Clinical features and natural history of Spitz-Reed nevus in children.

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Summary
Melanoma in children is so rare that a dermatologist cannot diagnose any during his/her professional career. Spitz nevus can mimic melanoma both in its classical angioma-like or hypopigmented variant and in its pigmented variant that according to some Authors is indistinguishable from Reed nevus. In the actual report we examined 56 cases of pigmented variant or Spitz-Reed nevus (SRN) in children less than 13 years, we focused its morphological characteristics and its natural history in the child. The latter in the child looks like that of one of the angioma-like variant of Spitz nevus and more generally to that of many benign proliferations of childhood in which an initial proliferative phase is followed by a phase with prevailing regressive phenomena.

Key words
Spitz nevus, Reed nevus, angioma-like variant, pigmented variant, natural history, spontaneous regression.

Melanoma in children is so rare that a dermatologist cannot diagnose any during his/her professional career. The melanocytic proliferation that may arouse the suspicion of melanoma in children is Spitz nevus (SN). The latter was really considered a melanoma before the reports of Spitz (15) and Allen (1).

The classic, angioma-like Spitz nevus can simulate clinically amelanotic nodular melanoma because of its rapid initial growth and some histologic atypia. Even the pigmented form of Spitz nevus, which according to some Authors (7) can not be distinguished from Reed nevus, can simulate melanoma from a clinical, dermoscopic and sometimes also histological point of view, especially in the adult.

In the actual report we are discussing the pigmented variant or Spitz-Reed nevus (SRN), focusing on its morphological characteristics and its natural history in children. The latter is not different from that of angioma-like variant of Spitz nevus and more generally to that of many benign proliferations of childhood where an initial proliferative phase is followed by a phase with prevailing regressive phenomena.

Materials and methods
Over the last 9 years (2006-2015) we observed 56 cases of SRN in children below the age of 13 (Table 1); the males were 29 (52%) and the average age at first visit was 6.4 years. 22 cases (39.3%) were located on the lower limbs, 17 (30.4%) on the trunk, 13 (23.2%) on the upper limbs and 4 (7.1%) on the head. The average diameter of the lesion was 5.2 mm (3-8).
Fig. 1, 2, 3, 4: Spitz-Reed nevus is more often junctional (Fig. 1) and is frequently characterized by a very irregular outline due to the presence of clinically evident pseudopodia (Fig. 2); SRN can be palpable in plaque (Fig. 3) or nodular (Fig. 4). The nevus in Fig. 4 was removed to confirm the clinical diagnosis.

Fig. 5, 6, 7, 8, 9: The irregular contour is the rule in Spitz-Reed nevus, specially in junctional forms.

| Table 1: Clinical features of 56 Spitz-Reed nevi in children under 13 years. |
|------------------------------|------------------|
| Sex                         | 29 males (52%)   |
| Average age at first visit   | 6.4 years        |
| Lower limbs                  | 22 cases (39.3%) |
| Trunk                       | 17 cases (30.4%) |
| Upper limbs                  | 13 cases (23.2%) |
| Head                        | 4 cases (7.1%)   |
Of the 56 Spitz-Reed nevi 34 were observed only once, 10 twice and 12 three times or more than three; 3 of 56 nevi were excised and histology confirmed the clinical diagnosis; the other 53 cases received a presumptive diagnosis based on clinical examination and dermoscopy: the clinical diagnostic criterion was medical history (the mother comes to visit just for that nevus in particular and reports its increase in recent months) and skin findings (intensely pigmented blackish or dark brown lesion); the dermoscopic criterion was the starburst pattern at least during one examination; in any case, all three criteria had to be satisfied to include the nevus in the study.

**Morphology**

As regards the morphological appearance of SRN 36 (65%) were not palpable (Fig. 1, 2), 15 (27%) in plaque (Fig. 3) and 5 (8%) nodular (Fig. 4). Spitz-Reed nevi were always intensely pigmented from dark brown to blackish; their shape was oval (Fig. 3) in 28 cases (50%) or rounded (Fig. 6). The contour of Reed-Spitz nevus in the child, was uneven due to the presence of protrusions and recesses, that is of irregular and coarse pseudopodia also clinically visible (Fig. 5-9) in 16 cases (29%); this irregularity of the outline was more common in non-palpable forms of child RSN.

