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Clinical, Dermoscopic, and Histopathological Features of Spitzoid Lesions in Adult Patients: Insights from a Retrospective Study

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Key message: In our cohort of adult patients, certain clinical-dermoscopic characteristics (lower limb location, largest dimension, pigmentation and palpability, multicomponent pattern) were associated with a diagnosis of melanoma in spitzoid lesions.

Key words: Spitz nevus, Reed nevus, Spitzoid tumor, Atypical spitzoid tumor, Melanoma

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ABSTRACT

Introduction: Spitzoid lesions are a group of melanocytic tumors, including Spitz nevi, atypical Spitz tumors, and Spitz melanomas, that pose a considerable diagnostic challenge.

Objectives: Our aim was to describe the clinical, dermoscopic, and histopathological characteristics of spitzoid melanocytic lesions in adult patients in our center and to find possible associations between certain clinical-dermoscopic characteristics and the diagnosis of melanoma.

Methods: We conducted a single-center retrospective study and included all cases of histopathologically-confirmed spitzoid melanocytic lesions diagnosed in adult patients between January 2012 and December 2022. We collected patient demographic characteristics and clinical, dermoscopic, and histopathological characteristics of the studied lesions.

Results: Histopathological examinations of the 103 lesions included in the study revealed four Spitz melanomas (3.9%) and 99 non-melanomas, of which 92 were Spitz nevi (89.3%) and seven atypical Spitz tumors (6.8%). The association between lower limb localization and diagnosis of melanoma was statistically significant (4/4 vs 45/99 patients, P=0.048). A statistically significant association between raised and pigmented morphology and malignant histology was found (4/4 vs 37/99 lesions, P=0.0229). Dermoscopy revealed that a multicomponent pattern was significantly associated with a

diagnosis of melanoma (100% vs 21.6%, *P*<0.01) and that a vascular pattern was significantly associated with atypical Spitz tumors (80% vs 28.8%, *P*=0.0343).

Conclusions: In our cohort, some clinical characteristics (lower limb location, greater size, pigmentation, and palpability) and dermoscopic patterns (multicomponent) were associated with a diagnosis of melanoma. Dermatologists should be careful whenever they encounter any spitzoid-looking lesions in adults, especially in cases of older patients.

Introduction

Spitzoid lesions are a group of melanocytic tumors that pose a considerable diagnostic challenge. The real prevalence of these lesions is undetermined, but it is currently estimated that they represent 1% of all excised melanocytic lesions, with an incidence rate of approximately 1.4 cases per 100,000 individuals. These lesions peak during the second and third decades of life and are uncommon after the sixth decade [1]. This entity was described in 1948 by Sophie Spitz, who presented a case series of 13 "juvenile melanoma" lesions in children, which were histologically diagnosed as malignant melanoma despite lacking aggressive behavior in all except one case [2]. In the following years, these lesions with large epithelioid melanocytes were described in adult patients [3] and considered universally benign, to the extent that cases of Spitz lesions with metastasis were explained as misdiagnoses [4]. In the following decades, the existence of morphologically-spitzoid lesions with malignant behavior was acknowledged, and the term "atypical Spitz tumor" was introduced to classify lesions of undetermined biologic potential [5]. Further attempts at classifying spitzoid lesions have been made, the most recent of which in light of the advances in molecular genetics. Recently, a distinction between "spitzoid melanoma" and "Spitz melanoma" has been introduced: in the revised WHO classification, Spitz melanoma was defined as the malignant counterpart of Spitz nevi, defined both morphologically and genomically [6]. Spitz melanomas are thus currently regarded a subtype of spitzoid melanoma that not only has the morphologic features of Spitz tumors, but also has the genetic hallmarks of Spitz lineage [7].

Methods

We conducted a single-center retrospective study including all cases of histopathologically-confirmed spitzoid melanocytic lesions diagnosed in adult patients (aged 18 or older) between January 2012 and December 2022 at the Department of Dermatology, IRCCS Ospedale Policlinico San Martino, Genoa,Italy. The following patient data were systematically collected and analyzed: histopathological diagnosis, sex, age at diagnosis, anatomical location of the lesion, clinical features, dermoscopic features [8], FISH test results, and further management of the lesions.

