Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2024;33:49-52
doi: 10.15570/actaapa.2024.2

Digging into uncertainty: a case report on Spitz lesions

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Abstract

Spitz lesions represent a spectrum of melanocytic proliferations, and they include Spitz nevi, atypical Spitz tumors, and Spitz melanomas. Atypical Spitz tumors are intermediate melanocytic lesions with features between benign Spitz nevi and malignant Spitz melanomas. They often present a diagnostic challenge to pathologists and dermatologists alike because they can mimic melanoma, especially high-grade atypical Spitz tumors. Importantly, they present a relevant clinical management challenge because definite recommendations for their management and treatment have not yet been established. Here we present the case of a young patient with a high-grade atypical Spitz tumor along with the diagnostic procedure and further management. We also review potential pitfalls in the literature that should alert clinicians to the more aggressive potential of the lesion, such as some *BRAF* fusions.

Keywords: atypical Spitz tumor, intermediate melanocytic tumor, *AGK-BRAF* fusion

Received: 2 February 2023 | **Returned for modification:** 8 May 2023 | **Accepted:** 16 October 2023

Introduction

Spitz lesions represent a spectrum of melanocytic proliferations, including benign Spitz nevi, atypical Spitz tumors with intermediate malignant potential, and malignant Spitz melanomas. Among the Spitz lesions, Spitz nevi are the most common and are mainly found in children and young adolescents. Atypical Spitz tumors are rarer than Spitz nevi, but they also appear in the same age group (1). They can be divided into two groups: low- and high-grade. This subtype can guide further management (2). However, the management of atypical Spitz tumors is challenging and often requires a multidisciplinary approach because definite recommendations for management and treatment have not yet been established.

Case report

A 23-year-old female patient presented to the dermatology department with a long-standing pink papule on her right thigh (Fig. 1). The patient could not remember how long the lesion had been present. The clinical and dermatoscopic examinations were inconclusive; hence, she was referred for total excision and histopathological examination of the lesion. Low-magnification pathological examination revealed a small, symmetrical, and well-circumscribed compound melanocytic neoplasm (Fig. 2). Moreover, at high magnification, pathological examination revealed melanocytes organized in large nests and short fascicles. The constituent melanocytes were plump and varied in shape, from epithelioid to spindle-like. Vertically oriented nests of melanocytes were observed at the dermoepidermal junction. At the central part of the lesion, there were large melanocytes in a pagetoid pattern at all levels of the epidermis, with a non-brisk lymphocytic infiltrate. Ulceration and mitotic activity were not observed (Fig. 3). Owing to the marked atypia of melanocytes, a significant diagnostic dilemma emerged in differentiating high-grade atypical Spitz tumor and melanoma. Immunohistochemical studies revealed negative BRAF V600E and n-RAS staining. Furthermore, a mosaic pattern of preserved p16, intradermally negative HMB45 that was positive in the junctional component was observed. MelanA/Ki67 showed no proliferation activity in intradermal melanocytes. ALK, ROS1, and pan-TRK staining was negative. Based on inconclusive immunohistochemical studies, mutational studies using RNA next-generation sequencing (NGS) have revealed an *AGK-BRAF* fusion. Taking all the data into account, the lesion was finally confirmed to be a high-grade atypical Spitz tumor. *BRAF* fusion has been proven to have a clear molecular genetic background without other genetic occurrences, such as mutations, deletions, and fusions. Owing to the final diagnosis of a high-grade atypical Spitz tumor, re-excision with 10 mm margins was recommended. Further management of the patient included regular follow-up visits every 6 months for at least 5 years, in accordance with recent recommendations (2). Due to the *AGK-BRAF* fusion, she was also referred for locoregional lymph node sonography twice yearly for 5 years. During the follow-up of 2 years, we observed no recurrence or metastasis, and locoregional lymph node sonography was negative each time. However, we will continue with patient follow-up.

