

Clinicopathologic and Dermoscopic Features of 20 Cases of Spark's Nevus, a Dermoscopic Simulator of Melanoma

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Abstract: Spark's nevus is a particular type of melanocytic nevus, with histology that shows features of both Spitz and Clark nevus. Detailed dermoscopic features in a series of Spark nevi have not been described yet. We performed a monocentric retrospective observational study on 20 lesions of Spark nevus excised from 19 patients (M:F = 10:9; mean age: 37,6 years), reviewed by 5 experts in dermoscopy and 2 dermatopathologists. A histologic review confirmed that Spark nevi were mostly symmetric (80%), well circumscribed (100%), mainly compound (65%) melanocytic lesions with either epithelioid (55%) or spitzoid (45%) cell morphology and bridging of the nests (100%). Spark nevi were more frequently found on the trunk (85%) in patients with a history of sunburns in childhood (84%), with skin phototype III (79%), and with high nevus count (>100 nevi, 7 patients (36%)). On dermoscopy, we observed different general patterns: multicomponent (40%), reticular-globular-homogeneous (15%), globular homogeneous (15%), reticular (15%), reticular-globular (5%), homogeneous (5%), and globular (5%). Spark nevi showed frequently dermoscopic asymmetry (63%), brown color (90%) with areas of central hyperpigmentation (41%) and peripheral hypopigmentation (28%), atypical pigment network (48%), irregular globules (42%), irregular dots (31%), irregular blotches (16%), blue-whitish veil (13%), peripheral island (25%), irregular hyperpigmented areas (12%), and regression (33%). BRAF mutation was present in 7 of the 10 analyzed cases (70%); all these cases presented a history of evolution. In conclusion, Spark nevi occur on the trunk of young adults with high nevus count and

history of sunburns; dermoscopic features are protean, often atypical and suspicious of melanoma.

Key Words: Spark nevus, Spitz nevus, Clark nevus, melanoma, dermoscopy, BRAF mutation

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LEARNING OBJECTIVES

After completing this CME activity, physicians should be better able to:

1. Describe clinical and dermoscopic features of Spark nevi
2. Identify Spark nevi upon histopathology

INTRODUCTION

Spark's nevus (SprkN) is an acronym (Spitz and Clark) defining mainly a histopathologic than a clinical or dermoscopic entity, coined by Glusac in 2009 but first conception and description has been attributed “verbally” to Ackermann who noted that Spitz nevus can have architectural features of Clark nevus.¹ In fact, SprkN is a peculiar benign melanocytic proliferation that on histopathology shows features of both Spitz and Clark nevus.¹

According to Glusac, pathology of SprkN shows a small size (<1 cm), flat/horizontal lesion with a symmetric outline and sharp circumscription composed by large monomorphic melanocytes with epithelioid or spitzoid morphology collected mainly in elongated oblong nests with clefts. Nests bridge adjacent rete ridges in the manner of a Clark nevus and are also frequently found at the periphery of the lesions. Epithelioid or spitzoid melanocytes bridge across rete with underlying fibroplasia giving a flat appearance; focal upward scatter of melanocytes is possible. SprkNs are mainly junctional or compound but with small round melanocytes only in the papillary dermis. The differential diagnosis includes Clark (severely atypical, dysplastic) nevus, Spitz nevus, and melanoma. Clinically, SprkN has been reported as an asymmetric, irregular, multicolor pigmented lesion, not clearly distinguishable by melanoma or dysplastic (Clark) nevus, more frequently on the trunk and lower extremities and in women with a mean age of 33.

Dermoscopic features of SprkN in a series of cases have not been described yet; only few single case reports are present in the literature.^{2–4} We performed an observational

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retrospective study at our institution to describe clinical and dermoscopic features of SprkN.

