Diagnostic Pathology

CASE REPORT

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# Spitz melanoma with MAP3K8::ABLIM1 rearrangement: a case report with review of the literature

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## Abstract

**Background** Spitz tumors are relatively uncommon melanocytic lesions, typically affecting a relatively younger population but can be encountered at any age. They are characterized by a proliferation of melanocytes with epithelioid and/or spindled cytomorphology features, and interpretation is often challenging. The majority of these tumors are driven by kinase fusions or *HRAS* mutations. *MAP3K8* fusions, although rare, are characteristic genomic events in Spitz tumors, especially in more atypical or malignant lesions.

**Case presentation** Here, we present the case of a 43-year-old woman with a clinically cystic mass in her right groin, histologically characterized as a spindle and epithelioid cell malignant tumor. Immunohistochemistry revealed diffuse expression of S100 protein, tyrosinase and SOX10, patchy weak PRAME, HMB45 and Melan-A reactivity, and negative staining for BRAF V600E. Next-generation sequencing analysis revealed the presence of a *MAP3K8::ABLIM1* fusion gene, as well as *GRIN2A* and *TERT* promoter mutations. The morphology, immunohistochemistry and molecular analysis confirmed Spitz melanoma with molecular features suggesting a worse prognosis.

**Conclusion** This case introduces a novel fusion partner of *MAP3K8* in the context of Spitz melanoma and expands the morphologic and molecular spectrum of Spitz melanoma.

**Keywords** Spitz tumors, Spitz melanoma, *MAP3K8*, *ABLIM1*, *GRIN2A*, *TERT* promoter

## Introduction

Spitz tumors are challenging melanocytic lesions in daily practice, as the morphologic features frequently overlap with those of melanoma [1]. They exist within a spectrum that goes from benign Spitz nevi to malignant Spitz tumors, passing through intermediate lesions (Atypical Spitz tumors / Spitz melanocytomas) [1–4]. We now recognize specific molecular determinants of these lesions, namely *HRAS* mutations [1] and translocations involving tyrosine and serine/threonine kinases [1], while the presence of conventional melanocytic lesion molecular determinants, such as *BRAF V600E* mutations, excludes these lesions from the Spitz category [1–4].

While documentation of the Spitz pathway aids in identifying Spitz tumors, it does not directly determine their benign or malignant nature [2]. However, it offers invaluable diagnostic insights. For instance, given the rarity of melanomas exhibiting *HRAS* aberration or specific kinase fusion, detecting such aberrations reduces the probability of a malignant melanoma, unless compelling clinical or histopathological contexts suggest otherwise,

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or co-existing mutations or genomic aberrations are present [2].

Malignant Spitz tumors, also known as Spitz melanomas, are rare and are characterized by additional molecular determinants, such as *TERT* promoter mutations, *CDKN2A* mutations, and other aberrations [2–4].

In this report, we present a unique case of Spitz melanoma in which a kinase fusion gene involving *MAP3K8*::*ABLIM1* was identified. The *ABLIM1* fusion partner has not been described before in the literature in the context of Spitz melanoma.

## Case presentation

A 43-year-old woman with a medical history of hypertension sought care at a general surgery clinic due to a painful and itchy ulcerated cystic mass on her right groin. The mass had been present for over a year but had grown larger in the last six months, measuring around 5 cm. It had a firm base underneath and ulceration on top, surrounded by redness without purulent drainage. Magnetic resonance imaging (MRI) of the pelvic muscular tissue (Fig. 1) revealed a lobulated mass within the subcutaneous soft tissues of the right inguinal region measuring 4.4×3.9×2.3 cm. The mass demonstrated significant enhancement, consistent with a neoplastic process. The deep surface margin of the lesion abutted the superficial myofascial margin of the pectineus. There was no evidence of intramuscular signal abnormality or invasion, and the mass was otherwise completely contained within the subcutaneous soft tissues. Additionally, there were some mildly prominent lymph nodes around the peripheral margins of the lesion.

