Coll. Antropol. **32** (2008) Suppl. 2: 171–176
Review

Nevus Spitz – Everlasting Diagnostic Difficulties – The Review

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A B S T R A C T

In 1910, Darier and Civatte described in details an unusual melanocytic tumor characterized by rapid growth on the nose of a young child. They could not state whether the tumor was benign or malignant. In 1947, Sophie Spitz described the same lesion as juvenile melanoma in which prognosis was frequently excellent. Later, the study was revised and it was concluded that juvenile melanoma was a benign tumor and can affect adults. Although, the prognosis was mostly excellent, Spitz reported in one of 13 cases fatal metastases from nevus Spitz. In 1999, Barnhill et al described one fatal case of the patient for whom it was thought to have typical Spitz nevus. Nowadays, there is still a lack of consensus about histopathology and also a terminology of the tumors that are neither typical nevus Spitz, neither malignant melanoma. All histopathological, clinical and ancillary criteria must be weighed in the final interpretation of epitheloid/spindle cell lesion. At the present, the final diagnosis remains pathohistological, with important emphasis given to clinical impression. Persistently changing lesion indicates malignancy potential of the lesion. Barnhill recommends that all Spitz tumors are completely excised. Atypical tumors should be excised with wider margins up to 1 cm. Patient should be carefully monitored by regular examinations for recurrence and metastasis.

Key words: *nevus Spitz, atypical nevus Spitz, Spitzoid melanoma, pathohistological analysis, surgical excision*

Introduction

In 1910, Darier and Civatte[1] described in details an unusual melanocytic tumor characterized by rapid growth on the nose of a young child. They could not state whether the tumor was benign or malignant. In 1947, Sophie Spitz[2] described the same lesion as juvenile melanoma in which prognosis was frequently excellent. Later, the study was revised and it was concluded that juvenile melanoma was a benign tumor and can affect adults[3]. Although, the prognosis was mostly excellent, Spitz reported in one of 13 cases fatal metastases from nevus Spitz. In 1999, Barnhill et al.[4] described one fatal case of the patient for whom it was thought to have typical Spitz nevus. Nowadays, there is still a lack of consensus about histopathology and also a terminology of the tumors that are neither typical nevus Spitz, neither malignant melanoma. The treatment of nevus Spitz is clear, but the surgical margins of the tumor remain unclear. Gelbard[5] investigated how American dermatologist and pediatrician manage nevus Spitz. The majority of dermatologist and pediatricians recommended 1–2 mm margin of normal appearing skin around the nevus. They were also less likely to monitor patients whose Spitz nevi were completely excised. 74% of respondents believed that nevus Spitz was entirely benign lesions, 4% believed that it was precursor of malignant melanoma, and 22% of the interviewed physicians were not sure.

Typical Nevus Spitz

The prevalence of nevus Spitz (NS) is unknown in general population, but they appear less often than acquired and congenital melanocytic nevi[6]. The incidence of NS in general population is about less than 0.2% and in children about 1%. There is no sex prevalence and the majority of nevi occur in children (about 60% by the age of 30). The majority of NS occur on the head and neck (37%), followed by 28% on lower extremities, 19% on the

Received for publication July 30, 2008

upper extremities and 6% on the trunk. NS is usually solitary papule, but could also be multiple, widespread, grouped, agminated or eruptive and usually less than 1 cm in diameter. The color is usually pink to red but could range from flesh colored to tan, dark brown and black depending on amount of melanin present and the vascularity of the lesion[7].

There are four clinical types of NS:

1. the light colored soft form which is pink to light tan, smooth, and flatters with dermatoscopy,
2. the light colored hard form, which appears like a dermatofibroma or keloid and may have halo and teleangiectases,
3. the dark form, which is variably pigmented and smooth,
4. the multiple form, which includes the grouped and widespread, disseminated, eruptive lesions[8].

Clinical differential diagnosis includes acquired melanocytic nevus, dysplastic melanocytic nevus, congenital melanocytic nevus, blue nevus, pyogenic granuloma, dermatofibroma, hemangioma, angiofibroma, scar, keloid, fibroma, xanthogranuloma, verruca vulgaris, molluscum contagiosum, epidermal nevus, histiocitoma, xanthoma, anthropod bite reaction, lichen planus, lupus vulgaris, granuloma faciale, eosinophilic granuloma, pseudolymphoma, seborrheic keratosis, chondrodermatitis, nodular helicis, actinic keratosis, pale cell achantoma, granular cell tumor, leiomyoma, glomus tumor, squamous cell carcinoma, basal cell carcinoma, Kaposi sarcoma and angiosarcoma[7].