PATIENTS AND METHODS

We conducted a retrospective descriptive study selecting equivocal melanocytic lesions excised between 2016 and 2021 at the Dermatology Unit, Galliera Hospital, Genoa, Italy. Corresponding histopathologic slides of cases were subsequently retrieved from the archive of Surgical Pathology, Galliera Hospital, Genoa, Italy. Histologic slides were reviewed by a highly experienced pathologist (S.S.) and a board-certified dermatopathologist (C.M.) for the previously published criteria for histologic diagnosis of SprkN as described by Ko et al¹ and are summarized in Table 1. The corresponding dermoscopic images of each SprkN were collected from the digital dermoscopic database of the Dermatology Unit, Galliera Hospital, Genoa, Italy. All photographs had been acquired by performing polarized, contact dermoscopy and stored on the internal server. All SprkN dermoscopic images were acquired at the time of surgery; dermoscopic follow-up images were also collected, when available. Clinical follow-up data were recorded.

All selected SprkN images were sent for blinded evaluation to 5 external experts (I.S., G.F., M.A.P., V.I., and M.G.) in dermoscopy who had to complete a spreadsheet evaluating the dermoscopic parameters that are given in Table 2. The 7-point checklist was assessed by an internal expert (AMGB).⁵

This study was approved by the Ethics Committee of Regione Liguria (#715/2021).

Statistical Analysis

Data were summarized by the means of common statistical indexes. Absolute numbers and percentages were used for categorical variables. Each SprkN was assessed by 5 different raters, and the interrater agreement for each parameter and criteria was estimated using the Gwet AC and relative 95% confidence interval. The mode among the values of the raters was used to determine the final classification of each nevus.

BRAF Analysis

A representative tumor area of at least 50% was selected. Genomic DNA was extracted from FFPE tissue with an extractor system and amplified by real-time PCR.

The analysis of the BRAF gene mutations was performed using “equipment,” which allows the qualitative detection of the main mutations within codon 600 of the BRAF gene (V600E, V600K, V600D, and V600R).

Sensitivity (minimum detectable percentage of mutated allele): The system allows to detect low percentages of mutated allele in the presence of high amounts of wild-type genomic DNA by real-time amplification with sequence-specific probes marked with FAM and HEX. LOD (limit of detection) was up to 0.5%

Molecular pathology laboratory at Surgical Pathology, Galliera Hospital, Genoa, Italy, is certified for the analysis of mutations in RAS and BRAF genes (according to European

Colon Quality Control and Melanoma External Quality Assessment Scheme 2019, European Society of Pathology, AIOM-SIAPEC 2020).⁶

RESULTS

Study Population

Data from 20 lesions excised between 2016 and 2019 and diagnosed as SprkN excised from 19 patients (M:F = 10:9; mean age: 37,6 years; median: 36 years; range: 23–55 years) were retrieved from the database of Surgical Pathology Division, Galliera Hospital, Genoa (Italy). One patient had a familial history of melanoma, and in 4 cases, a previous melanoma was recorded. Case #19 had been already published.² Clinically, SprkN presented as flat pigmented skin lesions in all cases. SprkNs were located mainly on the trunk (85%), of which 7 on the back (35%), 7 on the abdomen (35%), 3 on the chest (15%), and 15% on the extremities (2 cases on the legs and 1 case on the arm). Fifteen patients (79%) had skin phototype III. SprkN occurred in patients with high nevus count: >100 nevi, 7 patients (36%) and 50–100 nevi, 7 patients (36%). Four patients (21%) had a previous history of melanoma and 1 (5%) had a familial history of melanoma. Sixteen patients (84%) had a personal history of sunburns in childhood. Fourteen patients (74%) reported a history of evolution of the lesion or the new appearance (1 case). Table 3 resumes all clinical data of the patients.

Histopathologic Findings

The histologic review (Table 4) showed that SprkNs were mostly symmetric (80%) and well circumscribed (100%), mainly compound (65%) melanocytic lesions. A congenital pattern was rarely observed (20%). The cell morphology was either epithelioid (55%) or spitzoid (45%). Bridging of the nests and presence of melanophages in the dermis were described in all cases (100%); an inflammatory infiltrate in the superficial dermis was seen in 35% of cases.