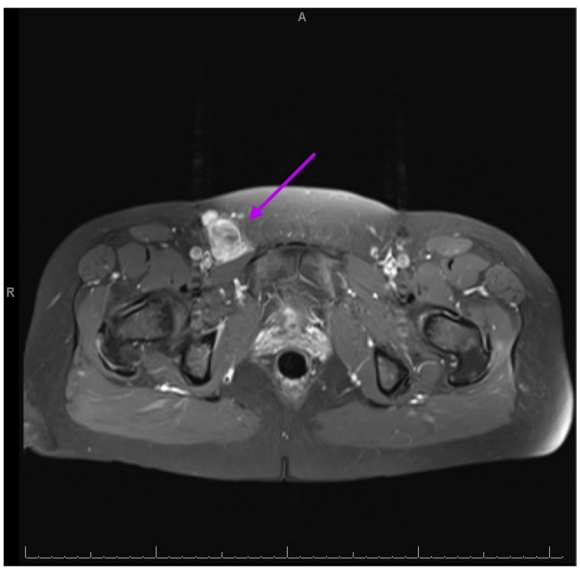


**Fig. 1** Spitz melanoma. MRI of the pelvic muscular tissue (T1 axial, post-contrast phase) shows a subcutaneous, soft tissue-enhancing mass in the right groin/ inguinal region, medial to the right femoral neurovascular bundle. The deep surface margin of the mass abuts the superficial myofascial margin of the right pectineus muscle, with mildly prominent lymph nodes around the peripheral margin of the mass

A needle biopsy performed on the right groin mass (Fig. 2) revealed a diffuse sheets of malignant pleomorphic spindled and epithelioid cells exhibiting elongated to ovoid hyperchromatic nuclei associated with moderate to abundant amounts of eosinophilic cytoplasm. Mitoses, including atypical forms, were present, and areas of necrosis were observed. Immunohistochemical stains showed that the tumoral cells were strongly positive for S100 protein, and SOX10. H3K27Me3 and INI1 were retained. The malignant cells tested negative for cytokeratin AE1/AE3, cytokeratin OSCAR, desmin, muscle-specific actin, smooth muscle myosin, caldesmon, tyrosinase, Melan-A, PRAME, HMB45, CD117, ERG, myogenin, myo-D1, BRAF V600E, and CD3. The differential diagnosis centered predominantly around malignant peripheral nerve sheath tumor, versus malignant melanoma. The clinical impression of a lymph node metastasis favored malignant melanoma. Next-generation sequencing analysis was performed to further characterize this lesion, and a multidisciplinary team recommended excision of the mass.

Molecular testing (Table 1), utilizing RNA sequencing, revealed a *MAP3K8*::*ABLIM1* translocation, while next-generation sequencing showed *TERT* promoter and *TP53* pathogenic mutations and a likely pathogenic *GRIN2A* variant. Other variants of unknown significance are listed in Table 1. In addition, copy number loss was detected in the *CDKN2A* and *MTAP* genes. Tumor mutation burden (TMB) was low (3 mut/Mb). No *BRAF* mutations were detected.

The resected specimen revealed a 7.4×4.2×3.8 cm well-defined, firm, tan-pink, focally necrotic, bulging mass continuous with a scar-like lesion on the skin surface. The mass was abutting the skin, and 0.5 cm from the closest soft tissue margin.

Microscopic examination (Fig. 3) of the resected mass revealed a deeply-seated mass in the deep dermis and subcutaneous tissue, composed of confluent expansile nests and sheets of malignant epithelioid cells with abundant eosinophilic cytoplasm. The cells exhibited high-grade nuclear atypia with irregular nuclear membranes and enlarged eosinophilic nucleoli. A focal area of melanin pigment was present. Mitoses, including atypical mitoses, and necrosis were observed. Neither neurotropism nor tumor-infiltrating lymphocytes (TILs) were identified. No epidermal or junctional activity was noted in the overlying epidermis. The tumoral cells were diffusely positive for S100, SOX-10 and tyrosinase,