**Natural history of Spitz-reed nevus**

In all 56 cases this was an acquired nevi that underwent a significant initial growth; the latter always stopped, on average after 6 months (4-9 months) when the nevus reached the average size of 5.2 mm (3-11 mm); after this initial phase a very variable period of time followed during which the nevus tended to regress. The regression manifested clinically and dermoscopically; in 7 cases we followed for an average period of 3 years (2-5 years) we documented the regression. From the clinical point of view palpable nevi became less tense and flattened (Fig. 10-14), especially on the periphery where a not palpable rim could appear; in junctional nevi there was a decrease of pigmentation (Fig. 20, 21) and attenuation of the irregularity of the outline was observed, ie the pseudopodia became less prominent and less visible.

The regression could also be followed dermoscopically: there was switching from an early globular stage to that of pseudopodia, then of thin striae up to look indistinguishable from a common melanocytic nevus (Fig. 15-19), usually with homogeneous structure in the middle and reticular in the periphery. A change was primarily observed at the periphery where the pigmentation and the irregularity of the outline decreased.

**Discussion**

The diagnosis, prognosis and therapy of a cutaneous proliferation of melanocytes that is observed due to its rapid growth are strongly influenced by the age of the subject (11): in children we are dealing almost always with a nevus, in adults very often with a melanoma. This dilemma did not exist until 1948: up to that time any fast growing melanocytic proliferation with cyto-architectural atypia was a melanoma regardless of age. In 1948 Spitz (15) sensed that the melanocytic proliferations of the child had a better prognosis and the following year Allen (1) declassified juvenile melanoma to the role of nevus; the latter is rightly now known by the name of Spitz nevus (SN). It is remarkable that to do this revolution were pathologists and not clinicians. But the memory of the previous situation is not entirely disappeared and still today dermatologists who do not see many children (16) treat Spitz nevus as if it was a melanoma; the natural history of SRN is so little known because usually it is removed.

There are two variants - angioma-like and pigmented - of Spitz nevus. The pigmented variant is not easily distinguished from Reed nevus based on clinical or dermoscopic and sometimes even histopathological findings: this is why some Authors (7) unify pigmented Spitz nevus and Reed nevus (13) under the name of Spitz-Reed nevus (SRN).

The amount of melanin pigment that the nevus produces varies and depends on genetic and environmental factors; among the latter sun ex-
Fig. 10, 11, 12, 13, 14, 15, 16, 17, 18, 19: Natural History of Reed-Spitz nevus in a 2-year-old child followed for 5 years. At the first examination you can see a fast growing, hyperpigmented, palpable nevus on the left thumb (Fig. 10) that on dermoscopy examination (Fig. 15) shows a starburst pattern; in the central region there are uniform in diameter globules; sometimes the latter are also present at the periphery where clavate pseudopodia prevail. After 5 months (Fig. 11) the nevus grew of about 1 mm. After 13 months from the first observation (Fig. 12) a junctional component appeared that after 3 years from the first observation (Fig. 13) was enlarged while the central dermal component appeared less infiltrated; after 5 years from the first observation (Fig. 14) the nevus became smaller and the junctional component further enlarged; on the other hand, the central dermal component appeared reduced. The dermoscopic changes were much more significant: the globules and pseudopodia of the first examination turned into radial strae (Fig. 16) which then became thinner almost to disappear (Fig. 17, 18, 19) while you could see central large clusters of pigment and then a blue-gray central component with reticulated depigmentation.

These concepts can well apply to angioma-like Spitz nevus and SRN. In some cases, mainly in the child, the cell proliferation involves the deep reticular dermis, and then you can see a non-pigmented nodular lesion (classic angioma-like Spitz nevus); in other cases the cell proliferation affects the dermal-epidermal junction and the papillary dermis, and then you can see a pigmented junctional, non-palpable or plaque lesion (Spitz-Reed nevus). Between the two extremes there are all the intermediate stages; the natural history of angioma-like SN (3) shows how, once exhausted

posure and hormonal factors prevail. There is not a direct relationship between cell proliferative capacity and production of melanin, but rather there is a relationship between superficiality of the proliferation and ability to produce melanin. A plausible explanation of this finding is that the production of melanin makes sense when it is superficial, namely when it stands where the ultraviolet (UV) rays arrive to prevent their mutagenic side effects on the epidermal cells; on the other hand, it makes no sense deeply where UV rays do not arrive.
the proliferative phase, in the phase of regression it can turn into a pigmented compound nevus.