Dermoscopic Findings

All lesions were examined by 5 different dermatologists with high experience on dermoscopy for the parameters listed in Table 2. High rates of concordance among evaluators were recorded; only in 2 parameters (blue-whitish veil and blue-gray color) the interrater agreement was fair (0.2–0.4).

The patterns observed were mainly multicomponent (40%), reticular–globular–homogeneous (15%), globular

TABLE 1. Histopathologic Features of Spark’s Nevus

- Small size (<1 cm)
- Flat/horizontal orientation
- Symmetric outline
- Sharp circumscription
- Melanocytes with epithelioid or spitzoid morphology
- Uniform cytology across the entire lesion
- Melanocytes collected mainly in elongated oblong nests with clefts
- Nests of similar size and shape when not bridged

TABLE 2. Dermoscopic Parameters Evaluated by the Experts

Parameters	% in all Cases	% in BRAF-Mutated Cases
Asymmetry		
Monoaxial asymmetry	25	
Biaxial asymmetry	38	
Pigmentation		
Central hypopigmentation	20	23
Peripheral hypopigmentation	38	43
Central hyperpigmentation	41	40
Peripheral hyperpigmentation	28	20
Color		
Light brown	65	97
Dark brown	91	83
Blue-gray	46	20
Black	25	11
Red	17	6
White	14	14
Criteria		
Regular dots	6	3
Irregular dots	31	46
Regular globules	12	6
Irregular globules	42	43
Island (only peripheral island)	25	9
Irregular hyperpigmented areas	12	17
Atypical network	48	51
Negative network	12	3
Regular streaks	3	3
Irregular streaks	16	11
SWS (shiny white streaks)	2	0
BWV (blue-whitish veil)	13	6
Blue regression	19	11
White regression	14	9
Peppering	10	14
Regular blotches	4	3
Irregular blotches	16	9
Vessels (absent, typical, or atypical)	0	0

homogeneous (15%), reticular (15%), reticular-globular (5%), homogeneous (5%), and globular (5%).

Thirty-seven percent of SprkNs were recorded as symmetrical, while in 25% of cases, asymmetry was registered on 1 axis and in 38% of cases were asymmetric on both axes.

Concerning colors and distribution of pigmentation, we found the predominance of brown (light brown: 65% and dark brown: 91%) followed by black (25%), red (17%), and white (14%) colors. Central hyperpigmentation (41%) and peripheral hypopigmentation (28%) were also detected in a proportion of cases.

When evaluating the structures, SprkN displayed atypical pigment network (48%), irregular globules (42%), irregular dots (31%), irregular blotches (16%), blue-whitish veil (13%), peripheral island (25%), irregular hyperpigmented areas (12%), and regression (33%). Atypical vessels were never observed. All cases except 1 (case #5) scored >1 at the 7-point checklist evaluation (Table 2).

Molecular Findings

BRAF mutation was analyzed in 10 cases from 9 patients and was present in 7 cases (70%): 5 cases presented the V600E mutation and 2 cases were V600D/R and V600K mutated, respectively (Table 3).

BRAF-mutated cases showed dermoscopic findings similar to the overall cases (refer to Table 2 for details).

Follow-up Data

Follow-up data were available for 18 cases. No recurrence of lesions and/or other local or distant manifestation was recorded.