All included lesions were completely surgically excised and examined by two qualified dermatopathologists (AG and FC). Conventional histology with hematoxylin and eosin (H&E) staining was performed in all cases, and immunohistochemical markers, such as MIB-1, HMB-45, ki67, p16, S100 and Melan-A, were used wherever deemed necessary for final diagnosis. Fluorescence in situ hybridization (FISH) conventional melanoma probes (Abbott Molecular Laboratories) with probes targeting four loci -cyclin D1 (CCND1), ras responsive element binding protein 1 (RREB1), centromeric enumeration probe control for chromosome 6 and V-myb myeloblastosis viral oncogene homolog (MYB) on 6q23 (Vysis LSI MYB-Spectrum gold) was performed wherever deemed necessary for final diagnosis.

The lesions were classified as benign Spitz nevi (SN), atypical Spitz tumors (AST), or Spitz melanomas (SM) [9].

Statistical Analysis

Data were analyzed using statistical tests (χ^2 test, odds ratio, and Fisher's exact test). P-values <0.05 were considered statistically significant.

Results

One hundred and three patients were included in the present study, for a total of 103 diagnosed lesions. The average age was 32.3 years (median age 32 years), and the female:-male ratio was almost 2:1. The histopathological examination revealed four SM (3.9%) and 99 non-melanomas, of which 92 were SN (89.3%) and seven AST (6.8%). No significant association between sex and diagnosis of melanoma was found. A diagnosis of melanoma was associated with greater mean age (49.3 years vs 31.6 years, *P*<0.01). On the contrary, there was no statistically significant difference in the age of patients with SN and with AST (31.3 years vs 36.7 years, *P*=0.13).

Clinical Features

The clinical characteristics of the studied spitzoid lesions are summarized in Table 1. Spitzoid lesions were located on the

Table 1. Clinical and Dermoscopic Characteristics of Studied Spitzoid Lesions.

	Benign Spitz Nevus	Spitz Tumor	Spitz Melanoma
Number of lesions (%)	92 (89.3)	7 (6.8)	4 (3.9)
Mean (median) dimension in mm	4.8 (5)	10.4 (7)	7.8 (6)
Localization			
Head and neck (%)	4/92 (4.3)	0/7	0/4
Trunk (%)	20/92 (21.8)	1/7	0/4
Upper limbs (%)	19/92 (20.6)	0/7	0/4
Lower limbs (%)	41/92 (44.6)	4/7	4/4
Perineum (%)	1/92 (1.1)	0/7	0/4
Hands and feet (%)	7/92 (7.6)	2/7	0/4
Shape			
Raised (%)	56/92	7/7	4/4
Flat (%)	36/92	0/7	0/4
Color			
Pigmented (%)	70/92 (74.8)	3/7	4/4
Hypo/non-pigmented (%)	22/92 (23.9)	4/7	0/4
Dermoscopic pattern			
Vascular (%)	21/69 (30.4)	4/5	0/4
Multicomponent (%)	15/69 (21.7)	1/5	4/4
Starburst (%)	10/69 (14.5)	0/5	0/4
Reticular (%)	8/69 (11.6)	0/5	0/4
Homogenous (%)	8/69 (11.6)	0/5	0/4
Globular (%)	7/69 (10.1)	0/5	0/4

lower limbs (49/103, 47.6%), trunk (21/103, 20.4%), upper limbs (19/103, 18.5%), hands and feet (9/103, 8.8%), head and neck (4/103, 3.9%), and perineum (1/103, 1%). In particular, SN were localized at the lower limb in 41 out of 92 patients (44.6%), trunk in 20/92 patients (21.8%), in upper limb in 19/92 patients (20.6%), hands and feet in 7/92 (7.6%), in head and neck in 4/92 patients (4.3%), and in perineum in 1/92 (1.1%). Of the AST, the majority were located at the lower limb (4/7 patients), followed by the hands and feet (2/7 patients) and trunk (1/7 patients). All the SM were located on the lower limbs. The association between lower limb localization and diagnosis of melanoma was statistically significant (4/4 patients vs 45/99 patients, P= 0.048).