The typical appearance under the dermatoscope is pigmented spindle nevus with a striking starburst pattern due to components that extend radially towards the corona, leaving targetoid pattern (Figure 1a). The branched streaks reach the surrounding skin only occasionally, usually dissipating before or in the corona and being replaced by pigmented globules and dots[9].

Although the bizarre histopathological features and frequent occurrence of dermal inflammation may cause diagnostic confusion, nevus Spitz when typical can be differentiated from malignant melanoma[10]. Spitz nevi are melanocytic nevi that are junctional (66%), compound (11%) and dermal (18%). Melanocytic elements are usually arranged in well-circumscribed nests in epidermis and dermis. The epidermis is usually hyperplastic, with elongated and bulbous pegs and knobs extending into the dermis (Figure 1b). Spindle cells preominate in 45–54% of Spitz nevi, epitheloid cells in 21% and relatively equal combination of cell types in 24–34%. The pigmented spindle cell nevus described by Reed et al.[11] is usually sharply demarcated, uniformly darkly pigmented papule or plaque consisting of compact and aggregated spindle-shaped, pigment-producing melanocytes, distinguished from melanoma by its uniform nuclei, uniform cellular detail, and distinctive pattern of growth. Unlike ordinary nevi and melanomas, melanocytic cells in Spitz nevus are large, often twice the size of epidermal basal keratinocytes (Figure 1c). Mitoses, usually few in number are nested in half the cases. The melanocytic cells in NS show progressive maturation with increasing depth, becoming smaller and more similar to ordinary melano-

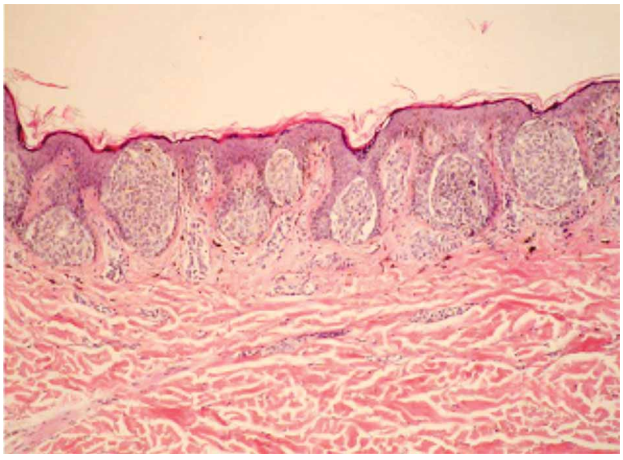

Fig. 1. b) Histological picture of typical nevus Spitz (100x HE).

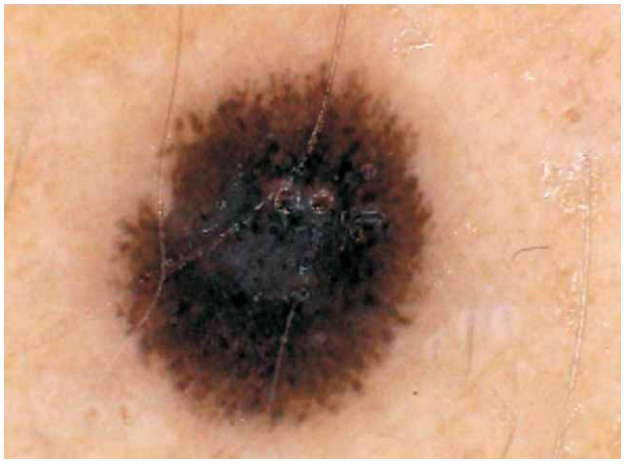

Fig. 1. a) Nevus Spitz under dermatoscope.