DISCUSSION

We collected a homogenous series of lesions of SprkN, those clinical and dermoscopic features have not been described in detail yet. In fact, after the work of Glusac and coworkers in 2009, only few single case reports and 1 small series of cases have been published.^{1,4}

TABLE 3. Clinical Data, 7-Point Checklist, and BRAF Mutation of the Patients

#	Sex	Location	Phototype	n° Nevi	Relatives With Melanoma	Previous Melanoma	History of Sunburns	History of Evolution	7-Point Checklist	BRAF Mutation
1	F	Left calf	III	50– 100	No	No	Yes	New appearance since months	2	n.a.
2	F	Back	III	20–50	No	No	Yes	Not reported	2	n.a.
3	F	Abdomen	III	20–50	No	No	Yes	Modified at 12-month digital FU	3	V600E
4	M	Right arm	II	>100	No	No	Yes	Modified at 12-month digital FU	2	V600K
5	M	Left flank	III	>100	Yes	No	Yes	Not reported	0	n.a.
6	M	Right flank	III	20–50	No	No	Yes	Not reported	2	n.a.
7	F	Back	III	>100	No	Yes	Yes	Modified at 16-month digital FU	3	WT
8	M	Chest	III	<20	No	No	Yes	Enlargment in last mo	3	n.a.
9	F	Abdomen	III	20–50	No	No	Yes	Modified at 12-month digital FU	3	V600E
10	F	Back	III	50– 100	No	No	Yes	Not reported	5	n.a.
11*	M	Back	II	>100	No	Yes	No	Modified at 15-month digital FU	5	WT
12*	M	Back	II	>100	No	Yes	No	Modified at 21-month digital FU	3	V600E
13	M	Right flank	II	>100	No	Yes	Yes	Modified at 12-month digital FU	3	V600E
14	M	Chest	II	50– 100	No	No	Yes	Enlargment in last mo	4	n.a.
15	M	Chest	III	50– 100	No	No	Yes	Enlargment in last months	4	n.a.
16	F	Abdomen	III	50– 100	No	No	Yes	Modified at 30-month digital FU	4	V600D/R
17	M	Right flank	III	>100	No	No	Yes	Enlargment in last months	5	n.a.
18	M	Back	III	20–50	No	No	No	Modified at 18-month digital FU	5	V600E
19	F	Back	III	50– 100	No	No	Yes	Modified at 6-month digital FU	6	WT
20	F	Right leg	III	50– 100	No	No	Yes	Enlargment in last months	5	n.a.

*Same patient.

As originally described,¹ also in our study, SprkN confirmed to be junctional or compound sharply circumscribed, symmetric, melanocytic proliferations that shares features of Clark nevi (bridging of the nests and elongated rete ridges) composed by monomorphic melanocytes with epithelioid or spitzoid morphology arranged mainly in nests.

It must be clearly underlined that SprkNs are underdiagnosed or not even always reported in histologic diagnosis by most dermatopathologists but are quite frequent in routine histopathologic work and are probably reported under other synonyms. Toussaint and Kamino⁷ found 67 of 2164 dysplastic nevi showing features of Spitz nevus. In 1991, Barnhill et al reported a series of 95 pigmented melanocytic spindle cell nevi (PSCN), 8 of which exhibited some overlap with dysplastic nevus that were called PSCN with dysplastic changes. In his last book, Barnhill defines lesions similar to

Spark's nevi as "atypical plaque-type (dysplastic) Spitz tumor."⁹ Massi and LeBoit reported SprkN as a variant of Spitz nevus and named it also as "spitzoid Clark".⁹ Other terms used are "dysplastic Spitz nevus," "dysplastic Spitz tumors," and "spitzoid Clark nevus."^{8–12}

In his original work, Glusac described SprkN as an asymmetric, irregular, multicolor pigmented lesion, not clearly distinguishable by melanoma or dysplastic (Clark) nevus, more frequently on the trunk and lower extremities and in women with a mean age of 33.¹ Recently, Cimmino et al³ reported 12 cases of SprkN in 6 female and 6 male patients aged between 12 and 51 years (mean 35.2 years), with more frequent localization in the lower extremities (6 cases), followed by the back (3 cases), upper extremities (2 cases), and 1 head/neck case. Compared with these reports, we also found that SprkN was equally occurring in young adults of both sex, but interestingly, in our experience, SprkN was more

