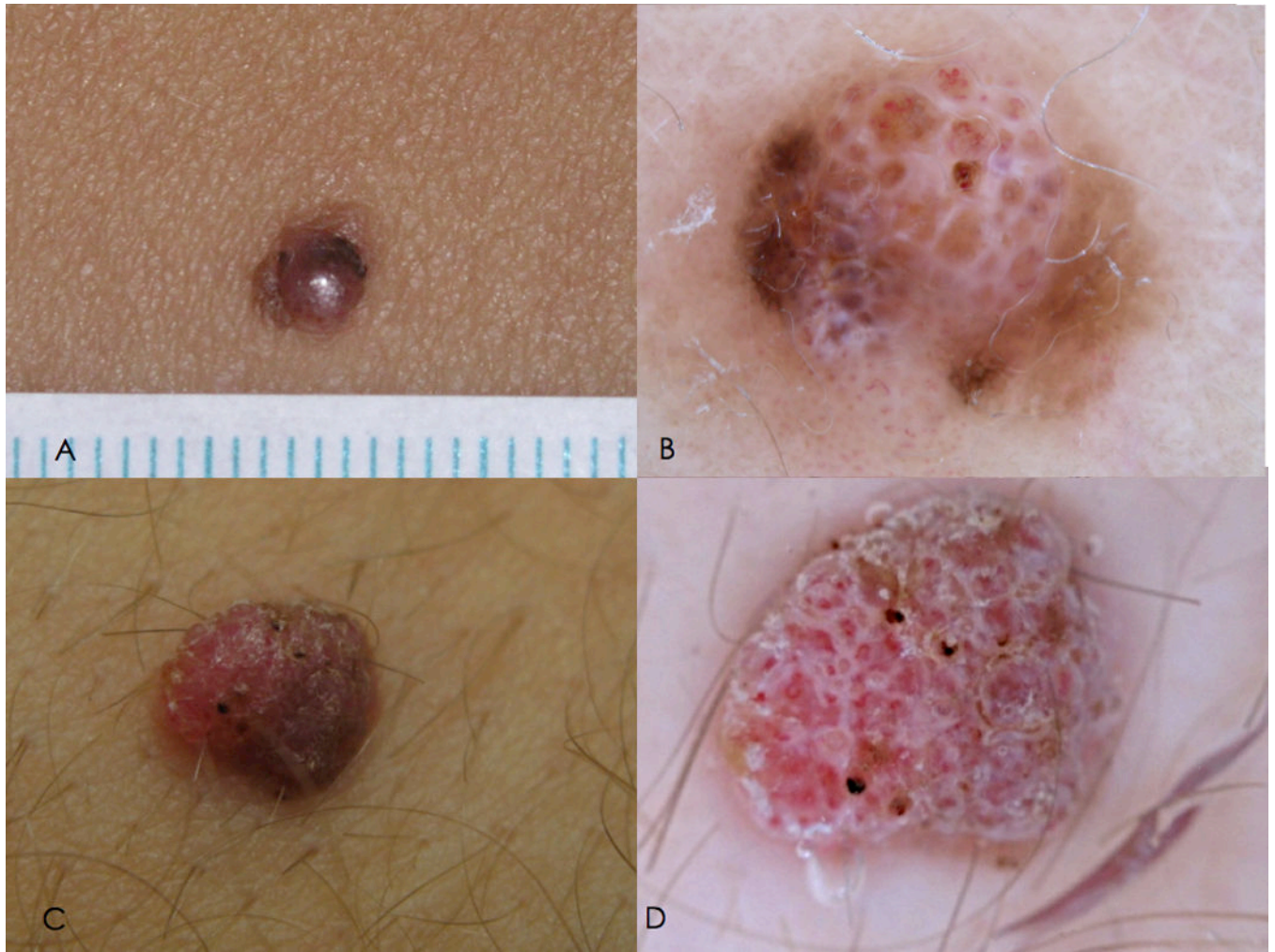


Figure 2. Clinical and dermoscopic features of hypomelanotic AST (atypical Spitz tumor). A. Clinical appearance of a hypomelanotic nodule arising on the lower limb of a 34 year-old woman. B. On dermoscopy the lesion exhibits a multicomponent pattern, with homogeneous brown pigmentation, white lines and polymorphic vessels. C. Clinical appearance of a hypopigmented nodule arising on the leg of a 22 year-old boy. D. On dermoscopy, nonspecific pattern is detected, with polymorphic vessels, brownish pigmentation, and ulceration.