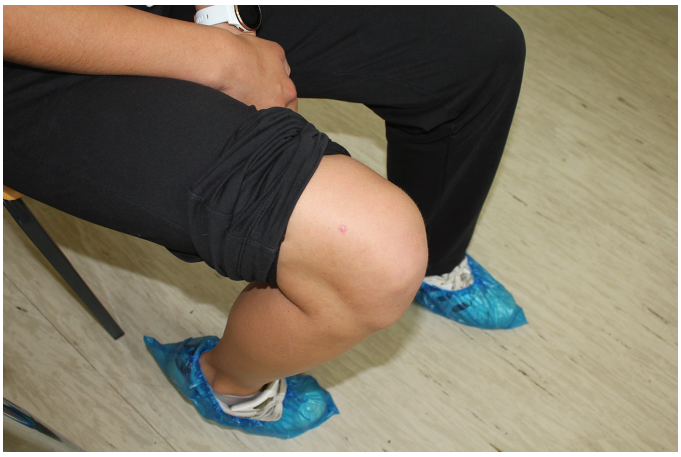

Figure 1 | Pink papule on the patient's right thigh.

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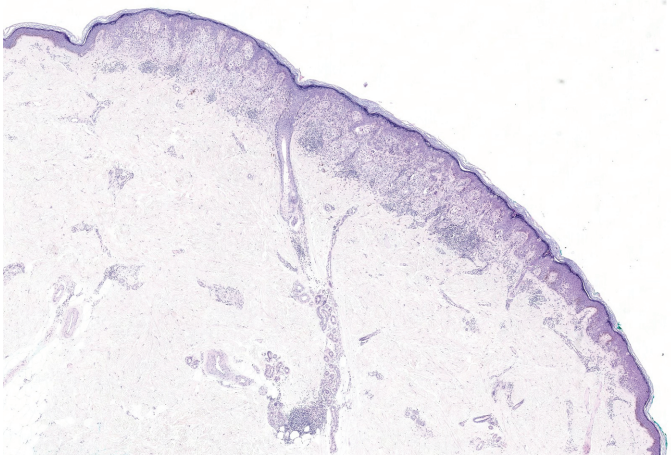

Figure 2 | Histological examination (low magnification): a small, symmetrical, and well-circumscribed compound melanocytic neoplasm identified as an atypical high-grade Spitz tumor.

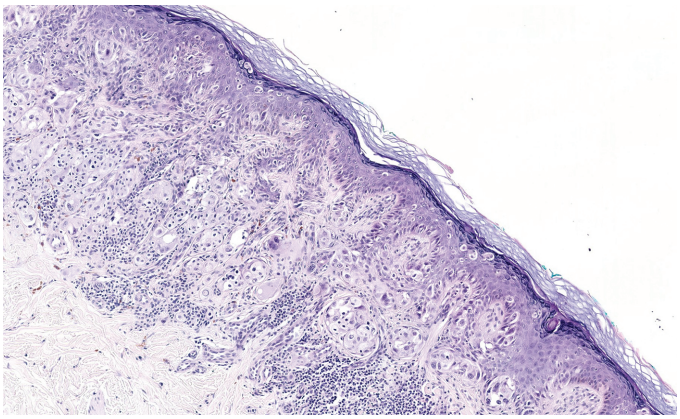

Figure 3 | Histological examination (high magnification): high-grade atypical Spitz tumor. Melanocytes are organized in large nests and short fascicles. Constituent melanocytes are plump and vary in shape from epithelioid to spindle-like. Vertically oriented nests of melanocytes are seen at the dermoepidermal junction. At the central part of the lesion there are large melanocytes in a pagetoid pattern at all levels of the epidermis. There is a non-brisk lymphocytic infiltrate. There is no significant mitosis in the melanocytes.

Discussion

Spitz nevi were initially termed juvenile melanomas because of their histological resemblance to melanomas. However, the young age of patients and their relatively good prognosis led to the assumption that their nature is indolent, unlike that of melanomas (3). Spitz lesions present epithelioid and spindle cell melanocyte morphology. Spitz nevi are rare; of all excised melanocytic lesions in all age groups, only 1% to 2% were diagnosed as Spitz nevi (4). Its incidence varies between one and 10 cases per 100,000 individuals (4). Many Spitz nevi are difficult to distinguish from melanomas (4). Therefore, the discovery of *BRAF* mutations in cancers, including melanoma, and the absence of *BRAF* mutations in Spitz nevi led to an easier distinction between the two. Moreover, kinase fusions and translocations, including *ROS1*, *ALK*, *RET*, *BRAF*, *NTRK1*, *MET*, *NTRK3*, and *MAP3K8*, which are commonly found in Spitz lesions, are of additional help (5, 6).