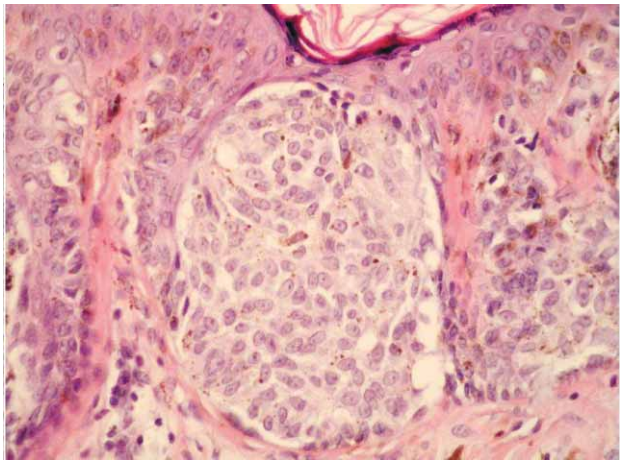

Fig. 1. c) Histological picture of typical nevus Spitz (400x HE).

cytes. Coalescent oesinophilic globules (Kamino bodies), PAS positive have been reported in 60% of Spitz nevi. Similar globules might be found in melanomas, but in only 2%.

Characteristics of conventional Spitz tumors from Barnhill at al[4]:

Clinical features:

1. Configuration: papule or nodule, often dome-shaped, or plaque,
2. Size: smaller than 1 cm,
3. Profile: often smooth surface,
4. Color: pink/red, pigment variants occur,
5. Age: major in children and adolescence, but also any age,
6. Location: face and extremities,
7. Symptoms: commonly asymptomatic,
8. History of growth: usually less than year.

Histopathological criteria:

1. Architectural features,
2. Symmetry,
3. Sharp lateral demarcation,
4. Regular pattern of epidermal hyperplasia,
5. Zonation with depth:
   a. Side to side uniformity, that is nests and fascicles of melanocytes with fairly uniform size and shape and regular spacing,
   b. Diminished cellular density with depth,
   c. Nests diminish in size and show transition to single cells with depth,
   d. Diminish non-disruptive infiltration of collagen by melanocytes.

Cytological features:

1. Spindle and/or epitheloid cell type,
2. Overall monomorphous population of cells,
3. Low nuclear-to-cytoplasmatic ratio,
4. Opaque or ground-glass cytoplasm,
5. Nuclei with open, delicate chromatin patterns,
6. Uniform nucleoli,
7. Occasional striking pleomorphism in minority of cells.

Other helpful diagnostic features:

1. Mitotic rate $<2/mm^2$,
2. Absent or rare, but not atypical, mitoses in deep parts,
3. Mononuclear and multinucleate giant cells,
4. Irregular contours of growth at deep margin,
5. Dull pink (Kamino) bodies- not pathogomonic feature,
6. Paucity or absence of single-cell upward spread (in central part of lesion present),
7. Junctional clefts,
8. Loss of cohesion between cells (retraction spaces),
9. Perivascular or diffuse inflammatory infiltrate,
10. Superficial distribution of pigmentation,
11. Teleangiectasia and edema.

Concerning the treatment options, there is no doubt that nevus Spitz should be completely excised with a clear margin of normal skin is usually sufficient. For histopathologically worrisome lesion, wider margin may be prudent.

Da Forno et al.[12] postulated a model according to the model of nevus progression to dysplastic nevus and then to melanoma (Table 1). Although, the model is not accepted by all, because the majority of melanoma rise from de novo, this has led to speculation that similar process occur in epitheloid cell tumors, whereby the NS becomes atypical NS and finally malignant melanoma. In support to this, atypical NS show a spectrum of histological features intermediate between classic NS and melanoma.

Atypical Nevus Spitz

The term atypical Spitz tumor was first used in the English literature in 1975 by Reed et al.[11], illustrating NS that differed from classical NS. The difference was that atypical tumor showed confluent and densely cellular fascicles of spindle cells that crowded and compressed their stroma. Smith et al.[13] described similar tumor as spindle and epitheloid cell nevus with atypia and metastasis. They were characterized by large size, more than 1 cm, with ulceration, deep extension into subcutaneous fat with bulbous margins, prominent cellular density, lack of maturation, cytological atypia, more than 2 mitosis and focal necrosis. These tumors developed in young

TABLE 1
THE SPECTRUM OF HISTOLOGICAL FEATURES, DIAGNOSTIC TERMINOLOGY AND CLINICAL BEHAVIOR OF NEVUS SPITZ AND OTHER EPITHELOID/SPITZOID CELL TUMORS BY DA FORNO ET AL