We already showed that the angioma-like variant of SN almost always regresses with atrophy or undergoes flattening and pigmentation turning into a non palpable pigmented nevus (3) in agreement with other Authors (9).

It was more difficult for us to document the natural history of the pigmented variant because the latter is less impressive for the parents being less raised and undergoing less significant clinical changes with time as compared with the classic angioma-like variant.

However, in cases that we were able to follow for at least three years we documented the regression, expressed by flattening, regularization of the contour and in some case decrease of the pigment.

The regression can be also followed dermoscopically and the changes observed are more significant of the clinical variations: an initial globular phase turns into that of pseudopodia, then of thin streaks up to an appearance indistinguishable from a common melanocytic nevus, usually with homogeneous at the center and reticular at the periphery structure.

As regards the treatment of these nevi we believe in agreement with other Authors (2, 9) that Spitz-Reed nevi in the first 12 years of life should be monitored clinically; an initial growing phase is not enough at this age to advise surgery; also an irregular outline with clinically obvious pseudopodia is not a sufficient criterion to decide removal because in our series 29% of SRN have this clinical feature; neither are the dermoscopic changes an indication to surgery (6, 12).
Spitz-Reed nevus in children is reminiscent of adult melanoma and for this reason it is often removed. However, child’s melanoma (cM) is not only exceptional (11) but it is also very different from that of the adult; it is more often amelanotic, nodular from its onset, monochrome, with regular outline. This is why some Authors (5), examining one of the widest case series of prepubertal melanoma, conclude that only E (Evolution) remains a valid criterion also for melanoma in children; for these Authors A becomes Amelanotic because cM is usually symmetrical and not pigmented; B becomes Bump and Bleeding, because the edges of cM are usually regular, and it often presents as a bloody nodule simulating lobular eruptive angioma; C becomes uniform Color because cM is most often monochrome; D becomes De novo and any Diameter, because cM hardly arises from a nevus (unless it is a giant congenital melanocytic nevus); on the other hand, it often occurs on normal skin and can have a diameter less than 6 mm.

Physicians supporting the removal of the Spitz-Reed nevus argue that the removal still serves to dispel doubts and to avoid periodic controls. Unfortunately, despite new techniques such as fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH) that give importance to gene and chromosomal abnormalities of malignant cells, more and more often the pathologist unable to decide between benign and malignant (8) use terms such as AST (Atypical Spitz Nevus), AMP (Atypical Melanocyte Proliferation) STUMP (Spitz Tumor of Uncertain Malignant Potential), SAMPUS (Superficial Atypical Melanocytic Proliferations of Uncertain Significance), MELTUMP (MELanocytic Tumor of Uncertain Malignant Potential) that do not quantify the percentage of risk of malignancy. And unfortunately more and more often the pathologist as a consequence of his/her indecision behaves as a clinician counseling enlargement, sentinel lymph node and periodic examinations: this is why sometimes the removal does not solve the problem but indeed accentuates it.

When you decide to remove a lesion suspected for a cM a collaboration between clinician and pathologist is necessary; the pathologist should specify the percentage of risk but more investigations and clinical controls should be suggested by the clinician. Enlargement in some locations, for example the nose is difficult to practice (8); the sentinel node is more often positive in the first decade of life (5), but the positivity has no effect on survival (10).

For these reasons we do not usually remove non palpable Spitz-Reed nevus and check in the first few months that growth stops. Sometimes we remove nodular or plaque SRN with esthetic purposes and to quell the anxiety of parents. When facing an already removed SRN, unless the histological diagnosis of melanoma is certain, we discourage enlargement and especially the execution of sentinel lymph node.

A limit of the actual report is the lack of a histological examination to confirm the diagnosis. In the literature cases of blue nevus with starburst pattern on dermoscopy were really reported, but the color of the lesion was bluish and not black or dark brown (14). Moreover, including in the actual report only the nevi that at least in one examination had a dermoscopic appearance of starburst, we may have lost some Reed nevi, especially of small dimensions, that according to some Authors (6) may not present such a characteristic.

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