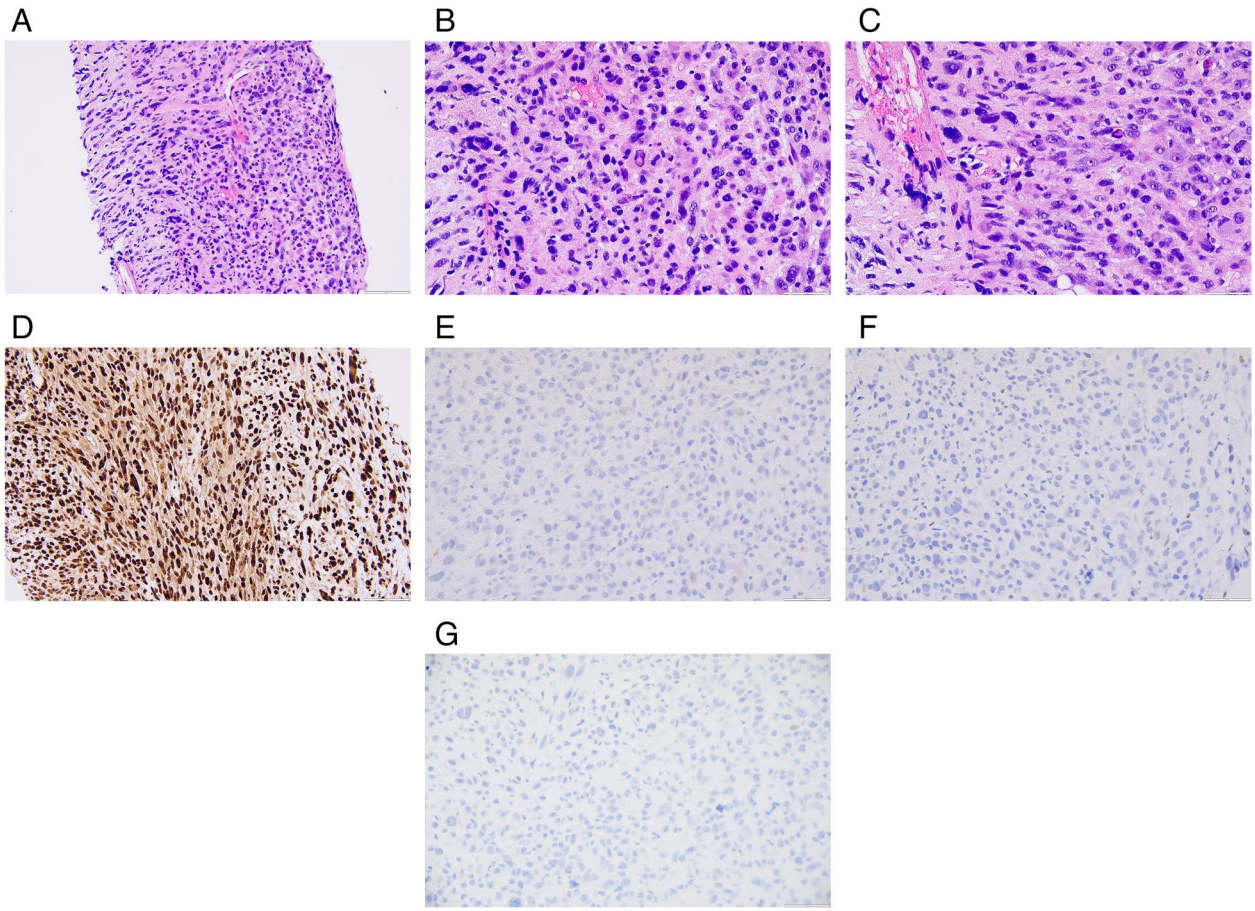


**Fig. 2** Spitz melanoma, needle core biopsy. **A** Malignant epithelioid and spindled cells exhibit moderate to severe pleomorphism, hyperchromatic nuclei and eosinophilic cytoplasms (x100). **B**-**C** Malignant cells also display prominent nucleoli, multiple nuclear inclusions, and mitoses (x200 and x400, respectively). **D** Malignant cells are diffusely positive for SOX10 immunohistochemical marker (IHC) (x200). **E** Malignant cells are negative for tyrosinase IHC (x400). **F** Malignant cells are negative for PRAME IHC (x400). **G** Malignant cells are negative for Melan-A IHC (x400)

weakly positive for PRAME and HMB45, Melan-A and negative for BRAF V600E. In addition, p16 showed a loss of nuclear and cytoplasmic expression.

Based on histomorphology, immunohistochemistry and tumor profile analysis with *MAP3K8* gene fusion, a diagnosis of Spitz melanoma was rendered. Additionally, the presence of copy number loss of *CDKN2A (*with p16 null type), *GRIN2A* and *TERT* promoter mutations predicted association with rapid disease progression.