Concerning clinical features, 77/103 (74.8%) of the lesions were pigmented, while 26/103 (25.2%) were hypo/non-pigmented. In particular, 70/92 (76.1%) of SN, 3/7 (42.9%) of AST, and 4/4 of the malignant lesions were pigmented. The association between pigmentation of lesions and diagnosis of melanoma was not statistically significant (P=0.57). A lack of pigmentation of lesions was more common in AST cases, although without statistical significance (4/7 patients vs 22/96 patients, P=0.066).

Sixty-seven lesions (65.1%) were raised, while 36/103 lesions (34.9%) were flat. Among 92 SN, 56 of them (60.9%) were raised, while 36 of them (39.1%) were flat. The entirety of the AST and of the malignant lesions was raised. Raised morphology was not significantly associated with a diagnosis of melanoma (P=0.29). Flat morphology was associated with a diagnosis of SN (36/92 lesions vs 0/11 lesions, P=0.0076). A statistically significant association between the combination of raised and pigmented morphology and malignant histology was found (4/4 lesions vs 37/99 lesions, P=0.0229). The median diameter of SM was 6 mm (range 5–14 mm), the median diameter of AST was 7 mm (range 5–28 mm), and the median diameter of SN was 5 mm (range 1–9 mm).

Both SM and AST were significantly larger than SN (P<0.01).

Dermoscopic Features

A record of dermoscopic features was available for 78 lesions (69 SN, 5 AST, and 4 SM). Among the 69 SN, the dermoscopic patterns were vascular (Figure 1) in 21 of them (30.4%), multicomponent in 15 of them (21.7%), starburst in 10 of them (14.5%) (Figure 2), reticular in eight of them (11.6%), homogenous in eight of them (11.6%), and globular in seven of them (10.1%). Among AST, the dermoscopic patterns were vascular in 4/5 lesions and multicomponent in

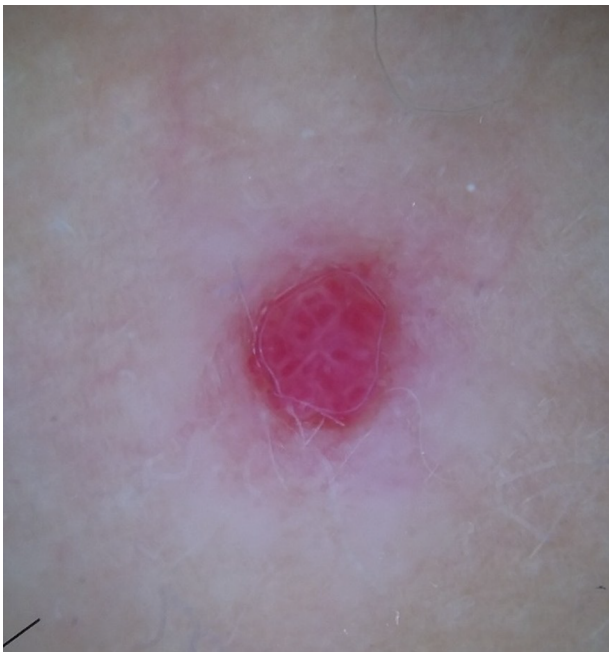

Figure 1. Vascular pattern.