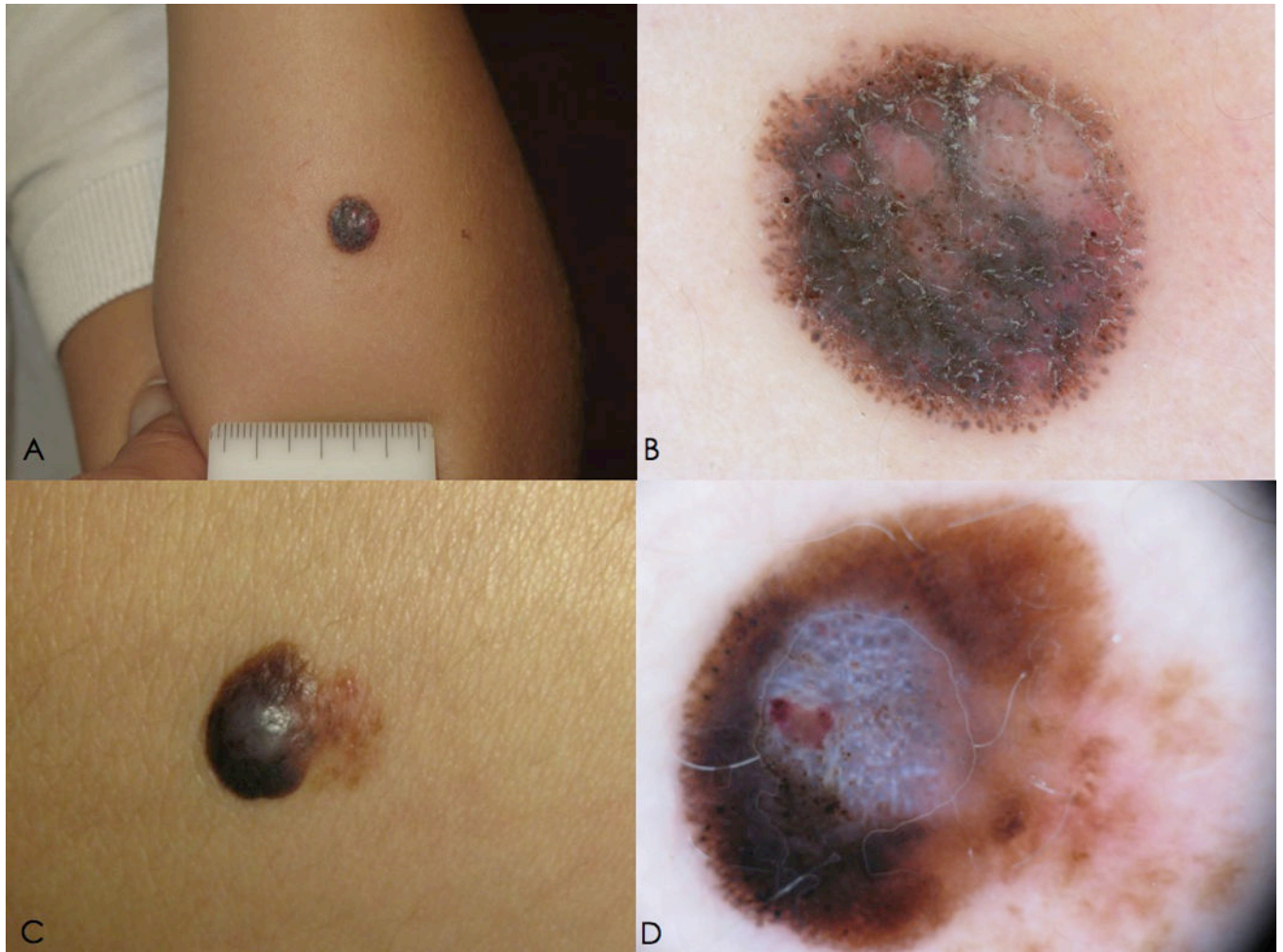


Figure 3. Clinical and dermoscopic features of pigmented AST (atypical Spitz tumor). A. Clinical image of a nodule arising on the forearm of a 3 year-old girl. B. On dermoscopy, a multicomponent pattern is detected, with irregular globules, and irregular homogeneous brown and pink pigmentation. C. Clinical appearance of a pigmented nodule arising on the lower limb of a 15 year-old girl. D. On dermoscopy, a multicomponent pattern is visible, with irregular streaks, homogeneous brown pigmentation, blue-white veil and crystalline structures.

Table 1

Definition of the observed dermoscopic features.

Dermoscopic feature	Definition
Vessels type	Identification of a vascular component and classification into one of the following morphologic categories: linear, comma, hairpin, polymorphic, dotted, coiled, and arborizing.
Vessels distribution	Central, peripheral, diffuse, irregular.
Streaks	Brownish-black linear structures of variable thickness, not clearly combined with pigment 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.
Brown globules	Regular: sharply circumscribed, usually round to oval, black to brown structures. Irregular: variously sized and colored globules irregularly distributed within the lesion.