The clinical differential diagnosis includes melanoma and other melanocytic lesions, including congenital melanocytic nevus, blue nevus, atypical nevus, and Clark nevus. Due to the pink or red coloration of the lesions, vascular lesions are also included in the differential diagnosis; namely, hemangioma, pyogenic granuloma, and angiofibroma. Finally, other lesions, such as dermatofibroma, seborrheic keratosis, or basal cell carcinoma, can resemble Spitz lesions (4). Nevertheless, the key question regarding diagnosis is the differentiation between high-grade atypical Spitz tumors and (Spitz) melanomas.

Diagnostic dilemma

Atypical Spitz tumors pose a diagnostic challenge to both clinicians and pathologists because they clinically and histologically mimic melanoma. Therefore, a stepwise histopathological approach is useful for differentiating between melanoma, Spitz nevus, or atypical Spitz tumors (2). In many cases, expert consultation is required to obtain the final diagnosis (2).

Clinical presentation

There are some clinical differences that can help differentiate Spitz lesions. Clinical characteristics such as patient age, lesion location, lesion appearance (color, shape, and size), and dermoscopic patterns are important (4).

Spitz lesions can present in all age groups. However, both Spitz nevi and atypical Spitz tumors are most frequent in people between 15 and 35 years old, with a mean age of 22 years, whereas Spitz melanomas present at a mean age of 55 years (7). The distribution of Spitz lesions appears to be equal in both sexes (7). All Spitz lesions most commonly appear in the lower extremities, followed by the trunk and upper extremities (4). Nevertheless, in studies exclusively observing pediatric cases, Spitz nevi and atypical Spitz tumors were more frequently located in the head and neck region (8).

Spitz lesions vary in color, ranging from pink to black. Spitz nevi are typically less than 6 mm in diameter and are dome-shaped, flat, or polypoid. Atypical Spitz tumors range between 5 and 10 mm in diameter and present as plaques or nodules. Spitz melanomas are typically nodular and larger than atypical Spitz tumors, with a mean diameter of 1 cm (4).

The most frequent dermatoscopic pattern found in Spitz nevi is a starburst pattern, followed by a dotted vessel pattern and globular pattern (9, 10). However, atypical Spitz tumors most commonly demonstrate a multicomponent and nonspecific pattern, followed by a pattern of dotted vessels and white lines (11, 12). The white line pattern is indistinguishable from melanoma, which shows significant clinical, dermatoscopic, and histological overlap with non-pigmented Spitz nevi (12). Nodular Spitz lesions and lesions with asymmetrically distributed spitzoid features should be excised regardless of patient age (9).

Histopathologic features

The hallmark of Spitz melanocytic proliferation upon histological examination is the presence of epithelioid and/or spindled melanocytes with abundant eosinophilic cytoplasm and frequently associated hyperplasia of the epidermis (13). Atypical Spitz tumors show histopathological characteristics of Spitz nevi and melanomas. They present with at least one of the following: asymmetry, ulceration, poor lateral demarcation, lack of maturation in the dermis, absence of Kamino bodies, greater extension downward, mitosis in the dermis (> 2–6 mitoses/mm^2), and abundant isolated melanocytes in the superficial dermis (1). Histopathological features that are correlated with a higher risk of metastasis are asymmetry, ulceration, a high degree of mitosis in the deep dermal part, and high-grade cytological atypia (14). However, there

is no single parameter that would place the lesion in the atypical Spitz tumor group.

Ancillary methods

Whenever histopathology is insufficient to make the final diagnosis, ancillary methods are utilized, such as immunohistochemical staining, fluorescence in situ hybridization (FISH), or molecular genetic analysis (1, 13).