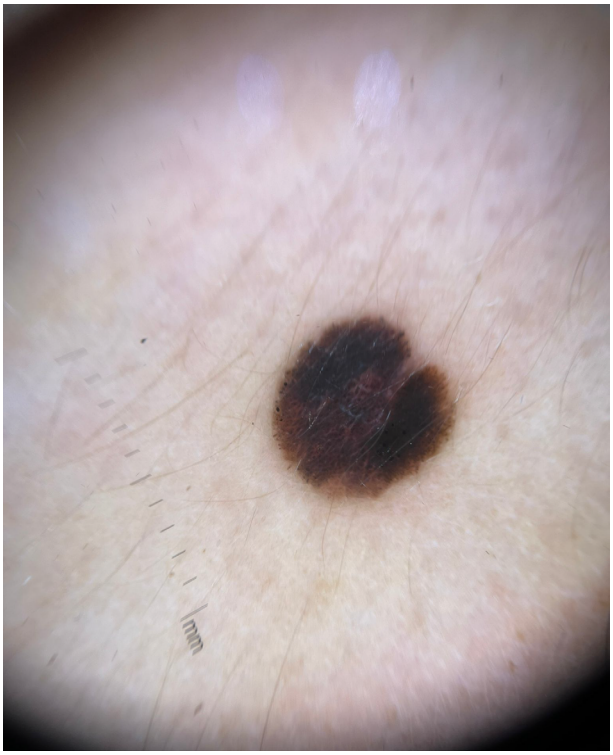

Figure 2. Starburst pattern.

1/5 lesions (Figure 3). SM were described as having a multicomponent pattern in 4/4 cases. Multicomponent pattern at dermoscopy was significantly associated with a diagnosis of melanoma (100% vs 21.6%, $P<0.01$). Vascular pattern was significantly associated with AST (80% vs 28.8%, $P=0.0343$).

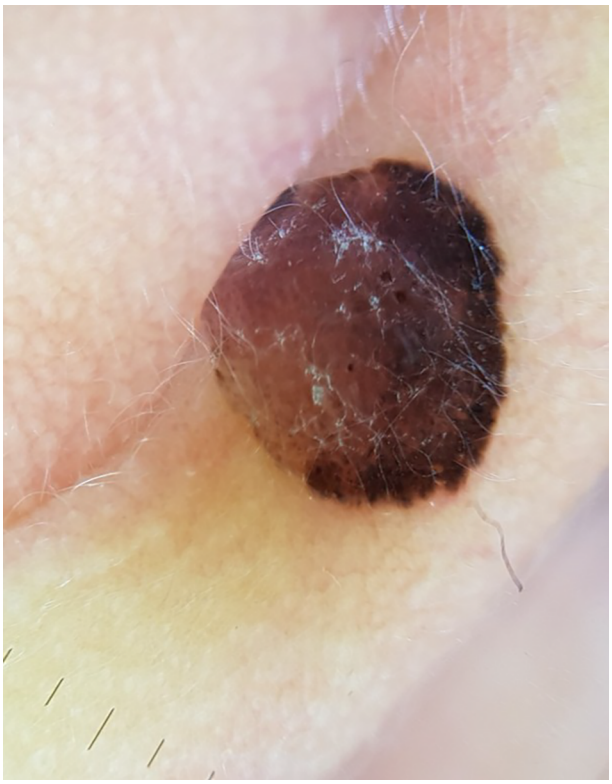

Figure 3. Multicomponent pattern.

Histopathological Features

The histopathological characteristics of the studied spitzoid lesions are reported in Table 2. FISH analysis was performed in 24/103 (24.3%) lesions, including 16/92 (17.4%) SN, 4/7 AST, and 4/4 melanomas. The entirety of benign and atypical lesions was reported as negative at FISH analysis, while 3/4 melanomas (75%) were positive. A diagnosis of melanoma was associated with positive FISH analysis ($P<0.01$). The SM in our population were invasive, with an average Breslow thickness of 0.98 mm (0.85–1.25 mm).

Management and Outcomes

The majority of the SN (80.4%) were managed by simple excision. In a small percentage of cases (19.6%), a re-excision was performed to obtain wider free margins. On the contrary, all AST were re-excised, but none underwent sentinel lymph node biopsy. All the SM underwent re-excision with 1 cm margins, and 2/4 patients underwent sentinel lymph node biopsy, which was negative in both cases. After a follow-up ranging from two to 12 years, all the patients with a diagnosis of SM or AST were alive, with no signs of metastases or recurrence.