White lines	White crossing lines in between the vascular structures or the pigmented globules and/or white parallel or orthogonal and disordered linear streaks or short lines.
Network	Regular: light- to dark-brown pigmented, regularly meshed and narrowly spaced network distributed more or less regularly throughout the lesion. Irregular: 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	Grey-blue areas, white areas, peppering.

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Table 2

Frequency of the evaluated clinical features in AST (atypical Spitz tumors) and SN (Spitz nevi).

CLINICAL FEATURES		AST (%)	SN (%)	TOT (%)
SEX	M	26 (47.3)	39 (35.5)	65
	F	29 (52.7)	71 (64.5)	100
LOCATION	trunk	13 (23.6)	21 (19.9)	34 (20.6)
	abdomen	1 (1.8)	5 (4.5)	6 (3.6)
	lower limbs	22 (40.0)	52 (47.3)	74 (44.8)
	upper limbs	9 (16.4)	22 (20.0)	31 (18.8)
	acral	5 (9.1)	2 (1.8)	7 (4.2)
	head/neck	3 (5.5)	5 (4.5)	8 (4.8)
	buttocks	1 (1.8)	3 (2.7)	4 (2.4)
	genital	1 (1.8)	0	1 (0.6)
PALPABILITY	macule	9 (16.4)	47 (42.7)	56 (33.9)
	papule	3 (5.5)	10 (9.1)	13 (7.9)
	plaque	11 (20.0)	42 (38.2)	53 (32.1)
	nodule	32 (58.2)	11 (10.9)	43 (26.1)
PIGMENTATION	amelanotic	14 (25.5)	15 (13.6)	29 (17.6)
	hypomelanotic	12 (21.8)	17 (15.5)	29 (17.6)
	pigmented	29 (52.7)	78 (70.9)	107 (64.8)
ULCERATION	no	42 (76.4)	107 (97.3)	149 (90.3)
	Present	13 (23.6)	3 (2.7)	16 (9.7)

Table 3

Frequency of the observed dermoscopic features.