Histological features	Classical Spitz nevus				Malignat melanoma
Diagnostic term applied	Nevus Spitz	Atypical Nevus Spitz	Atypical Nevus Spitz/STUMP	Spitzoid melanoma	»Common melanoma«
Implied likely behavior	Benign	Probably benign	Uncertain	Malignant	

STUMP – Spitz tumor of uncertain malignant potential

individuals and were located on the head and neck, and extremities. Six patients had positive regional lymph node metastases with involvement of the sinuses and parenchyma by tumor identical to the primary cutaneous lesion. The older the patients, especially beyond 20–30 years, the likelihood of malignancy are greater. The location of atypical tumors on sites less commonly involved by Spitz tumor, such as the back, is also another factor suggesting careful follow up of the patient[14]. However, there are some authors[15] who disagree about the terms »atypical« nevus Spitz »malignant« nevus Spitz, nevus Spitz and metastasizing nevus Spitz. They found out that an overwhelming majority of neoplasm that claimed to be »atypical«, »metastasing« and »malignant« Spitz nevi were in fact melanomas. Complementary to these facts are the results of study of 12 patients with »atypical« nevus Spitz who underwent sentinel node biopsy. Nodal micrometastases were found in 33.3% of patients[16].

Histopatological criteria for atypical Spitz tumors from Barnhill at al[4]:

1. Diameter in mm (≥10 mm considered abnormal),
2. Depth in mm (subcutaneous fat considered abnormal),
3. Ulceration,
4. Poor circumscription,
5. Pagetoid melanocytes over a larger front,
6. Prominent confluence of melanocytes,
7. Asymmetry,
8. Few or no dull pink (Kamino bodies),
9. High cellular densits,
10. Lack of zoonation and maturation.

Proliferation criteria from Barnhill at al[4]:

1. Significant mitotic rate ≥2–6/mm2,
2. Deep/marginal mitoses
3. Proliferation index-Ki-67 expression between 2–10%; ≥10%.

Cytological criteria from Barnhill at al[4]:

1. Granular vs. ground glass cytoplasm,
2. High nuclear to cytoplasmic ratios,
3. Loss or delicate or dispersed chromatin patterns,
4. Thickening of nuclear membranes,
5. Hyperchromatism,
6. Large nucleoli.

Spitzoid Melanoma

Spitzoid melanoma term should be used for melanoma with morphological resemblance to nevus Spitz[17]. The resemblance includes features: dome-shaped, plaque-like, wedge-shaped morphology, little or no asymmetry, epidermal hyperplasia, clefting about intraepidermal nests of melanocytes, presence of dull Kamino bodies, some evidence of zonation or maturation and population of enlarged epitheloid or/and spindelled melanocytes with abundant opaque or glass cytoplasm[18,19]. The importance of differentiation between NS and melanoma is emphasized in the literature. Recent data suggest that Spitz nevi differ from melanomas in their immunohistochemical pattern of expression of cell cycle and apoptosis regulators (bax, Ki-67, Rb, p-16, cyclin A, cyclin B1, p-27, p-53) and more closely resemble common benign nevi[20,21]. There are many authors who tried to find clear pathohistological hallmarks of NS and Spitzoid melanoma. Weedon D and Little JH[22] find these features important; presence of some nevus cells maturity at the base, an absence of atypical mitoses, no significant upward epidermal spread and the nuclear chromatin pattern. Crotty[23] reviewed several studies and concluded that histological features that support diagnosis of malignant melanoma rather than atypical nevi are deep and marginal mitoses, atypical mitoses, asymmetry, pleomorphisam and prominent epidermal involvement. The same author compared clinical and histopathological features of 13 malignant melanomas in children under the age of 13 with 15 NS[24]. Histological features favoring malignancy were mitoses within 0.25 mm of the dermal margin of the melanoma, a dermal mitotic rate exceeding 2/mm^2, ulceration, surface, exudates, large pigmented granules and clear-cell differentiation. The median thickness of malignant melanomas was 1.3 mm, but in 4 children, who died with melanoma, median thickness was 2.9 mm. Absence of mitoses, predominance of spindle cells and diffuse maturation favored NS. The median thickness of the NS was 0.7 mm. The most frequent clinical features found in the malignant melanoma were bleeding, ulceration, itching and black or variegated color. Kapur et al.[25] compared expression of Ki-67, p21 and fatty acids synthesis by immunohistochemistry in 10 atypical NS, 28 typical NS, 19 compound melanocytic nevi and 18 malignant melanomas. There was a progressive increase in fatty acid synthesis cytoplasmic expression with statistically significant differences observed between Ns and atypical NS and between atypical NS and malignant melanoma Ki-67 nuclear staining was lower in both typical and atypical forms of Spitz lesions than in malignant melanoma. The degree of p21 nuclear expression in atypical NS was not significantly different than in NS, but was significantly greater than expression in conventional nevi and approached significance after multiple comparisons corrections for malignant melanoma. Thus, a high level of p21 expression makes a tumor more likely to be a typical or atypical NS than a malignant melanoma, especially when coupled with a low Ki-67 index and weak expression of fatty acid synthase. These immunohistochemical observations support the concept that atypical NS are distinct lesions of borderline biologic behavior residing between NS and malignant melanoma. The study also compared a large array of histological features of 16 cases of typical NS in children with 12 typical NS in adults. The adult lesions were significantly more likely to be intradermal and to display dermal fibroplasia, but were histologically similar to their pediatric counterparts in all other respects. Vollmer et al.[26] in his study used previously published data, exponential and γ probability density func-