Post-surgical follow-up records (1 month later) showed a healing wound with minimal discomfort. Further imaging studies revealed a metastasis to the right lung. The patient is undergoing immunotherapy with nivolumab and ipilimumab.

## Discussion

Spitz melanomas (SM), or malignant Spitz tumors, constitute a distinct subtype of spitzoid melanomas, as recently characterized [1, 3]. The features of these lesions include a larger tumor size (>1 cm), broad ulceration, asymmetry, lack of maturation, nuclear pleomorphism, necrosis and high mitotic activity featuring atypical mitoses. Moreover, it presents spitzoid characteristics, such as the presence of large epithelioid and/or spindle melanocytes [1].

The molecular alterations of SM are characterized by initiating genomic alterations typical of Spitz nevus, including kinase fusions and *HRAS* mutations, alongside homozygous loss of *9p21*. Mutations in *BRAF V600E* or other molecular characteristics of conventional melanocytic tumors are not present by definition; that is, presence of such alterations excludes a diagnosis of SM. Furthermore, copy number loss of *CDKN2A*, *GRIN2A* and *TERT* promoter mutations and multiple chromosomal copy number aberrations may be observed, correlating with an adverse prognosis [5, 6]. Additionally, SM usually exhibit a lower tumor mutational burden when compared with conventional melanoma [2].