TABLE 4. Histopathologic Features of Spark Nevi

#	Symmetry	Sharp Circ.	Junctional/Compound	Cong. Patt	Combined Pattern	Epithelioid Morphology	Spitzoid Morphology	Elongated Rete Ridges	Bridging of the Nest	Melanophages	Inflammatory Infiltrate
1	Y	Y	C	N	N	Y	N	N	Y	Y	Y
2	Y	Y	C	N	N	N	Y	N	Y	Y	N
3	Y	Y	C	Y	Y	N	Y	Y	Y	Y	Y
4	Y	Y	J	N	N	Y	N	Y	Y	Y	N
5	Y	Y	C	N	N	Y	N	Y	Y	Y	N
6	Y	Y	J	N	N	N	Y	N	Y	Y	Y
7	Y	Y	C	Y	Y	Y	N	Y	Y	Y	N
8	Y	Y	C	N	N	N	Y	Y	Y	Y	N
9	Y	Y	C	N	Y	Y	N	Y	Y	Y	N
10	N	Y	J	N	N	N	Y	Y	Y	Y	Y
11*	Y	Y	J	N	N	Y	N	Y	Y	Y	Y
12*	N	Y	C	Y	Y	Y	N	Y	Y	Y	N
13	Y	Y	C	N	N	N	Y	Y	Y	Y	N
14	N	Y	J	N	N	N	Y	Y	Y	Y	Y
15	Y	Y	C	N	N	Y	N	Y	Y	Y	N
16	Y	Y	J	N	N	Y	N	Y	Y	Y	N
17	N	Y	J	N	N	Y	N	Y	Y	Y	Y
18	Y	Y	C	Y	Y	Y	N	Y	Y	Y	N
19	Y	Y	C	N	N	N	Y	Y	Y	Y	N
20	Y	Y	C	N	N	N	Y	Y	Y	Y	N
	16/20, 80%	20/20, 100%	7/20, 35% J; 65% C	4/20, 20%	5/20, 25%	11/20, 55%	9/20, 45%	17/20, 85%	20/20, 100%	20/20, 100%	7/20, 35%

*Same patient. Y, yes; N, no; J, junctional, C, compound; Cong, congenital; patt, pattern.

frequently found on the trunk (85%) and only 15% cases were located on the extremities. Moreover, we found that SprkN was more frequent in patients with a personal history of sunburns in childhood (84%), skin phototype III (79%), and with high nevus count (>100 nevi, 7 patients (36%)). A personal

or familial history of melanoma was also recorded in 25% of cases; Glusac et al did not report such association.¹

Dermoscopic features of SprkN have been previously described in only few single case reports. Park et al⁴ reported a single case that showed brown-to-black globules, diffuse

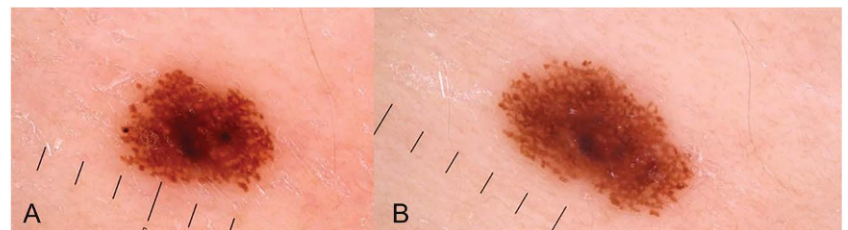


FIGURE 1. Case #9. A, Dermoscopy at baseline: A globular pattern with central hyperpigmentation. B, Dermoscopy at the follow-up visit (12 month): Enlarged lesion showing a globular pattern with asymmetry on 1 axis, central slightly hyperpigmented structureless areas, and few pseudopods at the periphery. C, Histology showed a junctional melanocytic proliferation organized in irregular, cohesive nests composed by epithelioid melanocytes and with elongation of rete ridges. In the dermis, few melanophages are present. This lesion was BRAF V600E mutated. (HE; original magnification: $\times 200$).