Discussion

In our population, the incidence rate of spitzoid lesions was significantly higher in females, confirming the findings of

Table 2. Histopathological Characteristics of Studied Spitzoid Lesions.

	Benign Spitz Nevus	Spitz Tumor	Spitz Melanoma
Symmetry (%)	66/88 (75.0)	4/7	1/4
Circumscription (%)	75/88 (85.2)	7/7	2/4
Epidermal hyperplasia (%)	66/90 (73.3)	7/7	1/4
Effacement of epidermis	0/92	2/7	2/4
Ulceration	0/92	1/7	0/4
Junctional nesting (irregular) (%)	52/78 (66.7)	3/7	0/4
Junctional nesting (confluent) (%)	16/78 (20.5)	4/7	4/4
Pagetoid S (focal) (%)	40/81 (49.4)	6/7	1/4
Pagetoid S (extensive) (%)	1/81 (1.2)	0/7	3/4
Deep Dermal Extension (%)	2/88 (2.3)	1/7	0/4
Maturation – partial (%)	28/76 (36.8)	4/7	2/4
Maturation - present (%)	15/76 (19.7)	1/7	0/4
Mitoses (0-2) (%)	2/83 (2.4)	0/7	0/4
Mitoses (2-6) (%)	80/83 (96.4)	4/7	4/4
Mitoses (>6) (%)	1/83 (1.2)	3/7	0/4
Pleomorphism – focal (%)	15/91 (16.5)	3/7	3/4
Pleomorphism - extensive	0/91	0/7	1/4
Necrosis	0/91	0/7	0/4
P16 – focal (%)	47/62 (75.8)	6/7	2/4
P16 - extensive (%)	13/62 (21)	1/7	0/4

other studies [10,11]. The female prevalence was especially marked in SN, while it was not noted in melanomas. This result could be explained by a greater participation of females to skin cancer screening programs, since females are more likely to perform self-examination and to undergo regular check-ups than are males [12].

While the overall incidence of cutaneous melanoma is higher in males [13], no significant association between sex and diagnosis of melanoma was found in ours and in the previous study [10]. On the other hand, melanomas were associated with higher average age, confirming the findings of Lallas et al., who reported that the risk of finding melanoma when excising a spitzoid-looking lesion is significantly higher with increasing age [10]. In particular, they found that the probability of finding a melanoma when excising a spitzoid-looking lesion was higher than 50% in patients aged 50 and above.

Lower limbs are reported in the literature as the most common location for both SN and SM [10], as we found in our study. However, we found for the first time a correlation between malignant histology and lower limb localization. On the contrary, Cesinato et al. [11] reported a greater prevalence of spitzoid lesions on the lower limbs only in females, while in males the most common location was the trunk.

The entirety of the malignant lesions in our population was raised and pigmented. While pigmentation and raised morphology alone were not significantly associated with a diagnosis of melanoma, the combination of both characteristics presents a significant correlation with malignant histology. This finding is partially in agreement with the literature [10], in which a correlation between nodular morphology and malignant histology is reported, but significant differences in pigmentation status between benign and malignant lesions were not found. The differences between our results and those reported in previous studies could be explained by the small number of SM cases in our population. Interestingly, a lack of pigmentation was more common in AST, which confirms the findings of De Giorgi et al. [14], who found that a significant percentage of AST were hypo- or amelanotic (45.3%).

In our population, malignant lesions were significantly larger than were benign lesions ($P<0.01$). This is aligned with the current knowledge on all kinds of melanocytic lesions, for which a 6 mm cutoff has been widely adopted as an indicator of increased suspicion [15]. However, we believe that this finding has not been previously reported specifically for spitzoid lesions in adult patients. As a general rule, we propose that the size of a spitzoid lesion should be a major factor when establishing whether to proceed with an excision.

