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Spitz melanocytoma with *AKAP9::BRAF* fusion: clinicopathologic and molecular insights

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Abstract

Spitz melanocytoma is a melanocytic neoplasm of intermediate malignant potential. *BRAF* fusions are rare in Spitz tumors, and *AKAP9::BRAF* rearrangements are exceptionally uncommon. We describe the clinicopathological and molecular features of a Spitz melanocytoma in a 41-year-old woman, analyzed by next-generation sequencing (NGS). The lesion was a well-circumscribed dermal proliferation of spindle melanocytes within a collagen-rich stroma, lacking cytological atypia, mitoses, or necrosis. Immunohistochemistry demonstrated positivity for S100, SOX10, and MART1, weak HMB45 staining, and a very low proliferative index (<1%) on MART1/Ki-67; preferentially expressed antigen in melanoma protein (PRAME) expression was weak and focal. NGS identified an *AKAP9* (exon 32)::*BRAF* (exon 9) fusion, without *TERT* promoter mutations or other high-risk alterations. This case highlights a rare molecular subset of Spitz melanocytoma and underscores the importance of integrated molecular and histopathological assessment for accurate diagnosis, prognostic evaluation, and potential targeted therapy.

Introduction

Spitz melanocytoma is a rare melanocytic lesion of uncertain malignant potential that presents a significant diagnostic challenge for dermatopathologists because of its intermediate biological behavior and morphological overlap with both benign Spitz naevi and malignant melanoma. It exhibits distinct histopathological and genetic characteristics that differentiate it from conventional melanocytic neoplasms.[1] Consequently, the World Health Organization (WHO) has recently recommended the term *Spitz melanocytoma* instead of *atypical Spitz tumor*, reflecting the lesion's intermediate biological potential and promoting consistency in dermatopathological nomenclature.[2]

From a molecular perspective, the mitogen-activated protein kinase (MAPK) pathway plays a central role in melanocytic tumorigenesis. The *BRAF* gene encodes a serine/threonine kinase within the RAF family, regulating MAPK/ERK signaling – critical for cell proliferation, differentiation, and survival. Oncogenic activation of *BRAF*, most commonly through the V600E substitution, is among the most frequent driver events in cutaneous melanoma.[3] However, point mutations are not the sole mechanism of *BRAF* activation. Structural rearrangements that fuse the *BRAF* kinase domain with upstream partners can produce constitutively active kinases independent of canonical upstream signaling, representing a distinct molecular subset of melanocytic lesions. *BRAF* fusions have been identified in approximately 5% of Spitz neoplasms, although their clinical and histopathological features remain incompletely defined.[4]

A-kinase anchor protein 9 (AKAP9) is a scaffolding protein that organizes multiple signaling complexes, including components of the MAPK and protein kinase A (PKA) pathways. Rare

AKAP9::BRAF fusions have been reported in melanocytic tumors, potentially driving oncogenesis through aberrant activation of downstream signaling cascades.[5,6] Advances in next-generation sequencing (NGS) have enabled precise detection of these rare fusion events, offering valuable diagnostic, prognostic, and therapeutic insights.[7]

Histopathological evaluation alone often proves insufficient to distinguish benign from malignant Spitz lesions harboring kinase fusions, owing to the substantial overlap within the morphological spectrum.[8,9] Emerging evidence suggests that specific kinase fusions may correlate with distinct cytomorphological features and biological behavior, underscoring the importance of integrating histopathology with molecular analysis.[10] Moreover, the identification of actionable gene fusions holds direct relevance for personalized therapy, as emerging kinase inhibitors may offer targeted treatment options in selected cases.[11]

Case Report

A 41-year-old woman with no significant personal or family medical history presented with a 1.5×1.2 cm nodular lesion on the left buttock. The lesion displayed irregular pigmentation and had gradually enlarged over two years. Clinical suspicion of malignancy prompted an excisional biopsy.

Histopathological examination revealed an acanthotic epidermis with a thin layer of compact orthokeratotic hyperkeratosis. In the dermis, a well-circumscribed melanocytic proliferation with a wedge-shaped profile was observed. The lesion consisted predominantly of spindle-shaped, monomorphic “Spitzoid” melanocytes arranged in nests and fascicles of variable size, as well as single units embedded within a dense desmoplastic stroma. Occasional balloon-like cells with foamy cytoplasm and rare multinucleated “wreath-like” cells were scattered throughout the lesion. The proliferation was largely confined to the dermis, with only a single micronest extending into subcutaneous adipose tissue. No junctional component, mitotic figures, or necrosis were identified (Figure 1 a-c).