tions to model statistical distributions of proliferation index (PI), respectively, in NS and melanomas and Bayes rule to estimate the predictive probability that a lesion is a NS, given an observed PI. Results indicate that PIs more than 10% favor a melanoma diagnosis and PIs less than 2%, NS. PI values between 2% and 10% yield various predictive values for NS, depending on the *a priori* probability that the lesion is a NS.

Conclusion

All histopathological, clinical and ancillary criteria must be weighed in the final interpretation of epitheloid/spindle cell lesion. At the present, the final diagnosis remains pathohistological with important emphasis given to clinical impression. Persistently changing lesion indicates malignancy potential of the lesion. Barnhill recommends that all Spitz tumors are completely excised. Atypical tumors should be excised with wider margins up to 1 cm. Patient should be carefully monitored by regular examinations for recurrence and metastasis. The approach should be individual with efforts to avoid over treatment or suboptimal treatment. The need of proper patient counseling cannot be overemphasized, especially considering the psychological aspect of coping with malignant skin tumors[27].

Protocol for Spitz tumor from Barnhill et al.[4]:

1. Examination of the entire lesion,
2. Application of all histopathological, clinical and other attributes for assessing abnormalities present,
3. Seek consultation,
4. Placement into risk category[28] (Table 2),
5. Management of the patient.

TABLE 2
RISK FOR METASTASIS FOR SPITZ TUMORS

Parameter	Score
Age	
0–10	0
11–17	1
Diameter /mm/	
0–10	0
>10	1
Involvement of subcutaneous fat	
absent	0
present	2
Ulceration	
absent	0
present	2
Mitotic activity /mm^2/	
0–5	0
6–8	2
>19	5

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NEVUS SPITZ – PATOHISTOLOŠKA DVOJBA

S A Ž E T A K

1910. godine Darier i Civatte su detaljno opisali brzorastuću, melanocitnu promjenu na vrhu nosa djeteta. Nisu sa sigurnošću mogli reći jeli promjena benigne ili maligne naravi. 1947. godine Sophie Spitz je opisala identičnu leziju kao juvenilini melanoma sa relativno odličnom prognozom. Kasnije je napravljena revizija studije te je zaključeno da se radi o juvelnilnom melanomu koji je benigan, a može se pojaviti čak i u odrasloj dobi. Iako je prognoza odlična, Spitz je opisala jedan slučaj sa fatalnim metastazama. Barnhill i sur. su također opisali smrtni ishod bolesnika za kojeg se vjerovalo da ima Nevus Spitz. I u današnje vrijeme, također postoji nesuglasje oko histopatologije i terminologije promjena koje nisu ni atipični nevus Spitz, ali ni melanom. Kod donošenje konačne odluke, trebaju se uzeti u obzir sva histološka i klinička obilježja promjena. Promjene koje se neprestano mijenjaju upućuju na maligni potencijal. Barnhill i sur. predlažu da se svi tipični Spitz nevusi trebaju operativno odstraniti u cijelosti. Za atipične promjene predlaže rubove do 1 cm. Sve bolesnike treba redovito kontrolirati radi lokalnog recidiva i/ili metastaza.