Our results confirm that spitzoid lesions can present a variety of dermoscopic patterns. The most prevalent patterns were starburst in SN and vascular in AST, which confirm the findings of previous studies [8,14]. All lesions diagnosed as melanoma presented a multicomponent pattern, and the latter was significantly associated with malignant histology. The multicomponent pattern, which is characterized by a combination of different dermoscopic features, generally arranged asymmetrically, is particularly indicative of malignancy. As underlined by Lallas et al. [9], even though benign Spitz nevi can be characterized by a multicomponent pattern (2.3% in our population), these lesions cannot be differentiated from melanoma and should be excised. Differently, due to the fact that many AST presented a vascular pattern, which is characterized by uniformly distributed multiple glomerular vessels, these lesions need to be carefully differentiated from other lesions with the same pattern, such as Bowen carcinoma [14].

While in our study we found that some clinical characteristics (lower limb location, greater size, pigmentation, and palpability) and dermoscopic patterns (multicomponent) were associated with malignant histology, we believe that dermatologists should be careful whenever they encounter any spitzoid-looking lesions in adults, especially in cases of older patients. Lallas et al. [8] propose excision or extremely close monitoring of all spitzoid lesions, including symmetric ones, in patients over 12 years old. However, we think that a very close dermoscopic follow-up often presents some difficulties in a public healthcare setting, and an excision is recommended in the great majority of spitzoid lesions in adult patients in our center.

In our study, FISH positivity correlated with a diagnosis of melanoma, as previously reported by other studies involving spitzoid lesions [16].

In our population, the majority of the SN (89.8%) were managed by simple excision, followed by re-excision in some cases (10.2%). Despite the benign nature of Spitz nevi, a 2002 survey of dermatologists in the United States reported that 69.3% of the respondents would re-excise an incompletely removed Spitz nevus [17]. However, it has been more recently suggested that, at least in pediatric patients, clinical follow-up could be sufficient in incompletely excised histologically-confirmed Spitz nevi [18]. In any event, since it is known that pediatric spitzoid lesions are characterized by an overwhelmingly favorable prognosis, these considerations should not be automatically applied to adult patients. Considering the difficulties in histopathologically characterizing spitzoid lesions, we suggest that excisional biopsies with clean margins should be obtained for maximum diagnostic certainty.

In our study, most AST were re-excised (68.2%), but none underwent sentinel lymph node biopsy. Since AST are regarded as lesions with uncertain malignant potential, wide local excision with 5–10 mm clear margins has been suggested [14]. The appropriateness of sentinel lymph node biopsy in these lesions has been long debated. Although cell deposits are often detected in the sentinel lymph nodes of patients with AST, this does not seem to be predictive of a poorer outcome for these patients [19]. Consequently, as of 2024, sentinel lymph node biopsy is no longer recommended as a standard procedure in AST [20].

The prognosis of SM in adults is considered similar to that of other variants of melanoma of equal Breslow thickness [21]; the management is therefore generally the same. However, a 2019 study reported that SM tends to present favorable prognostic histopathological variables, such as less thickness and lower mitotic rate, the absence of ulceration, neurotropism and lymphovascular invasion, and the presence of tumor-infiltrating lymphocytes and are consequently associated with better survival outcomes [22]. This knowledge is confirmed by our data on the follow-up of the four patients with melanoma, who are all still alive and with no sign of recurrence or metastasis.

Our study has several limitations. First and foremost, the retrospective nature of the study limited the amount of data that could be collected; for example, a significant percentage of lesions lacked a dermoscopic description. Moreover, the number of included lesions was relatively small, thus reducing the significance of our findings.

Conclusion

Spitzoid are a challenging entity, both in terms of diagnosis and management. In our retrospective study including 103 spitzoid lesions excised in adult patients, we found that lower limb location, greater size, pigmentation, palpability, and multicomponent dermoscopic pattern were associated with a diagnosis of Spitz melanoma. Nonetheless, in agreement with the current management guidelines [8], we believe that, particularly in adult patients, dermatologists should be cautious whenever they encounter any spitzoid-looking lesion.

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