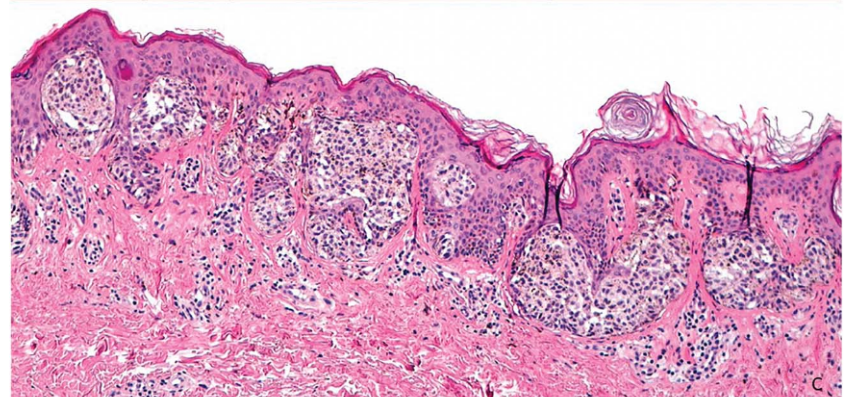
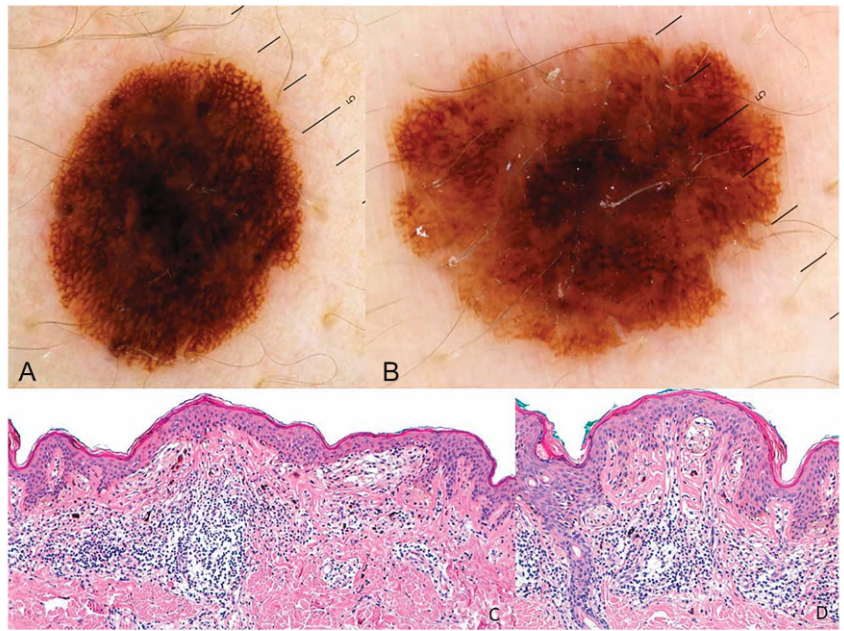


FIGURE 2. Case #11. A, Dermoscopy at baseline: A reticular pattern with central slightly hyperpigmented structureless area and atypical network. B, Dermoscopy at the follow-up visit (15 month): Enlarged lesion showing a multicomponent pattern with asymmetry on 2 axes, atypical network, irregular dots, and central slightly hypopigmented and hyperpigmented structureless areas. C, D, Histology showed a junctional melanocytic proliferation organized in irregular, cohesive nests composed by epithelioid melanocytes, elongation of rete ridges, and concentric fibroplasia. In the dermis, few melanophages and a superficial lymphohistiocytic infiltrate are present. (HE; original magnification: $\times 200$).