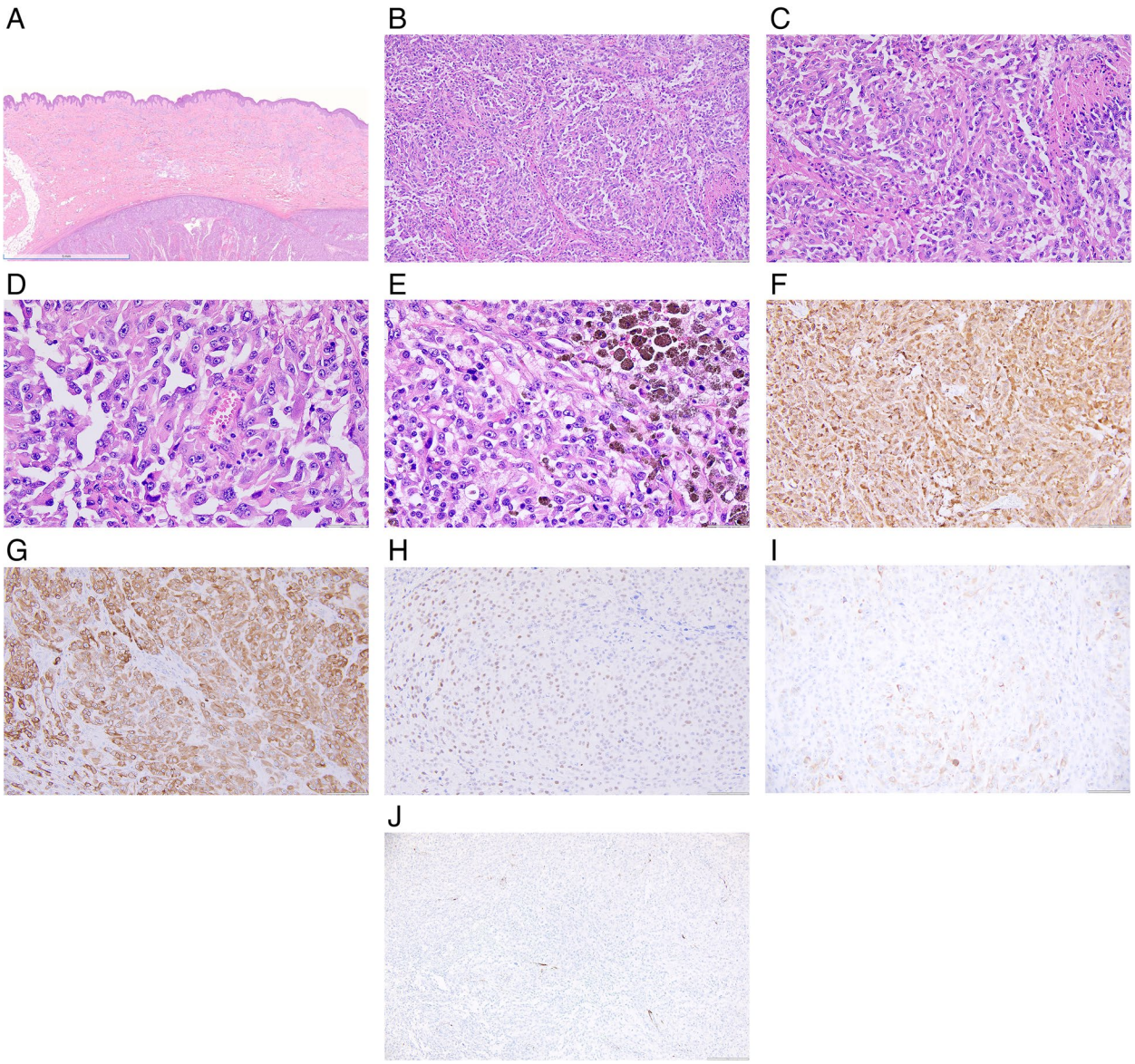


**Fig. 3** Spitz melanoma, resected specimen. **A** The deep dermal/subcutaneous tumor with overlying epidermis shows mild spongiosis with no epidermal or junctional melanocytic activity, and dermis shows a perivascular inflammatory infiltrate (x20). **B** Confluent nests of malignant epithelioid cells with abundant eosinophilic cytoplasms and focal necrosis (x100). **C**-**D** Epithelioid cells exhibit very prominent nucleoli (x200 and x400, respectively). **E** Malignant cells with adjacent areas of prominent pigmentation (x400). **F** Malignant cells are diffusely positive for S100 IHC (x200). **G** Malignant cells are diffusely positive for tyrosinase IHC (x200). **H** Malignant cells are weakly positive for PRAME IHC (x200). **I** Malignant cells are weakly positive for Melan-A IHC (x200). **J** Malignant cells show loss of p16 expression (x200)

The differential diagnosis of SM encompasses the spectrum of Spitz melanocytic neoplasms, which share common features such as clinical aspects, histological characteristics like epithelioid and spindled melanocytes, and specific genetic alteration. However, non-melanoma Spitz tumors typically exhibit low to intermediate grade histomorphological features, fewer DNA alterations, and a low risk of progression compared to their malignant counterparts. Atypical Spitz tumors, also known as Spitz melanocytomas, represent intermediate Spitz melanocytic neoplasms that may display some high-grade histomorphological features. Moreover, the umbrella term 'spitzoid melanomas' includes melanomas with spitzoid cytomorphology that lack Spitz-defining genetic alterations and demonstrate conventional melanocytic aberrations, most commonly *BRAF V600E* mutations, as mentioned above [2, 3]. Other differentials to consider, especially in cases of dermal lesions without an epidermal

**Table 1** Summary of molecular findings

| Translocation | Location |
|---|---|
| *MAP3K8::ABLIM1* | exon 7:exon 5 NM_001244134.1/NM_001322885.1 |
| **Mutations** | |
| **Pathogenic Variants** | |
| *TERT* | c.-146 C > T 52 NM_198253.2 |
| *TP53* | c.659_672 + 44del58 29 NM_000546.5 |
| **Likely Pathogenic Variants** | |
| *GRIN2A* | p.S929F 14 c.2786 C > T 20 NM_000833.4 |
| **Variants of Unknown Significance** | |
| *PLCG2* | c.3756–3 C > T Splice region variant |
| *APOB* | c.8524G > A p.E2842K Missense variant |
| *SPEN* | c.698 C > A p.P233Q Missense variant |
| *ETV5* | c.1343T > A p.V448D Missense variant |
| *SYNE1* | c.5045 A > G p.E1682G Missense variant |
| *FANCL* | c.857T > C p.L286S Missense variant |
| *POLQ* | c.5944T > G p.L1982V Missense variant |
| *CASR* | c.1553G > A p.G518E Missense variant |
| *NRG1* | c.1747G > A p.E583K Missense variant |
| *GATA1* | c.113 C > T p.P38L Missense variant |
| **Copy Number Loss** | |
| *CDKN2A* | |
| *MTAP* | |
| **Tumor mutation burden (TMB)** | Low (3 mut/Mb) |

component (as in our case), include clear cell sarcoma, which is characterized by *EWSR1* translocations [7]; alveolar soft part sarcoma, which features *ASPSCR1-TFE3* fusion [8], epithelioid sarcoma, and epithelioid malignant peripheral nerve sheath tumor, usually demonstrating *SMARCB1 (INI1)* deletion [9, 10].