Molecular genetic analysis reveals driver genetic aberrations required for melanocyte proliferation, whereas additional genetic events, such as biallelic inactivation of *CDKN2A* and *TERT* promoter mutations, are required for the development of a malignant Spitz lesion in most cases, but not in all cases (13). Identification of a primary genetic alteration helps distinguish a Spitz lesion from other melanocytic tumors. However, it cannot distinguish between atypical Spitz tumors and Spitz melanomas (15). Some driver genetic aberrations are more commonly associated with the benign spectrum of Spitz lesions, namely 11p amplification/*HRAS* mutation and tyrosine kinase fusions, whereas others are more common in atypical or malignant Spitz lesions, such as serine/threonine kinase fusions. The latter also has the potential for aggressive biological behavior. However, none of the genetic aberrations has been found to be specific to a particular Spitz lesion (13).

BRAF fusions in melanocytic Spitz lesions are rare, occurring in 5% to 6% (15). However, when present, they are more common in atypical or malignant Spitz lesions because they are more likely to develop chromosomal copy number imbalances and progress to Spitz melanoma (15, 16). Chromothripsis is another mechanism involved in melanoma development (17). There are numerous fusion partners with the *BRAF* gene, with *AGK-BRAF* being the most common (13, 16). An *AGK-BRAF* fusion was also observed in our case report. *BRAF* fusions can only be reliably detected by NGS, in contrast to tyrosine kinase fusions (*ALK*, *ROS*, and *NTRK*) and *MAP3K8* fusions, which can also be detected by immunohistochemistry and FISH, respectively (13, 15). Molecular genetic analysis has two limitations: availability and cost. However, identification of the driver genetic change is particularly important in (Spitz) melanoma because of the availability of targeted therapies. Treatment with BRAF or MEK inhibitors appears to be effective for BRAF-fused melanomas (15).

Prognosis

Atypical Spitz tumors, especially high-grade tumors, have been reported to metastasize to sentinel lymph nodes in up to 30% of cases (18). However, the 5-year survival rate exceeds 99% (19). This is because the disease does not progress beyond the nodal basin (20, 21). This was also confirmed by a recent meta-analysis in which the outcome of patients with a positive sentinel lymph node biopsy did not differ from that of patients with a negative sentinel lymph node biopsy (19). Furthermore, complete lymphadenectomy and adjuvant therapy are no longer recommended for patients with positive sentinel lymph node biopsy (19, 20). According to the available data, sentinel lymphadenectomy in atypical Spitz tumors does not have significant diagnostic value. However, whether removal of metastatic lymph nodes is of therapeutic benefit remains unclear (20). Additional techniques, such as molecular genetic analysis of the primary tumor, might have a role in predicting which atypical Spitz tumor might have the potential to progress beyond the sentinel lymph node. It has been shown that atypical Spitz tumors with chromosomal copy number aberrations, homozygous deletions of 9p21 (22), *BRAF* or *MAP3K8* fusions (2, 23), and *TERT* promoter mutations (2, 24) may correlate with tumor progression beyond the sentinel lymph node. Therefore, additional techniques, such as molecular genetic analysis, are not only important for the correct histopathological diagnosis but also for further management and prognosis of the patient.

Management

Atypical Spitz tumors can be low- or high-grade. According to recent recommendations by experts, their management differs (2). In low-grade atypical Spitz tumors, excision with a 2 mm margin is recommended. In cases of complete removal of the tumor, re-excision is not mandatory but is recommended. In high-grade atypical Spitz tumors, excision with a 5 to 10 mm margin and follow-up physical examination every 6 months for at least 5 years is recommended (2). Sentinel lymph node biopsy is not recommended; however, caution is recommended in cases in which *BRAF* or *MAP3K8* fusions (2, 23), *TERT* promoter mutations (2, 24), or homozygous 9p21 deletions (22) are present because these cases may follow a more aggressive course. In such cases, 10 mm margins are recommended (2) and possibly locoregional lymph node sonography every 6 months for at least 5 years. This recommendation was also followed in our patient because of the *AGK-BRAF* fusion.

Conclusions

Atypical Spitz tumors present not only a diagnostic challenge but also a management challenge. Because many questions regarding diagnosis, prognosis, and further management remain, a multidisciplinary approach is needed in challenging cases. Moreover, new studies are needed to clarify existing issues, such as the precise malignant potential of atypical Spitz tumors, screening for metastases, and predictors of metastatic disease.

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