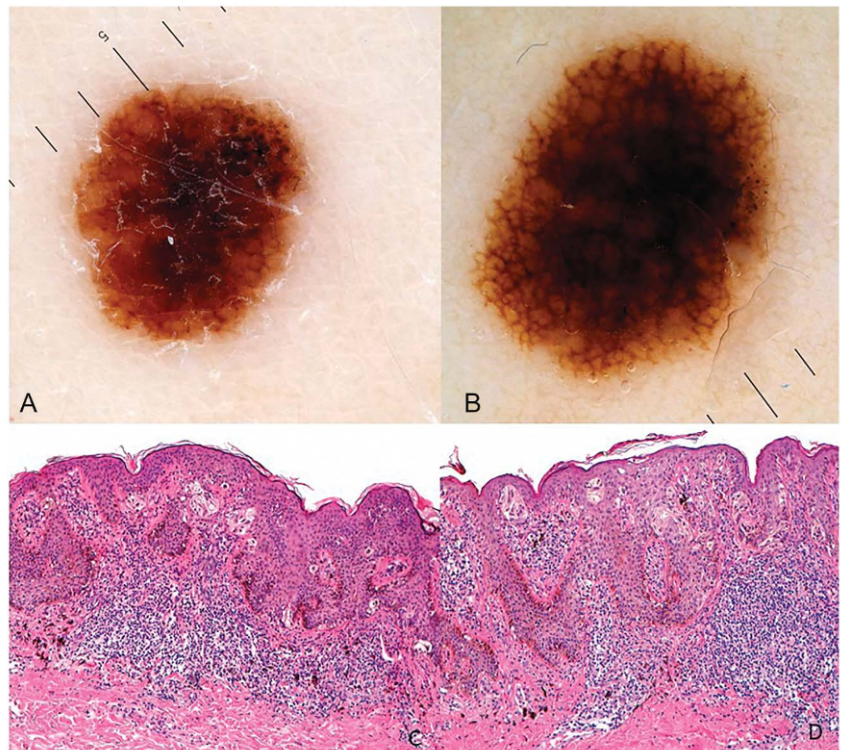


homogenous pigmentation with blue-white structures, brown dots, and isolated eccentric hyperpigmentation. Cimmino et al³ reported a small series of the lesions characterized by a combined pattern with a central homogeneous blackish and a regular gradient-edged lattice in the peripheries.

With our study, we can expand the knowledge on this topic because we observed that SprkN may present on

dermoscopy with different general patterns: multicomponent (40%), reticular-globular-homogeneous (15%), globular homogeneous (15%), reticular (15%), reticular-globular (5%), homogeneous (5%), and globular (5%). SprkN showed frequently asymmetry (63%), brown color (90%) with areas of central hyperpigmentation (41%) and peripheral hypopigmentation (28%). Interestingly, criteria of atypia were

FIGURE 3. Case #3. A, Dermoscopy at baseline: A reticular-homogeneous pattern with central slightly hyperpigmented structureless areas and irregular dots. B, Dermoscopy at the follow-up visit (12 month): Enlarged lesion showing a reticular-homogeneous pattern with asymmetry on 1 axis, central slightly hyperpigmented structureless areas, and irregular dots. C, D, Histology showed a junctional melanocytic proliferation organized in irregular, cohesive nests composed by epithelioid melanocytes, elongation of rete ridges with basal hyperpigmentation, and concentric fibroplasia. In the dermis, few melanophages and a dense superficial lymphohistiocytic infiltrate are present. This lesion was BRAF V600E mutated. (HE; original magnification: $\times 200$).



observed in a high proportion of cases: atypical pigment network (48%), irregular globules (42%), irregular dots (31%), irregular blotches (16%), blue-whitish veil (13%), peripheral island (25%), irregular hyperpigmented areas (12%), and regression (33%). Moreover, 95% of SprkN scored >1 point with the 7-point checklist, justifying clinical concern and therefore surgical excision.¹³

In summary, dermoscopic features of SprkN are protean, not univocal, and often atypical or suspicious of melanoma and therefore lesions are excised. This conclusion is in agreement with the experience of Glusac because most of the SprkN that he described were clinically irregular lesions with the differential diagnosis of atypical nevus/melanoma.¹