Dermoscopic features		AST (N=55) (%)	SN (N=110) (%)	TOT (N=165) (%)
GLOBAL PATTERN	multicomponent	24 (43.6)	29 (26.4)	53 (32.1)
	typical spitzoid	11 (20.0)	58 (52.7)	69 (41.8)
	unspecific	11 (20.0)	11 (10.0)	22 (13.3)
	reticular	3 (5.5)	8 (7.3)	11 (6.7)
	homogeneous	6 (10.9)	2 (1.8)	8 (4.8)
	globular	0	2 (1.8)	2 (1.2)
VESSELS	absent	21 (38.2)	73 (66.4)	94 (57.0)
	linear	5 (9.1)	2 (1.8)	7 (4.2)
	comma	0	1 (0.9)	1 (0.6)
	hairpin	0	0	0
	polymorphic	14 (25.5)	5 (4.5)	19 (11.5)
	dotted	13 (23.6)	24 (21.8)	37 (22.4)
	coiled	1 (1.8)	5 (4.5)	6 (3.6)
	arborizing	1 (1.8)	0	1 (0.6)
VESSEL DISTRIBUTION	central	7 (12.7)	6 (5.5)	13 (7.9)
	peripheral	7 (12.7)	5 (4.5)	12 (7.3)
	diffuse	10 (18.2)	20 (18.2)	30 (18.2)
	irregular	10 (18.2)	7 (6.4)	17 (10.3)
STREAKS	absent	45 (81.8)	60 (54.5)	105 (63.6)
	regular	2 (3.6)	34 (30.9)	36 (21.8)
	irregular	8 (14.5)	15 (13.6)	23 (13.9)
HOMOGENEOUS PIGMENTATION	absent	27 (49.1)	64 (58.2)	91 (55.2)
	regular	12 (21.8)	29 (26.4)	41 (24.8)
	irregular	16 (29.1)	17 (15.5)	33 (20.8)
SUPERFICIAL BLACK NETWORK	present	0	11 (10.0)	11 (6.7)
BROWN GLOBULES	absent	32 (58.2)	68 (61.8)	99 (60.0)
	regular	8 (14.5)	20 (18.2)	29 (17.5)
	irregular	15 (27.3)	22 (20.0)	37 (22.4)
INVERSE NETWORK*	present	15 (27.3)	31 (28.2)	46 (27.9)
CRYSTALLINE STRUCTURES*	present	20 (36.4)	7 (6.4)	27 (16.4)
NETWORK	absent	40 (72.7)	88 (80.0)	128 (77.6)
	typical	4 (7.3)	9 (8.2)	13 (7.9)
	atypical	11 (20.0)	13 (11.8)	24 (14.5)

Dermoscopic features		AST (N=55) (%)	SN (N=110) (%)	TOT (N=165) (%)
BLUE WHITE VEIL	present	13 (23.6)	13 (11.8)	26 (15.8)
REGRESSION	no	45 (81.8)	95 (86.4)	25 (15.2)
	present	10 (18.2)	15 (13.6)	

* The features "inverse network" and "crystalline structures" were considered together in the statistical analysis, as a unique parameter named "white lines". AST (atypical Spitz tumors) and SN (Spitz nevi).

Table 4

Univariate predictors of AST (Atypical Spitz Tumor) versus Spitz nevus (SN).

	Sig.	OR	95% C.I. for EXP(B)	
			Lower	Upper
Palpability nodule	0,000	15,192	5,651	40,838
Ulceration	0,000	11,040	2,993	40,716
Global pattern typicalspitzoid	0,001	0,229	0,099	0,532
Pigmentation pigmented	0,033	0,398	0,171	0,926
Vessels linear	0,013	8,690	1,572	48,056
Vessels polymorphic	0,000	9,733	3,142	30,149
Streaks regular	0,001	0,078	0,018	0,344
White lines	0,032	2,066	1,064	4,013
Bluewhiteveil	0,054	2,310	0,987	5,402

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Table 5

Multivariate Adjusted Predictors of AST (Atypical Spitz Tumor) versus Spitz Nevus. Odds Ratios (OR) mutually adjusted for all variables in the model.

	Sig.	OR	95% C.I. for EXP(B)	
			Lower	Upper
Palpability: nodule	0,000	9,395	3,063	28,820
Streaks regular	0,020	0,154	0,032	0,744

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