Although primarily composed of spindle melanocytes, rare balloon-like and multinucleated cells were also present. No morphological evidence suggested a distinct secondary cell population, and molecular analysis did not reveal any additional pathogenic alterations; in particular, no *BAP1* rearrangement was detected.

Double immunostaining for MART1/Ki-67 demonstrated low proliferative activity (<1%) (Figure 1d). Preferentially expressed antigen in melanoma protein (PRAME) expression was weak and patchy (Figure 1e), while beta-catenin was negative in the nucleus but positive in the cytoplasm. The immunophenotype was positive for S100 (cytoplasmic with occasional nuclear staining), SOX10,

MART1, HMB45 (weak), and MITF (strong), and negative for desmin, ALK (clone 01), and panTRK. p16 staining displayed a normal mosaic pattern.

Fluorescence *in situ* hybridization analysis for *EWSR1* and *FUS* rearrangements was negative, excluding soft tissue sarcomas. NGS identified an *AKAP9* (exon 32)::*BRAF* (exon 9) fusion transcript. No pathogenic *TERT* promoter variants were detected, and NGS analysis revealed no pathogenic variants or copy number alterations in *TP53* or *PTEN*, genes frequently implicated in melanomagenesis.[5] Array comparative genomic hybridisation was not performed.

Discussion

This case represents a Spitz melanocytoma harboring an *AKAP9::BRAF* fusion – a rare molecular event with only isolated reports in melanocytic lesions.[6,8] *BRAF* fusion-positive melanocytic lesions, including *AKAP9::BRAF*, have been described in Spitz neoplasms and other melanocytic tumors, suggesting a shared oncogenic mechanism through constitutive activation of the MAPK pathway.[9] The presence of *BRAF* fusions is increasingly recognized as a distinct molecular subset with potential diagnostic and therapeutic implications.[11]

Histologically, the lesion lacked definitive features of malignancy, and the clinical behavior of *BRAF* fusion-positive Spitz melanocytoma is generally indolent, supporting a conservative management approach. The lesion was completely excised with a 1 cm margin, without sentinel lymph node biopsy, in accordance with current recommendations for low-risk atypical Spitz neoplasms.[12] High-risk features in Spitz melanocytomas, as defined by the Children's Oncology Group, include elevated mitotic rate, deep subcutaneous extension, ulceration, tumor-infiltrating lymphocytes, necrosis, and marked cytological atypia.[13] None of these features were present, and subcutaneous extension was minimal, reinforcing a low-risk designation. At six months post-excision, the patient remains disease-free with no evidence of local recurrence or metastasis, and clinical follow-up is ongoing.

The biological significance of *AKAP9::BRAF* fusions is an area of active investigation. The fusion preserves the *BRAF* kinase domain, resulting in constitutive MAPK signaling independent of upstream regulation. Current evidence suggests that, while the fusion partner may not substantially alter morphological or clinical behavior, accumulating case reports are crucial to refining genotype-phenotype correlations and risk stratification in Spitz melanocytomas. Additionally, the presence of kinase fusions may offer opportunities for targeted therapy in selected cases. Although complete surgical excision remains the standard of care for localized Spitz melanocytomas, understanding molecular drivers can inform the use of emerging kinase inhibitors in cases of recurrence, metastasis, or unresectable disease.

From a broader perspective, *BRAF* fusions define a distinct molecular subclass of melanocytic lesions. These alterations are more frequently observed in younger patients and are commonly associated with Spitzoid morphology. Importantly, they differ from conventional *BRAF* V600E-mutant melanomas in both clinical behavior and prognosis. Comparative studies indicate that *BRAF* fusion-associated lesions typically exhibit indolent biological behavior and low metastatic potential, although rare aggressive cases have been documented.[5,10] Integration of histopathological evaluation, immunophenotypic characterization, molecular profiling, and relevant clinical data is therefore essential to ensure accurate classification, prognostication, and therapeutic decision-making.

Emerging genomic technologies, including whole-exome sequencing and RNA-based fusion detection, continue to expand our understanding of kinase fusions in melanocytic tumors. These tools enable the identification of rare events such as *AKAP9::BRAF*, which may be missed by conventional molecular assays. Furthermore, large-scale genomic studies are beginning to reveal potential correlations between fusion type, histopathological features, and clinical outcomes, paving the way for personalized risk assessment and management.[14]

Long-term follow-up is essential to fully elucidate the behavior of *BRAF* fusion-positive Spitz melanocytoma. While most reported cases follow an indolent course, the rarity of these lesions and the limited availability of longitudinal data necessitate continued surveillance and reporting. Prospective registries and multicenter collaborations may provide the statistical power required to define prognostic factors and establish therapeutic guidelines.