SprkN showed frequently asymmetry on dermoscopy (63%), but on histopathology, SprkNs were mostly symmetric (80%). It should be noted that, on dermoscopy, symmetry is judged based on the distribution of patterns and colors within the whole lesion and on a horizontal surface; moreover, the presence of melanin at different levels of the epidermis or the superficial dermis results in different nuances of colors at dermoscopy. Regarding histopathology, symmetry refers to the distribution of architectural structures judged in a single or few sections of the lesion on a vertical level. Therefore, dysplastic/atypical nevi may present asymmetry on dermoscopy but may show overall symmetry on histopathology.^{11,20}

Interestingly, 14 of our patients (74%) reported a history of evolution of the lesion, and we were able to document in 8 cases an enlargement of the lesion from baseline to the time of excision. BRAF mutation was present in 7 of the 10 analyzed cases (70%); all these BRAF-mutated SprkN presenting a history of evolution and enlargement were documented on digital dermoscopic follow-up (Figs. 1–3).

BRAF mutations are found approximately in 80% of melanocytic nevi.^{14–18} Marchetti et al¹⁴ reported that nevi with a dermoscopic globular pattern or peripheral rim of globular nevi are 3-fold more likely to have an underlying somatic BRAF V600E activating mutation than those with a reticular pattern (approximately 90 vs. approximately 30 percent, respectively). Tan et al found that reticular nevi were 67% BRAF V600E/K.^{16,17} Recently, Donati et al¹⁹ reported 4 melanocytic lesions resembling the SprkN and harboring a MAP2K1 mutation.

In conclusion, we expand the existing literature on SprkN. In our study, we confirm that SprkNs are benign melanocytic proliferations that on histopathology share features of both Clark and Spitz nevi, but on dermoscopy, they show frequently atypical features simulating melanoma. Moreover, they are usually BRAF mutated growing melanocytic lesions on the trunk of young adults with high nevus count and history of sunburns in childhood. Limitation of this study is represented by the small number of cases examined; further studies on a larger population

are needed to better characterize this type of melanocytic nevus.

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CME EXAM

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CME EXAMINATION

March 2023

Please mark your answers on the ANSWER SHEET.

After participating in this activity, physicians should be better able to: 1. Describe clinical and dermoscopic features of Spark nevi. 2. Identify Spark nevi upon histopathology.

CME QUESTIONS

1. Spark's nevus is an acronym of:
 - A. Spitz's nevus and Kamino nevus
 - B. Spitz's nevus and Clark's nevus
 - C. Spitz's nevus and acral nevus
 - D. Spitz's nevus and blue nevus
2. Upon histopathology, Spark's nevus is characterized by:
 - A. Asymmetric, compound sharply circumscribed melanocytic proliferation
 - B. Irregular nests of atypical melanocytes with pagetoid spread in all layers of the epidermis
 - C. Dendritic dermal melanocytes around the adnexal structures
 - D. Symmetric, junctional or compound sharply circumscribed melanocytic proliferation composed by monomorphic melanocytes with epithelioid or spitzoid morphology
3. Clinically, Spark's nevus is more frequently characterized by:
 - A. Asymmetric, irregular, multicolor pigmented lesions
 - B. Symmetric, regular, multicolor pigmented lesions
 - C. Asymmetric, irregular, homogeneous pigmented lesions
 - D. Exophytic ulcerated amelanotic lesions
4. Upon dermoscopy, the most frequent general pattern of a Spark's nevus is:
 - A. Cobblestone pattern
 - B. Parallel furrow pattern
 - C. Parallel ridge pattern
 - D. Multicomponent

5. Upon dermoscopy, Spark's nevus may show:
- A. Atypical pigment network, irregular globules, irregular dots, irregular blotches
 - B. Atypical vessels
 - C. Fingerprint-like structures
 - D. Leaf-like/spoke wheel areas
6. Molecular findings of Spark's nevus are characterized by:
- A. BRAF wild type
 - B. N-RAS mutation
 - C. H-RAS mutation
 - D. BRAF mutation