Kinase fusions activate downstream cell signaling pathways such as MAP kinase signaling, JAK/STAT signaling, and PI3K/AKT1/MTOR signaling. This activation leads to the promotion of gene transcription, cell growth, proliferation, differentiation, and survival [11, 12]. In Spitz neoplasms, kinase fusions represent important mechanisms of oncogene activation and may serve as therapeutic targets for metastatic SM. Spitz neoplasms frequently harbor fusions involving various receptor tyrosine kinases such as *ROS1*, *NTRK1-3*, *ALK*, *RET*, *MET*, as well as serine/threonine kinases including *BRAF* and *MAP3K8* [12, 13].

*MAP3K8*, a serine-threonine protein kinase, activates extracellular signal-regulated kinase (ERK) 1/2 by phosphorylating its direct substrate, mitogen-activated protein kinase (MEK). High *MAP3K8* expression in melanoma leads to resistance against BRAF inhibitors via a MEK-dependent mechanism that does not necessitate *BRAF* activation upstream [14]. Various *MAP3K8* fusion partners have been identified in Spitz neoplasms, with *SVIL* being the most common 3' fusion partner [15]. The details of *MAP3K8* kinase fusion partners identified in the literature in Spitz tumors are provided in Table 2. Other 3′ fusion partners, not mentioned in Table 2, include *SFMBT2*, *MIR3681HG*, *CDC42EP*, *SLC4A4*, *CCNY*, *LINC00703*, and *PIP4K2A* [15].

**Table 2** Summary of *MAP3K8* kinase fusion partners identified in the literature in Spitz tumors

| MAP3K8 Kinase Fusion Partners | Type of Spitz Tumor and Number of Cases | | References |
|---|---|---|---|
| | Spitz Nevus | Atypical Spitz Tumor or Malignant Spitz Tumor | |
| *SVIL* | 1 | 20 | [14–16] |
| *DIP2C* | 1 | 5 | [14–16] |
| *UBL3* | 0 | 4 | [14–16] |
| *GNG2* | - | 2 | [14, 15] |
| *STX7* | - | 2 | [14, 15] |
| *LYZL2* | - | 2 | [14, 15] |
| *RSU1* | - | 2 | [14, 15] |
| *SPECC1* | - | 1 | [14, 15] |
| *CUBN* | - | 1 | [14, 15] |
| *PRKACB* | - | 1 | [14, 15] |
| *PCDH7* | - | 1 | [16] |
| *ATP2A2* | - | 1 | [16] |
| *ABLIM1* | - | 1 | Current study |

*MAP3K8*-rearranged cases exhibit epithelioid features, amelanotic melanocytes, marked pleomorphism, p16 loss, ulceration, and are more prevalent in atypical Spitz tumors and SM compared to other kinase fusions [4].

*ABLIM1*, known as Actin-binding LIM protein 1, is a cytoskeletal protein that binds to actin filaments and interacts with cytoplasmic targets [17]. Dysregulation of *ABLIM1* is associated with different types of cancers, and its loss in melanoma serves as a tumor suppressor [18]. *MAP3K8*::*ABLIM1* fusion has been previously reported in peritoneal mesothelioma [19]. Interestingly, there have been no previous reports of fusions involving *MAP3K8*::*ABLIM1* in melanoma to our knowledge.

In conclusion, we report an unusual aggressive Spitz melanoma with a novel *MAP3K8*::*ABLIM1* fusion gene and absence of identifiable in-situ component, contributing to the expanding morphologic and molecular spectrum of Spitz melanoma.

#### Informed consent
Informed consent was obtained from the patient involved in the study.

#### Authors' contributions
RS: Designed the study, interpreted the data, prepared the manuscript, and critically reviewed the manuscript. AV: Prepared the manuscript (clinical history), and reviewed the manuscript. AG and PM: Designed the study, and critically reviewed the manuscript. All authors read and approved the final manuscript. All authors agreed on submission.

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#### Availability of data and materials
The data generated during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

#### Data availability
No datasets were generated or analysed during the current study.

## Declarations

#### Competing interests
The authors declare no competing interests.

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## Publisher's Note