Conclusions

This report describes a rare case of Spitz melanocytoma harboring an *AKAP9::BRAF* fusion, contributing to the growing body of evidence on the molecular landscape of these tumors. It highlights the importance of integrating histopathology, immunohistochemistry, and molecular profiling for accurate diagnosis, risk assessment, and potential therapeutic guidance. Although surgical excision remains the cornerstone of treatment, identification of actionable kinase fusions aligns with the principles of precision oncology and may guide targeted therapies in selected clinical contexts. Continued molecular characterization and long-term follow-up are warranted to clarify the full spectrum of clinical behavior, prognostic significance, and therapeutic vulnerabilities of *BRAF* fusion-positive Spitz melanocytomas.

References

1. Hagstrom M, Fumero-Velázquez M, Dhillon S, et al. An update on genomic aberrations in Spitz naevi and tumours. Pathology 2023;55:196-205.
2. Elder DE, Massi D, Scolyer RA, Willemze R, editors. WHO classification of skin tumours. 4th ed. Lyon: International Agency for Research on Cancer; 2018.
3. Castellani G, Buccarelli M, Arasi MB, et al. BRAF mutations in melanoma: biological aspects, therapeutic implications, and circulating biomarkers. Cancers (Basel) 2023;15:4026.
4. Wiesner T, He J, Yelensky R, et al. Kinase fusions are frequent in Spitz tumours and Spitzoid melanomas. Nat Commun 2014;5:3116.
5. Quan VL, Panah E, Zhang B, et al. The role of gene fusions in melanocytic neoplasms. J Cutan Pathol 2019;46:878-87.
6. Perron E, Pissaloux D, Neub A, et al. Unclassified sclerosing malignant melanomas with AKAP9-BRAF gene fusion: a report of two cases and review of BRAF fusions in melanocytic tumors. Virchows Arch 2018;472:469-76.
7. Roth A, Lampley N 3rd, Boutko A, et al. Next-generation sequencing improves agreement and accuracy in the diagnosis of Spitz and spitzoid melanocytic lesions. J Cutan Pathol 2022;49:868-74.
8. Kim D, Khan AU, Compres EV, et al. BRAF fusion Spitz neoplasms; clinical morphological, and genomic findings in six cases. J Cutan Pathol 2020;47:1132-42.
9. Sharma N, Patel P, Chen A, et al. The clinical, morphologic, and molecular spectrum of BRAF fusion spitz tumors. Am J Surg Pathol 2024;48:1588-99.
10. Daruish M, Ambrogio F, Colagrande A, et al. Kinase fusions in Spitz melanocytic tumors: the past, the present, and the future. Dermatopathology (Basel) 2024;11:112-23.
11. Bhamidipati D, Pellatt A, Subbiah V. Targeting all BRAF alterations: the (re)-search continues. JCO Precis Oncol 2024;8:e2300670.
12. Mazza M, Cavallin F, Galasso E, et al. Sentinel Lymph Node Biopsy in Atypical Spitz Tumor: A Systematic Review. J Clin Med 2024;13:3232.
13. Sargen MR, Barnhill RL, Elder DE, et al. Evaluation and surgical management of pediatric cutaneous melanoma and atypical Spitz and non-Spitz melanocytic tumors (melanocytomas): a report from Children's Oncology Group. J Clin Oncol 2025;43:1157-67.
14. Hillen LM, Van den Oord J, Geybels MS, et al. Genomic landscape of spitzoid neoplasms impacting patient management. Front Med (Lausanne) 2018;5:344.

Figure 1. Histologic and immunohistochemical features of a Spitz melanocytoma with *AKAP9::BRAF* fusion from the left buttock of a 41-year-old woman. **a**) H&E, ×2: low magnification showing a well-circumscribed, dermal melanocytic lesion. **b**) H&E, ×10: intermediate magnification illustrating melanocytes arranged in nests and fascicles within a dense fibrous stroma. **c**) H&E, ×20: high magnification depicting single and clustered spindle-shaped melanocytes within a collagen-rich background, showing minimal cytological atypia. **d**) MART1/Ki-67 dual staining highlighting diffuse MART1 positivity confirming melanocytic lineage, with Ki-67 labelling restricted to isolated cells, indicating minimal proliferative activity. **e**) PRAME staining showing weak and focal nuclear positivity in approximately 50% of lesional melanocytes, consistent with an intermediate-grade melanocytic neoplasm.